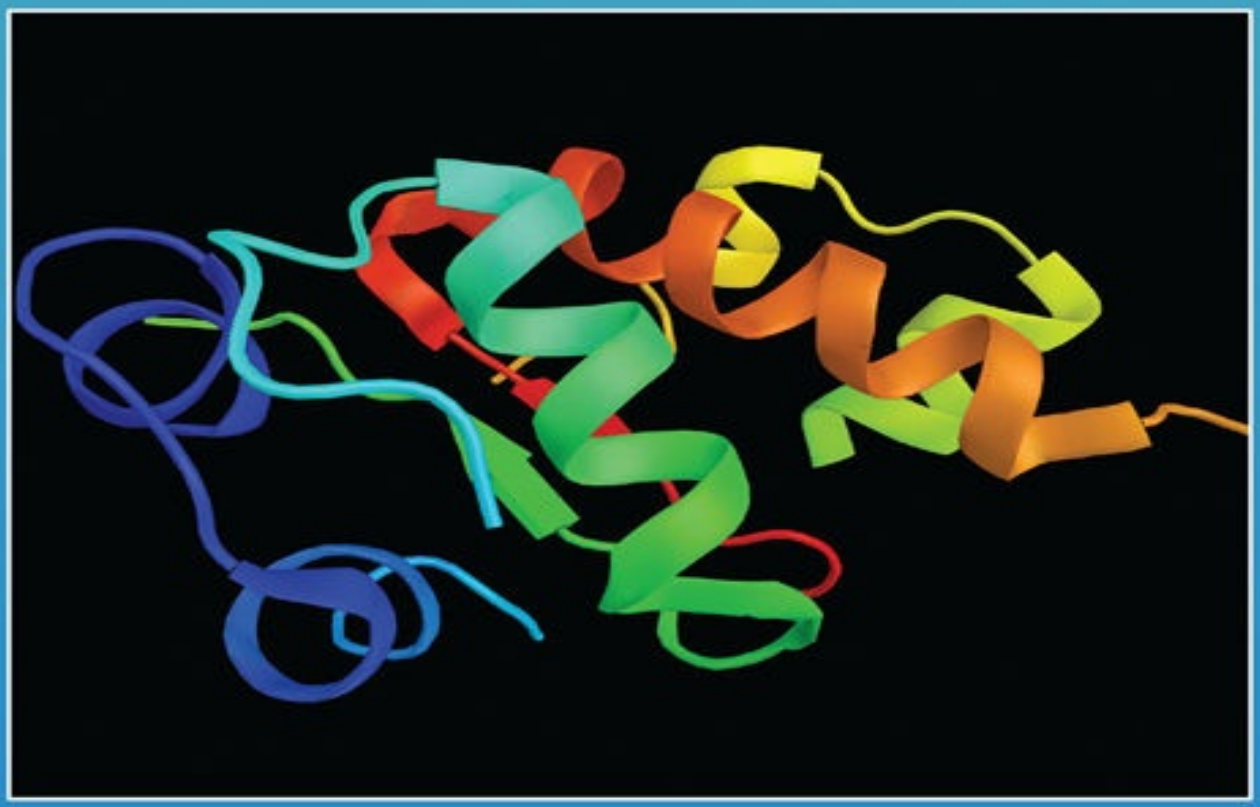
LIPPINCOTT MANUAL®

Manual of Endocrinology and Metabolism

5TH EDITION

Norman Lavin MD, PhD, FAAP, FACE



Wolters Kluwer

MANUAL OF ENDOCRINOLOGY AND METABOLISM

Fifth Edition

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A Brief Autobiography of Norman Lavin, MD, PhD, FAAP, FACE

Stories change shape as you read them. Understandings are loaded in, revised, and perhaps discarded. Then, when the book is closed, a kind of spirit image remains in the mind, a remnant. Sometimes the reader knows that a lasting connection has been made only by the intensity of the effect, the memory, and aftershock … that is, when the book is back on the shelf.

LOS ANGELES ZOO NURSERY

After completing medical school, graduate school, internship, and residency, as well as a fellowship in pediatric and adult endocrinology at UCLA Medical School, I was invited to a fundraiser at the L.A. Zoo on behalf of the new inhabitants. The zoo director was a veterinarian who specialized in nondomesticated animals; he was excited to announce the birth of many new breeds. We discussed medical issues, but when I asked who specializes in hormone abnormalities for the animals, he replied, “No one.” With great surprise and delight, I was immediately hired (as a volunteer) to consult on the “babies” in the nursery who possibly had endocrine or metabolic diseases.

The director escorted me through the newborn nursery. I was delighted, enchanted, and elated to meet my new “friends” (I hoped they would remember me when they got older so they wouldn’t “eat me”)! I petted them; they petted me. I sang to them; they sang to me. I looked in their eyes; they stared back at me. I knew that they knew that I was an endocrinologist!

They were all extremely beautiful… no ugly ducklings; in fact, no ducklings at all. I was convinced I was in the middle of the movie *Avatar*—on another planet, in another world… maybe even in “Heaven”!

First, the baby tiger—born prematurely and not growing well, but cuddled… wow, could he cuddle! Along with the veterinarian, I concocted a special formula adapted from human formula for prematures. He gained weight, he grew, he recovered, and, of course, he “smiled”! We all, the zoo personnel, smiled back and then he growled… no, not a growl… a roar… a loud, healthy, happy roar! And, of course, we all roared back in unison.

A few weeks later, a baby Masai giraffe was brought to our nursery. I guess he was a baby, but at 6 feet tall and 160 pounds in weight, I had some doubts. The zoo director assured me he was normal size for a giraffe. “What is the problem?” I asked the giraffe. Obviously, he was a baby… he couldn’t “talk.” Allegedly, shortly after birth, giraffes are mobile and start walking within days to a few weeks. But he seemed sleepy, even obtunded. The veterinarians examined him and he underwent x-rays and ultrasound studies, but all images were normal. They turned to me and said, “Now what?” I ordered blood tests immediately and discovered he was severely hypothyroid. His lethargy and immobility was caused by low levels of thyroid hormone—most likely caused by a congenital disorder. With daily hormone replacement, he fully recovered and was running in the yard with his mom. A few weeks later, I reexamined him; he clearly was normal. How was I certain? The blood tests normalized, and more importantly he was now 6 feet 5 inches tall and weighed 180 pounds. It was our final day together, so I stood on a chair and looked directly in his eyes, and tearfully said “Goodbye.”

Preface

This fifth edition of the *Manual of Endocrinology and Metabolism* offers a vast archive of information that both influences and challenges the basic medical knowledge we construct for ourselves. As Einstein said, “Everything should be made as simple as possible, but no simpler.” Our book is as simple as possible, but no simpler—a fusion of the ever-broadening world of endocrinology with specific criteria for evaluation and treatment for a vast number of endocrine disorders. It is robust and precise, with the authors firing on all cylinders. The power of this edition lies in its vibrant and resonant themes and sense of intellectual ferment. It offers a vast archive of current basic pathophysiology, clinical assessment, and the most modern treatment of endocrine disorders.

The purpose of this book is to lead endocrine science and medicine toward the goal of improved healthcare throughout the world including contributions from Saudi Arabia, Spain, Canada, France, Belgium, Taiwan, Israel, United Kingdom, India, Hong Kong, and Sweden. We are fortunate to be enriched by collaborations that cross international boundaries. This worldwide participation enriches the experiences and goals to optimally serve all endocrinologists. It is encyclopedic in scope, covering 89 chapters and several hundred topics with 149 contributors. I have carefully chosen some of the most outstanding clinical experts in their respective fields of endocrinology. I have not simply chosen experts, but I have chosen doctors who feel empathy for their patients.

The intended audience is obviously the endocrinologist, but equally so the general practitioner, internist, pediatrician, subspecialist, physician’s assistant, nurse practitioner, nurse, medical student, intern, resident, fellow, and any medical personnel who comes in contact with an endocrine patient.

I believe the book is a paean to ingenuity—to the power of science, technology, engineering, and comprehension. It is a bracing swim in the waters of science and technology. The writers’ voices are natural, robust, and precise. The book is wide ranging, but not confusing, packed with details that are clearly focused, and the chapters reverberate long after the final page.

The ancient Greek philosopher, Herodotus, wrote: “The only thing that is constant is change.” Certainly, in medicine, and particularly endocrinology, there have been significant changes regarding new therapies, new methods of treatment, new understandings of endocrine physiology, and new surgical approaches to disease states. But concurrently, many “older” fundamental understandings and treatment modalities still exist. In this fifth edition, I have attempted to integrate both roads into one main highway. Therefore, I have brought together the latest guidelines and consensus agreements for prevention and management of many endocrine disorders, extracted from the wide range of endocrine organizations, including the Endocrine Society, the American Academy of Clinical Endocrinology, and the Pediatric Endocrine Society. I believe it is a work of great ambition, beautifully executed, a worthy successor to the previous four editions, and the harbinger of great hope for even more editions to come.

As in the fourth edition, the manual blends three primary subdivisions—adult, pediatric, and reproductive—that examine each of these entities alone, as well as what they have in common and how they differ. Thus, an underlying theme of this book is to present evaluation, pathophysiology, management, and treatment at every age of life with short- and long-term goals of reversibility and prevention. Each chapter allows the reader to quickly identify and understand the etiology, causality, differential diagnosis, and treatment plans of the most common endocrine disorders.

Many new chapters have been added to this edition, including transgender medicine, flushing and sweating, nasal administration of hormones, the growth plate, as well as traumatic brain injury and hypopituitarism. We have also added galactorrhea, preoperative, intraoperative, and postoperative management following pituitary surgery, growth hormone in adults, polycystic ovary syndrome, hypercalcemic crisis, parathyroid hormone–related protein, congenital hyperinsulinism, and hypokalemic periodic and nonperiodic paralysis. Additional chapters include fetal and neonatal endocrine emergencies,

as well as biomarkers p. vip. viiin the screening, diagnosis, management, and surveillance of endocrine disorders. Our section on diabetes mellitus is further enlarged to include new areas of interest, such as hypoglycemia-associated autonomic failure, glucocorticoid-induced hyperglycemia, C-peptide, cystic fibrosis–related diabetes, artificial pancreas, glycated proteins, inhaled insulin, and an exciting chapter on the application of stem cells in diabetes mellitus by a new author, Arye Lavin, MS.

Once again, in the last section of the book, there are many protocols for stimulation and suppression tests used in clinical endocrinology. As Nietzsche put it, “There are no facts, only interpretations. Furthermore, those interpretations thrive not because they are evenhanded or fair, but because they have the brute strength of a consensus behind them.”

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Dedication

To my mother and father, and my brother, Sheldon: Every day I think of you. Every day I talk to you. Every day I love you.

To my sister, Barbara: Thanks for always helping and guiding me as we grew up and continue to grow up.

To my sons, Arye and Jonah: In the last edition of the book, we talked about the challenge and complexities of becoming adults. Now you are adults! Arye at medical school; Jonah at law school. We all dreamed of this moment. As we all know, it is a challenge, but it is an exciting and worthwhile challenge that you will go forward in the world to help all people of every background, of every nationality, of every color, of every race, and of every gender—no matter what their financial assets. While your mother and I have tried to teach you all about life—you have taught us what life is all about. You both are amazing, important, special, unique, kind, precious, and you are loved by your mother and me, and virtually everyone that you encounter from every walk of life.

My sons have been able to keep the lights on and burning bright. They hum with intelligence and ambition. Each one approaches the world with a strong heart full of love and wonder, full of tenderness and toughness, blessed by a powerful sense of place. As they grew up, they were equal parts of euphoria and exhaustion. Now they are a humming force of personality and humor. One might say that each one is a child confection—there is no end to their sweetness and pleasure.

The challenges to my sons are obvious and apparent. Sometimes the fence is so high and the top is invisible. But it is what we are designed to reach for. Everything else is scaffolding. They have created an immersive and wonderfully realized world. I would be happy to sign up for their next expedition.

To my wife, Michele: We have all experienced the delicious madness when love first blooms—whether it happens in a bar, on a snowy street, or when one person slips a hand into yours by a campfire. Your faces glow with that radiating aura. You marvel at the miraculous ways in which you both are the same. You are up all night, sleepless, not eating. There are bursts of overflowing communication and having crazy, silly fun in public. Every second apart produces an ache, and every minute together grows too fast. I imagined a giant bubble of love encompassing both of us as I looked into her eyes. I felt as if I were glimpsing infinity. I felt as if the solar system had a new sun. I recall our life together in its vitality, complexity, and memory-shaping force. She is a woman of quiet humanity and probing intelligence. I can tell you that I am thrilled being with her at all times. Her intelligence, her beauty, her kindness, her sense of justice—oh, I am simply wild about her. I constantly relearn her and rediscover her, constantly finding a new beloved with a woman I have always loved. She is intelligent, ambitious, confident, and gorgeous inside and out, essentially the embodiment of what great women represent. She is a woman whose selfless devotion to her work as a nurse manager is matched only by the goodness of her heart. At its core, our marriage is a touching love story, as well as a message about the human spirit.

Michele, to have been together and to have known you and loved you, to have grasped what joy exists, accompanied by the ring and peal of your romantic sensibilities—it is what it was and is really—life. Loving you now and forever. It has been said that you only fall in love once—no, every time I see you, I fall in love again.

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To Dr. Rosalyn Yalow: Rosalyn Yalow and Solomon Berson developed a procedure that uses radioactive materials to investigate the human body for small amounts of substances. In 1959, they perfected their

measurement technique and named it radioimmunoassay (RAI), which is extremely sensitive and can measure one-trillionth of a gram of material per milliliter of blood. Dr. Yalow later won the 1977 **Nobel Prize** in physiology or medicine for her discovery.

She was a remarkable woman and a remarkable scientist—a nuclear physicist who never took a course in biology, but developed a method to identify and measure vanishingly small amounts of almost any substance in body fluids and tissues. As a result, her work revolutionized virtually every aspect of medicine and biomedical science. Her story is about a great woman who was not an actress nor an heiress, but a towering intellectual figure who changed the world. The biography of Dr. Rosalyn Yalow is the story of a woman who prevailed against class, religion, and gender prejudice to reach the pinnacle of the science world. I was very honored that she contributed to early editions of our textbook. I was even more honored to be her friend.

To Dr. Andrew Schally: Andrzej Viktor (Andrew) Schally was a corecipient with Rosalyn Yalow of the **Nobel Prize** in physiology or medicine in 1977. In September 1939, when Poland was attacked by Nazi Germany and the Soviet Union, Schally escaped to then neutral Romania. In 1952, he moved to Canada, where he received his doctorate in endocrinology from the McGill University in 1957. He then came to the United States, where he worked principally at Tulane University and currently conducts research in endocrinology at the Miami Veterans Administration Medical Center in Miami, Florida.

Dr. Schally developed a new realm of knowledge concerning the brain's control over the body chemistry. Together with Roger Guillemin, he described the neurohormone GnRH, which controls FSH and LH, for which he was awarded the Nobel Prize. Approximately 30 years ago, I was very honored to spend an entire day with Dr. Schally, discussing history, current events, and, of course, the hypothalamus and the pituitary gland. Following our discussion, I immediately knew that I had better go home and "study harder." I am further honored that he has contributed a chapter to all four editions of our textbook, and I am even more thrilled that he has contributed another chapter to this fifth edition.

Dr. Yalow and Dr. Schally: You both left fingerprints of knowledge on all the authors' lives—you shall never be forgotten.

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I thank all of my old friends, new friends, and colleagues who have contributed to this fifth edition with their expertise and tremendous scholarship. I particularly thank Ms. Nancy Herbst, MAEd (master's degree in elementary administration), currently director of general studies at a prestigious private elementary school, for her skillful and unmatched literary and technical assistance (more a partner than an assistant), as well as her unyielding patience and wonderful sense of humor (but who rarely laughed at my jokes).

I want to acknowledge my academic relationship of 40 years with the endocrinology department at UCLA, with particular thanks to the first division chief, Dr. Solomon Kaplan, and the entire faculty throughout my tenure. I now welcome the new, impressive chair, Dr. Steve Mittleman.

I also thank the friendship and guidance from colleagues and friends to include Dr. Ben Fass; Dr. Al Sils; Dr. Cesar Chavarria; Randee Jackson; Rabbi Jay Levy, JD; Rabbi Bernard Cohen, PhD; Rabbi Gershon Klein; and Chaplain Mark Tomidy. I shall never forget UCLA coach, John Wooden, for his embracing friendship and transcendent inspiration. Unfortunately, in 2010 he passed away at the age of 99. In a message to all of us, he said, "Do not let what you cannot do interfere with what you can do."

Beyond all the friendships, academic colleagues, family members, and friends from every walk of life, stands Gracie, our golden retriever, whose support to me is unyielding and boundless.

Norman Lavin, MD, PhD, FAAP, FACE

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SECTION 1

Basic Science of Clinical Endocrinology

1

Clinical Molecular Endocrinology Laboratory Testing

Wayne W. Grody

Because genetic testing becomes ever more commonplace in medical decision-making, the perceived mystery surrounding “molecular” diagnostics has fallen away, only to be replaced all too often by naïve (over-)confidence in the clinical utility of DNA- and RNA-based testing. As with all clinical laboratory testing, the best diagnostic results are achieved after much forethought before any testing is even ordered, and when clinicians understand the limitations and caveats of the testing they use. This is especially true in the area of endocrine disorders, where modern genomic sequencing is often the approach of choice, because many different genes and disorders may be in the differential diagnosis. Such testing is orders of magnitude more complex (and expensive) than traditional single-gene testing. Above all, one must ask whether a positive or negative result of the test will actually influence clinical management, and whether the potential benefits of the test outweigh the risks. Here, we offer a checklist to help clinicians avoid the most common diagnostic pitfalls and to help ensure rational use of endocrine genetic testing.

I. THE CHECKLIST FOR CLINICIANS

A. **Purpose:** Is genetic testing appropriate for this patient?
B. **Probability:** Is the diagnosis likely enough to warrant genetic testing?
C. **Proper test and procedure:** Which test (and method used to perform that test) is most appropriate?
D. **Place:** Is there an available laboratory with the proper certifications, quality control, and expertise to assist with diagnostic interpretation?
E. **Cost/benefit:** Is the benefit worth the potential cost to the patient and society?
F. **Pitfalls:** What are the diagnostic, interpretive, and psychosocial pitfalls to watch out for?
G. **Politics:** Are there legal, regulatory, and ethical currents that might affect my choice of diagnostic approach, or even whether to order the test at all?

II. STEP 1: STARTING WITH THE PURPOSE

A. **Proof of diagnosis.** Genetic testing may be useful to provide independent confirmation of a diagnosis made through clinical acumen and biochemical p. 1p. 2laboratory testing, although it must be kept in mind that the **positive predictive value** (PPV, probability of disease among patients with a positive test) of most molecular genetic testing is generally better than the **negative predictive value** (NPV, probability of no disease among patients with a negative test). This is not because molecular techniques are inherently inferior at the analytical level, but because they are highly specific and targeted: Gene- or mutation-targeted tests will only detect the mutation or gene region examined and will not even assess other potential molecular etiologies of the condition in question. DNA sequencing tests, while less specifically targeted, only address selected regions of the genome and at present ignore noncoding regions. For that reason, **in general, negative results on genetic testing should not be used to rule out a clinical diagnosis**, though they may substantially reduce the likelihood, depending on the nature and current knowledge of the gene(s) in question.
B. **Prognosis.** Knowledge of a specific mutation may be helpful in predicting future outcome. For example, identification of a mutation affecting the glucokinase gene in maturity-onset diabetes of the young type 2 (MODY2) predicts a much milder progression of pancreatic *β*-

cell dysfunction than other types of MODY.

C. Pharmacogenetics. Genetically determined differences in metabolism of and response to different medications may influence dosing decisions. In some cases, specific mutations may influence not only the dose but also the choice of medications: Mutations in the *HNF-1α* gene (MODY3) are associated with far better response to oral sulfonylurea treatment than are mutations in the *HNF-1β* gene (MODY5).

D. Psychosocial benefit. For conditions in which genetic testing has a strong clinical utility, both the patient and the clinician may benefit from having a firm diagnosis that avoids many of the methodologic problems (interferences, population variability, and reference interval limitations) inherent in clinical biochemical testing. We have found that even for those disorders with no treatment, there can be a certain psychosocial benefit to finally bringing closure and ending the so-called **"diagnostic odyssey"** which entails continued futile, costly, and sometimes risky consultations and studies through other specialists.

E. Presymptomatic diagnosis. Making a diagnosis of disease prior to the appearance of any symptoms carries potential psychological and even financial risks (e.g., insurability and employability). These considerations are especially pointed in pediatric patients who are below the age of consent and at greater risk of being stigmatized by the test result. However, there are exceptions, such as the testing for *RET* proto-oncogene mutations in relatives of patients with multiple endocrine neoplasia type 2 (MEN-2A or MEN-2B), where early detection of mutations associated with aggressive disease, particularly medullary carcinoma of the thyroid, allows early treatment (prophylactic thyroidectomy) that can be lifesaving. The decision to pursue such testing is based on the age of onset of the disorder and the overarching question raised at the start: Will a positive result of this test influence clinical management? If there is no preventive intervention that would be done during childhood, then such testing is better deferred until the patient reaches the age of consent.

III. STEP 2: ESTIMATING PRIOR PROBABILITY OF DISEASE.

As noted earlier, genetic testing tends to have a better PPV and worse NPV than more traditional clinical laboratory modalities. Therefore, if the preexisting risk of disease is very low and the causative mutation targets

are only partially known, genetic testing is most likely to give a noninformative negative result. Conversely, for a diagnosis of very low likelihood, there is a greater chance that any positive result obtained represents a technical false positive rather than a true positive. Estimates of pretest probability of disease (also called *a priori* risk) are affected by:

A. Prevalence of disease in the population segment (ethnic group, age, and sex) to which the patient belongs. Disease prevalence also directly affects the PPV for mutations with **penetrance** of <100% (see **Section VII.E**).

B. Presentation. Certain associated symptoms or signs (biochemical and histologic) may increase the pretest probability of a genetic disorder, as does the presence of early-onset or multifocal disease.

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C. Pedigree. Family history is helpful in risk assessment and should always be queried prior to ordering a genetic test. A previously affected sibling will greatly raise the probability of a **recessive disorder**, whereas multigenerational affected cases will raise the likelihood of a **dominant disorder**. Transmission (or lack thereof) through male versus female parents may point suspicion toward **X-linked** or **mitochondrial** disorders. Such patterns are best detected by constructing a detailed pedigree as opposed to a few informal questions about family history. However, recognizing that many clinicians have neither the time nor the background to undertake such an effort, referral to a medical genetics clinic should be considered if familial transmission is suspected. That facility can also facilitate proper ordering of the test, especially if it is an esoteric one, and can provide genetic counseling to the patient and family regarding recurrence risk, testing of other at-risk relatives, and prenatal diagnosis.

IV. STEP 3: PICKING THE PROPER TEST AND PROCEDURE/METHOD

A. Consider right at the beginning whether the available “nonmolecular” diagnostic alternatives should be used first or instead of genetic testing. Such tests are often less expensive, easier to order, and have shorter turnaround times.

1. For example, look for hyperandrogenism by endocrinologic measurements first, before using genetic testing, for suspected

congenital adrenal hyperplasia (CAH).

2. On the other hand, DNA-based testing should be favored if available alternatives do not pick up disease until it actually develops (e.g., C-cell hyperplasia or malignancy in MEN2/familial medullary thyroid cancer [FMTC]).

B. Choose a test method of appropriate analytic sensitivity and specificity for the intended purpose (Table 1-1).

1. For example, **polymerase chain reaction** (PCR) testing for the presence of a cryptic *SRY* gene in Turner syndrome (to assess risk of gonadoblastoma) may pick up positive cases that would be missed by standard **cytogenetics** or **fluorescence *in situ* hybridization** (FISH). PCR, by virtue of its exponential amplification of small regions and small amounts of target DNA by repeated cycles of DNA polymerase-mediated replication, is exquisitely sensitive and specific.

C. On the other hand, in the work-up of a syndromic presentation caused by potential deletion of an unknown gene(s), a less targeted (albeit less sensitive) technique such as chromosomal microarray (CMA) would be preferred. Choose a test method of appropriate breadth for what is known about the causative gene(s) and the type of mutation suspected.

1. For example, for a single known **point mutation** (single-nucleotide substitution, microdeletion, or microinsertion), a targeted approach using PCR amplification of the gene region in question followed by hybridization with an **allele-specific oligonucleotide** (ASO) probe, or limited DNA sequencing, will be most efficient. The suspected point mutation may be known up front either because it is the only p. 3p. 4one identified in patients with the particular disorder (e.g., the M918T variant in the *RET* gene in MEN-2b) or because an affected index case in the family has already been tested and the familial mutation identified.

TABLE 1-1 Examples of Molecular Tests to Order for Specific Endocrine Diseases

Multiple endocrine neoplasia, type 1	Sequencing of the *MEN1* gene
Multiple endocrine neoplasia, type 2	Sequencing of the *RET* gene
Multiple endocrine neoplasia, type 2b	ASO probe hybridization for the M918T mutation
Turner syndrome	PCR or FISH for the *SRY* gene
Hypoparathyroidism in DiGeorge syndrome	Karyotype or FISH for 22q11.2 deletion

Congenital adrenal hyperplasia	Sequencing of *CYP21A2* and related genes
Disorders of sexual development	DSD gene panel
Undiagnosed syndromic conditions	Chromosomal microarray and whole-exome sequencing

ASO, allele-specific oligonucleotide; DSD, disorder of sex development; FISH, fluorescence *in situ* hybridization; PCR, polymerase chain reaction.

2. For disorders in which a small set of point mutations accounts for most or all of the cases as in MEN-2a, **multiplex PCR** amplification of the various gene regions followed by hybridization with a panel of ASO probes covering each of the mutations, often in a **reverse hybridization** or **microarray** format, is an efficient option.
3. For disorders with a greater number of possible mutations that may be found across the gene, as in MEN1, **DNA sequencing** of the entire **gene** (in practice usually limited to the coding regions or **exons**) is the "gold standard," casting the widest possible net for detection of whatever unknown mutation may be lurking there.
4. For disorders that can be caused by mutations in any of a family of genes, as in CAH, complete DNA sequencing of a **gene panel** is the most efficient and cost-effective approach. Such panels now exist for many families of genetic disorders and are offered by both academic and commercial molecular genetics laboratories.
5. If the suspected mutation is a large deletion of one or several exons or even the entire gene, the most appropriate method will be **multiplex ligation-dependent probe amplification, exon array,** or **chromosomal microarray** (CMA), all of which are much better at detecting large structural rearrangements than is DNA sequencing. In fact, heterozygous deletion of a large gene region will usually be invisible to standard PCR-based sequencing, because only the opposite normal allele will amplify and be sequenced, resulting in a false negative.
6. For disorders characterized by chromosome aneuploidies, such as Turner syndrome and Klinefelter syndrome, or translocations such as *RET-PTC* in papillary thyroid carcinoma, standard **karyotyping** is the best method for a quick survey of the entire complement of chromosomes. If a specific change is suspected, targeted molecular cytogenetic testing by FISH using the specific

probes complementary to the chromosome(s) or breakpoints involved is appropriate. The same approach can be used for targeted detection of specific chromosomal deletions, such as in hypoparathyroidism associated with the 22q11.2 deletion of DiGeorge/velocardiofacial syndrome.

7. For complex clinical situations of unknown etiology, such as nonspecific multiple congenital malformations, CMA is an efficient method for scanning the entire genome via millions of probes on a microarray hybridization platform ("DNA chip"), for dosage alterations (copy number variants, either insertions [duplications] or deletions) in the patient's genome.

D. Comprehensive versus targeted DNA sequencing. There is an important interpretive difference between those approaches that sequence gene hot spots to detect recurrent, well-documented mutations (as in MEN2) and those that assess every nucleotide in the entire gene (or at least in the exons). The latter approach will detect *any* sequence alteration that is present, whether pathologic or not. We now know, through the discoveries of the Human Genome Project, that **single-nucleotide polymorphisms** are remarkably common throughout the genome, in both coding and noncoding regions. Experience with full sequencing of the *BRCA1* and *BRCA2* genes associated with familial breast/ovarian cancer has shown us that for every true disease-causing mutation, there are many more missense changes of no apparent clinical significance in the genes of all human beings; these are the so-called polymorphisms that make up each individual person's unique DNA "fingerprint" but that do not in themselves disrupt gene function or cause disease. The problem in molecular diagnosis arises when such a missense change is found in a patient at risk, but this particular change has never been seen or reported before. In many cases, it can be difficult or even impossible to deduce, in the absence of clinical correlative evidence, whether the change is a true disease-causing mutation as opposed to a benign polymorphism of no clinical significance. One can attempt to do so by considering the nature of the resulting amino acid substitution, the degree of cosegregation of the alteration with p. 4p. 5the disease state in the family, the evolutionary conservation of the codon in question, and online variant assessment algorithms, but there are no firm rules that apply in all cases. Needless to say, the ability, or lack

thereof, to make this distinction, can have a tremendous impact on the genetic counseling and medical management of the patient and family, and it is not unusual, when sequencing entire genes (or even the entire genome; see below), that the patient will be left with an equivocal test result in the form of a **variant of uncertain clinical significance** (**VUS**).

E. Genomic sequencing. The newest and perhaps most exciting approach to molecular genetic diagnosis is called **next-generation sequencing (NGS)** or **massively parallel sequencing**. In contrast to the mutation- or gene-targeted approaches described so far, this high-throughput technique allows us to obtain full DNA sequence of the entire human genome (**whole-genome sequencing**) or (as most laboratories do at present) all of the protein-coding regions (exons) in the human genome (**whole-exome sequencing**), encompassing about 30 million nucleotides of genetic code comprising about 23 000 genes. The technique thus allows testing not only of the small subset of known genes associated with a particular genetic disorder but also any and all other genes that might be involved or yet to be discovered. Thus, the technique is especially advantageous for those patients with unusual presentations that are not readily suggestive of a particular disorder or group of disorders; such patients often go undiagnosed for many years, because the more routine single-gene and other tests are inconclusive (the "diagnostic odyssey"). And, all 23 000 genes are interrogated in parallel, in a single test, offering the chance to quickly put an end to the "diagnostic odyssey" that so many patients with mysterious presentations typically go through, taking many years, visits to countless specialists, and tens of thousands of dollars of laboratory testing and imaging. Because NGS is so efficient and the cost continues to diminish, it has become the preferred technique also used for gene panel testing (Section IV.C.4).

V. STEP 4: FINDING THE RIGHT PLACE TO PERFORM THE TEST

A. Prior knowledge of the genetic aspects of the disease in question allows more rational use of molecular testing. For example, understanding of the relative incidence of different forms of MODY leads to a strategy of screening for *HNF-1α* (*TCF1*) mutations prior to genetic analysis of glucokinase or other genes, and clinical distinction of the various forms of MEN allows for targeted gene testing rather than the more expensive gene panels.

B. Preferred nomenclature. Genes may have multiple different names, which may complicate literature searches or attempts to find a testing laboratry. For example, the search for a laboratory offering testing for congenital adrenal hypoplasia should search for both *DAX-1* and *NROB1* gene mutations. A good site to find "official" gene names as well as common synonyms ("aliases") is **GeneCards** (www.genecards.org). As of 2016, about 40 000 protein-coding genes and over 100 000 RNA-coding genes were listed. Each search entry brings up descriptions of the gene, reported benign and pathologic variants, data on the respective protein products, and links to other medical and scientific databases.

C. Performing laboratories. One of the most useful Internet sites for clinicians is **GeneTests** (www.genetests.org). This extraordinarily useful resource lists laboratories performing a particular genetic test on either a research and/or clinical basis. The target diseases range from the relatively common, with many testing laboratories listed, to the ultrarare, for which there may be only a single laboratory in the world offering testing. Searches may be performed by disease name, gene symbol, or geographic location of the laboratories. For each laboratory identified, contact information, scope of services offered, laboratory licensure (see next section), and often a link to the laboratory's own website are provided. As of early 2016, a total of over 600 laboratories testing for more than 3 000 diseases were featured on the site. Another site, the **Genetic Testing Registry (GTR)** (www.ncbi.nlm.nih.gov/GTR/), housed at the National Institutes of Health, boasts an even larger collection of genes and laboratories because it also includes tests for somatic (acquired) mutations and NGS tests; it can be searched in the same way. Both sites include links to another p. 5p. 6very useful resource, **GeneReviews** (www.ncbi.nlm.nih.gov/books/NBK1116/), a large set of scholarly, up-to-date summaries of the diseases in question, and the modes of testing available.

D. Proper certification. Laboratories that provide molecular test results for clinical diagnostic and management purposes must be certified under the **Clinical Laboratory Improvement Amendments (CLIA)**. It is a matter of federal law that only CLIA–certified laboratories may provide clinical test results to physicians and patients. In addition to CLIA, most high-complexity genetic testing

laboratories submit voluntarily to inspection and accreditation by the **College of American Pathologists (CAP)**, which has more stringent and specific criteria for evaluation of molecular genetic laboratories. Further information can be obtained at www.cap.org, and the CAP offices can be contacted directly to inquire whether a certain laboratory has passed inspection and is accredited. Laboratories that perform testing on residents of certain states (e.g., California, New York) must also have that testing certified for those states. The GeneTests and GTR websites provide information about the current accreditation status of each listed laboratory, so ordering physicians can make an informed choice about where to send their patient's specimen.

E. Professional resources. An important resource for endocrinologists is the availability of specialists with particular expertise in genetics, medical geneticists and genetic counselors. These specialists will be more familiar with the caveats and limitations of these tests and how to go about ordering them. Almost all of the larger academic and commercial genetic testing laboratories recognize the importance of this aspect and have genetic counselors and/or medical geneticists on hand for pre- and post-test consultation with ordering physicians. As an alternate source, the websites of the **American College of Medical Genetics and Genomics** (www.acmg.net/) and the **National Society of Genetic Counselors** (www.nsgc.org) both feature search functions for locating nearby experts by zip code.

VI. STEP 5: OTHER USEFUL INTERNET RESOURCES.

Online Mendelian Inheritance in Man (www.omim.org/) remains the classic resource for general information about all known genetic diseases, the causative genes, the symptoms and signs, and comprehensive literature references (over 23 000 entries as of 2016). The **Human Gene Mutation Database** (www.hgmd.cf.ac.uk/ac/index.php) is an ongoing catalog of disease-related DNA sequence variants, classified as to likely pathogenicity. It is especially useful for checking out novel variants and VUSs reported by the testing laboratory. As of 2016, there were >180 000 mutations listed in 7 000 genes.

VII. STEP 5: IDENTIFYING POTENTIAL PITFALLS

A. Phenocopy phenomenon. Overlapping clinical phenotypes may

lead to improper selection of genetic testing. For example, a female with mild hyperandrogenism as a result of polycystic ovary syndrome might be referred inappropriately for testing for a *CYP21A2* mutation because of overlap with nonclassical adrenal hyperplasia.

B. Paternity issues. An eternal problem in genetic analysis is the difficulty of verifying paternity based on history-taking alone, yet it is often essential to have this information in order to assess risk for genetic disease and appropriate mutation targeting and interpretation in offspring. Additional testing to determine paternity (using DNA fingerprinting techniques) may be helpful but is fraught with legal, social, and psychological risk.

C. VUS. The downside of the powerful NGS technology is that for every real mutation it identifies, thousands or even millions of DNA sequence variants of unknown clinical significance are also revealed. The expertise required to distinguish clinically impactful pathogenic mutations from benign variants is considerable and highly specialized, and this is another reason to be discerning in the choice of testing laboratory.

D. Promoter and other noncoding region mutations. The majority of gene sequencing tests focus on exons (coding regions) and the boundaries between exons and introns (intervening noncoding regions) where RNA splice-site mutations are most likely to lie. Other regions of DNA may still be clinically relevant: Mutations in the promoter (regulatory) region can affect gene expression, and mutations within introns may p. 6p. 7lead to altered RNA processing during transcription of DNA into RNA. Yet at this time, it is still impractical and overly costly to pursue comprehensive sequencing of these lengthy noncoding regions. In a few years, when whole-genome sequencing becomes a reality at the clinical level, this may no longer be an issue, though many other challenges (such as the countless nucleotide VUS that will be found in these regions) will ensue.

E. Penetrance and expressivity. For the vast majority of genetic disorders, including those in the endocrine system, the penetrance (i.e., the proportion of individuals with the mutation(s) who actually exhibit the disease) and expressivity (i.e., the variability in severity and type of symptoms) is not uniform. These phenomena can cause the apparent "generation skipping" often seen in dominant disease pedigrees, and can make the interpretation of novel variants even more difficult. If

anything, the advent of clinical exome sequencing has revealed even more variability in genotype–phenotype correlation than we had previously suspected.

F. Predictive value of the genetic test. As noted above, this important attribute of genetic testing can vary substantially depending on the condition being tested. At one extreme, identifying the M918T mutation in the *RET* proto-oncogene essentially proves the diagnosis of MEN-2B and guarantees future manifestation if the testing is being done presymptomatically. At the other extreme, finding a VUS in one of the genes associated with MODY may have little or no correlation with eventual blood glucose levels.

G. Phase. If whole-exome analysis reveals two different "severe" mutations in *CYP21A2*, can we be certain that this indicates a diagnosis of CAH? To be certain, we need to know the phase of the mutations, that is, whether they are present on opposite alleles (in *trans*) or within the same allele (in *cis*). Only the former situation would result in CAH; an individual with the latter genotype would be a healthy carrier. Distinguishing between these two possibilities usually requires DNA testing of the parents.

H. Parental effects. Some genes are subject to **imprinting** phenomena, in which their expression depends on which parent they were inherited from. For example, the hyperinsulinism of Beckwith–Wiedemann syndrome will be seen only if the copy of chromosome 11 containing the causative mutation or deletion is inherited from the mother.

VIII. POLITICAL AND ETHICAL ISSUES

DNA-based diagnostic testing for genetic diseases is unique from the other areas of molecular diagnostics, such as molecular microbiology and molecular oncology. It is primarily in the area of genetic disease testing that issues of privacy and discrimination arise, simply because the test by definition is assessing the patient's fundamental genetic makeup. Although endocrinologists typically order these procedures for purposes of **diagnostic testing** in a symptomatic patient, which raises fewer of these concerns, it is important to remember that the same technology can be used for **presymptomatic testing** of later-onset dominant disorders, **carrier screening** for recessive mutations, and **prenatal diagnosis**. Each of these applications carries its own set of ethical concerns.

A. **Genetic discrimination** in employment or insurance is a theoretical risk of genetic testing, although in most situations patients are protected by the Genetic Information Nondiscrimination Act, an important piece of federal legislation that was passed in 2008. Providers should be prepared to address patients' concerns in this area when they arise.

B. **Abortion** remains a subject of intense religious, political, and constitutional debate in the United States. It is important in the context of prenatal testing in that it must be legal and available in order to justify the expense and potential risk to the fetus of prenatal diagnostic procedures. Prenatal testing for later-onset or treatable diseases, such as MEN, raises its own set of ethical questions, centered around whether the natural history and prognosis (given prophylactic treatment, e.g., thyroidectomy) are of sufficient severity to justify termination of a pregnancy. Some couples in this situation may opt for the procedure of **preimplantation genetic diagnosis**, in which embryos are produced by *in vitro* fertilization (IVF) and then biopsied for p. 7p. 8single-cell PCR testing. Only embryos not found to carry the mutation(s) in question are implanted in the mother's uterus.

C. **Eugenics** has traditionally referred to "improvement" of the gene pool of the human species through selective or coercive breeding, mandatory sterilization, or genocide. The advent of molecular medicine now raises the possibility of more subtle forms of eugenics based on differential access of certain groups to prenatal diagnosis, IVF, gene therapy, and potentially, human cloning. The recent advent of easier forms of gene editing (e.g., CRISPR/*cas*) has brought these once theoretical concerns into the fore of public debate, so providers may be confronted with such questions from patients.

D. **Predictive genetic testing of children** who are asymptomatic is generally to be avoided because of potential stigmatization and informed consent issues, unless there is a beneficial medical or surgical intervention that must be started in childhood to be effective. MEN2 is one of the best counterexamples for which predictive DNA testing in early childhood is justified, because of the young age of onset of medullary thyroid carcinoma (MTC) and the preventive effectiveness of early prophylactic thyroidectomy.

E. **Incidental findings.** Whenever genomic sequencing is performed (whole-exome or whole-genome), variants in all of the patient's

23 000 genes will be uncovered. Some of the deleterious mutations detected will have nothing to do with the clinical indication for ordering the test but could potentially be life-threatening: one example would be detection of a mutation in the *BRCA1* gene in a patient being sequenced to discover the cause of her diabetes. Because *BRCA* mutations do not cause diabetes, should this "off-target" or "incidental" finding be reported? Though irrelevant to the patient's primary diagnosis, it could carry life-changing implications for her future health, and conveying this knowledge would allow for preventative and/or surveillance measures to be instituted (e.g., prophylactic bilateral mastectomy/oophorectomy). Presently, there is much debate within the genetics community over how such incidental findings should be handled. But at the very least, the patient should be warned prior to testing that such findings are possible, and given the choice of whether to receive them or not.

F. **Privacy and confidentiality** must be maintained in all genetic testing situations in order to prevent inadvertent discrimination or stigmatization. In some cases, patients may not want their test results to be placed in the medical record or conveyed to other physicians or family members. Depending upon local laws and institutional policies, some effort to meet these requests is sometimes justified.

G. **Informed consent** is sometimes appropriate before embarking on certain types of molecular genetic testing, especially predictive tests or those whose clinical utility is not yet fully understood. It should not normally be necessary for routine diagnostic molecular tests in symptomatic patients. Because of the complexity of genome-level sequencing and the chance of revealing VUS's and incidental findings, informed consent prior to NGS testing is uniformly recommended.

H. **Gene patents.** For many years, large portions of the genome were under exclusive patent ownership by the commercial or academic entities who had first discovered the relevant genes. This situation severely limited the choice of laboratories offering particular genetic tests, and the resultant monopolies led to high pricing. The most widely appreciated example was the ownership of the *BRCA1* and *BRCA2* genes, associated with familial breast/ovarian cancer, by Myriad Genetics, a commercial reference laboratory in Salt Lake City. But these patents, and all other gene patents, were overturned in 2013 in a landmark Supreme Court Case, *Association for Molecular Pathology et al. v. Myriad Genetics*, so patients and providers now

have ample choices of where to send virtually any genetic test.

IX. EXAMPLES OF MOLECULAR APPROACHES TO SOME TYPICAL ENDOCRINOLOGIC CONDITIONS

A. MTC/ MEN2. The father and paternal uncle of a 6-year-old girl have been diagnosed with MTC. Should the daughter have genetic testing?

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Yes. MTC is potentially a component of MEN2, in which case the child would be at 50% risk of having inherited this often lethal condition from her father. Because almost all the mutations associated with MTC are found in exons 10, 11, 13, and 14 of the *RET* gene, targeted mutation testing is usually the procedure of choice. But if that test is negative and high clinical suspicion persists, full-gene sequencing can be ordered, as well as gene panel or whole-exome sequencing to identify mutations in related disorders. In this particular case, however, testing should begin first with an affected index case in the family, specifically the father. Once his mutation is identified (likely within the *RET* gene), the daughter (and any other at-risk relatives) need be tested only by a simple test targeting this one mutation. If she tests positive, she would receive prophylactic thyroidectomy and continued surveillance for other tumors in the MEN2 spectrum; if negative, she can be spared regular imaging and calcitonin or calcium-stimulation challenges, along with the associated anxiety.

B. MODY. A father diagnosed with type 2 diabetes mellitus has a daughter diagnosed with diabetes mellitus, assumed to be type 1 despite little or no evidence of autoimmunity. Her glycemic control remains excellent despite relatively small doses of insulin. Is genetic testing indicated?

Yes. Based on the clinical picture (including the family history), the probability of MODY is reasonably high. Several CLIA-certified laboratories perform sequencing of the five genes associated with different forms of MODY. Testing can be approached either sequentially or by examining all five genes at the same time (as a gene panel test). Results of this testing may be informative of prognosis and alternative (oral hypoglycemic agent) therapies, if certain subtypes of MODY are identified.

C. Suspected nonclassical 21-hydroxylase deficiency. A

hyperandrogenic woman has borderline elevation of basal follicular phase 17-hydroxyprogesterone. Is there an alternative to cosyntropin-stimulation testing to diagnose nonclassical CAH?

Yes. Especially in cases like this one where hormonal assays are inconclusive, genetic testing can be of great value in providing a definitive diagnosis and justification for a trial of corticosteroid treatment. Many laboratories (which can be found using the websites given above) offer either targeted mutation testing or full-gene sequencing of the *CYP21A2* gene. Also available are gene panels encompassing other genes (e.g., *CYP11B1*, *CYP17A1*, etc.) which are associated with clinically related disorders that may be in the differential diagnosis.

D. Disorder of sexual development. A newborn presents with ambiguous genitalia, including clitoromegaly and undescended testes; karyotype is 46,XY. Will genetic testing assist in determining the etiology and management?

Yes. There are many different kinds of intersex disorders, caused by hormonal or developmental blocks in any of the complex steps of embryonic and fetal sexual differentiation. Precise diagnosis is essential for determining appropriate sexual assignment and corrective surgery and hormonal therapy. Genetic testing is an invaluable complement to standard chromosome analysis, endocrinologic evaluation, and imaging for this purpose. Gene panel testing is available with as many as 35 or 40 genes, but because the genetics are so complex and new genetic etiologies are being discovered all the time, whole-exome sequencing would now be considered the procedure of choice.

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2 Hormone-Resistant States

Mitchell E. Geffner

I. GENERAL PRINCIPLES

A. Hormones were originally thought to signal only at sites distant from their glands of origin after transfer via the circulation (**endocrine** action). It is now well known that hormones can act on cells near their site of origin (**paracrine** action), immediately next to their cell of origin (**juxtacrine** action), and directly on their own cells of origin (**autocrine** action). Most recently, it has been shown that certain hormones/growth factors (see later) may act within their cells of origin without ever exiting these cells (**intracrine** action). In theory, resistance to hormone action can involve any or all of these pathways. Many hormones, such as insulin and growth hormone (GH), have both metabolic and growth-promoting/anabolic (mitogenic) activities.

B. Mechanisms of hormone resistance. Causes of hormonal resistance into two categories.

1. **Intrinsic or primary defects** are genetically mediated within the target cell. For example, >150 naturally occurring variations in the **insulin receptor** gene **(most of which are missense or nonsense mutations**) have been described, which, depending on the specific abnormality, can affect insulin binding to the receptor, internalization of the insulin–insulin receptor complex, subsequent autophosphorylation of the β subunit of the receptor (see later), or/and phosphorylation of other protein substrates involved in the intracellular signaling cascade.
2. **Extrinsic or secondary defects** result from circulating serum factors and are reversible following therapeutic perturbations that remove the resistance-causing factor from the bloodstream. These defects do not persist in cultured cells. Using insulin resistance as the paradigm, extrinsic factors that reduce insulin action include states of counterregulatory hormone excess (e.g., glucocorticoid excess such as occurs in Cushing syndrome), antibodies blocking the insulin receptor (type B syndrome of insulin resistance—see later), and uremia.

C. Molecular characterization of genes coding for hormones and their receptors (Table 2-1). These discoveries and other experimental work have clarified three generic peptide-hormone signaling mechanisms and the general mode of steroid hormone action, and have facilitated the grouping of receptors into superfamilies.

1. Generic peptide-hormone signaling mechanisms

a. Receptor autophosphorylation. As an example, insulin signals by binding to its cell membrane-anchored receptors, leading to the autophosphorylation of its β subunits and the tyrosine phosphorylation of various downstream intermediary proteins (see later).

b. The α subunit of the stimulatory G protein (α-Gs) of adenylyl cyclase, which serves as an on–off switch that is necessary for the action of various peptide hormones (e.g., parathyroid hormone [PTH]) that use cyclic adenosine 3,5-monophosphate (cAMP) as an intracellular second messenger, leads to protein phosphorylation and dephosphorylation of numerous, often cell-specific targets.

c. Stimulation of inositol lipid hydrolysis. G-protein–coupled receptors (GPCRs) regulate the activity of every cell in the body by linking to G proteins and activating effectors, such as adenylyl cyclase, ion channels, or phospholipase C, that lead to increases (or decreases) in intracellular mediator molecules, such as cAMP, calcium ions, inositol 1,4,5-trisphosphate, and 1,2-diacylglycerol.

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TABLE 2-1 Gene Products Involved in Genetic Hormone-Resistant States

Chromosome Location	Gene Product	Genetic Disorder
1p31	Leptin receptor	Morbid obesity
1q21.2	Lamin A	Partial lipodystrophy
2p21	LH/CG receptor	Male pseudohermaphroditism/primary amenorrhea in females
2p21-p16	FSH receptor	“Resistant ovary” syndrome

3p22-p21.1	PTH/PTHRP receptor	Blomstrand lethal osteochondrodysplasia
3p24.3	Thyroid hormone receptor *β*	Dominant-negative thyroid hormone resistance
3p25	Peroxisome proliferator-activated receptor-γ	Partial lipodystrophy
3q21–q24	Calcium-sensing receptor	Benign hypercalcemia (familial hypocalciuric hypercalcemia)
4q21.2	GnRH receptor	Hypogonadotropic hypogonadism
4q31.1	Mineralocorticoid receptor	Autosomal dominant type 1 pseudohypoaldosteronism
5p13-p12	GH receptor	Severe GH insensitivity syndrome (Laron dwarfism)
5q31	Glucocorticoid receptor	Generalized inherited cortisol resistance
6q25.1	Estrogen receptor	Tall stature with osteoporosis in a male
7p14	GHRH receptor	Recessive GH deficiency
7p21-p15	CRF receptor	None as yet
7q11.23–q21.11	Peroxisome proliferator-activated receptor-γ	Partial lipodystrophy
8p11.23	FGFR1	Hypogonadotropic hypogonadism
8q23	TRH receptor	Central hypothyroidism
9p12–21	CNP receptor (NPR-B)	Acromesomelic dysplasia, Maroteaux type
9q34.3	1-Acylglycerol-3-phosphate *O*-acyltransferase	Congenital generalized lipodystrophy
11q13	Seipin	Congenital generalized lipodystrophy
12q12–q14	Vitamin D receptor	Familial (vitamin D–resistant) rickets with alopecia
12q12–q13	Aquaporin-2 receptor	Autosomal recessive nephrogenic diabetes insipidus
12q13	ALADIN	ACTH insensitivity
12q13	AMH receptor	Persistent Müllerian duct syndrome
12q22–q24.1	Insulin-like growth factor I	GH resistance
12q24.1	Protein tyrosine phosphatase, nonreceptor-type, 11	Noonan syndrome
14q31	TSH receptor	Familial nongoitrous hypothyroidism
15q25–q26	Type 1 IGF receptor	Intrauterine and postnatal growth failure
16p12.2-p12.1	Amiloride-sensitive epithelial sodium channel	Autosomal recessive type 1 pseudohypoaldosteronism
17q11.2	Signal transducer and activator of transcription 5b	GH insensitivity and immunodeficiency
17q11.2	Thyroid hormone receptor *α*	None as yet
17q12–q22	CRF receptor	None as yet

18p11.2	ACTH (melanocortin-2) receptor	Familial glucocorticoid deficiency
19p13.3	G-protein–coupled receptor 54	Hypogonadotropic hypogonadism
19p13.3–p13.2	Insulin receptor	Type A syndrome, Rabson-Mendenhall syndrome, leprechaunism
19q13.2–q13.3	Dystrophia myotonica protein kinase	Myotonic dystrophy type 1
20q13.2	Guanine nucleotide-binding protein, *α*-stimulating activity polypeptide 1	Pseudohypoparathyroidism types 1A and 1B
Xq11.2–q12	Androgen receptor	Partial or complete androgen insensitivity syndrome (testicular feminization)
Xq28	ADH receptor	X-linked nephrogenic diabetes insipidus

ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; AMH, anti-Müllerian hormone; CNP, C-type natriuretic peptide; CRF, corticotropin-releasing factor; FGFR1, fibroblast growth factor receptor 1; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IGF, insulin-like growth factor; LH/CG, luteinizing hormone/chorionic gonadotropin; PTHRP, parathyroid hormone–related protein; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

2. **Steroid hormone action.** Steroid hormones enter cells by diffusion, following which they bind to receptor proteins both in the cytoplasm and in the nucleus. Such binding leads to conformational changes of the steroid–steroid receptor complex that result in its activation and heightened affinity to regulatory elements of DNA in the nucleus. This activation of target genes leads to appropriate protein synthesis, which in turn alters cell function, growth, and/or differentiation.
3. **Superfamilies.** Receptors can be grouped into superfamilies based on the sharing of significant amino acid sequence homology (Table 2-1).
   a. **Protein tyrosine kinase receptors** include structurally related receptors for insulin and insulin-like growth factor-I (IGF-I). Both insulin and IGF-I receptors (officially known as type 1 IGF receptors) are heterotetramers that possess intrinsic tyrosine kinase activity (see later).
   b. **Class 1 cytokine receptors** share structurally related extracellular domains and include a diverse group of proteins,

including the receptors for GH, prolactin, interleukin 2 (IL-2), IL-3, IL-4, IL-6, IL-7, erythropoietin, and granulocyte-macrophage colony-stimulating factor.

c. **GPCRs** represent the largest superfamily of receptors known to date and, traditionally, are subdivided into three subfamilies (rhodopsin/β_2-adrenergic receptors, calcitonin/PTH/PTH–related receptors, and metabotropic glutamate/calcium-sensing receptors). A more recent classification uses the Glutamate, Rhodopsin, Adhesion, Frizzled/Taste2, and Secretin (GRAFS) system. Genes that encode G proteins and GPCRs are susceptible to loss-of-function mutations that result in reduced or absent signaling by the corresponding agonist and cause resistance to hormone action, thereby mimicking a state of hormone deficiency. Mutational changes in G proteins that are unequivocally p. 13p. 14linked to endocrine disorders occur in α-Gs. Heterozygous loss-of-function mutations of α-Gs in the active, maternal allele cause resistance to hormones that act through α-Gs–coupled GPCRs. Loss-of-function mutations involving GPCRs have been described for adrenocorticotropic hormone (ACTH)/melanocortin 2, angiotensin II, antidiuretic hormone (ADH), calcium-sensing receptor, catecholamines, corticotropin-releasing hormone, follicle-stimulating hormone (FSH), ghrelin, gonadotropin-releasing hormone (GnRH), growth hormone–releasing hormone (GHRH), kisspeptin, luteinizing hormone (LH), melanocortin 4, NK3R (TACR3), prokineticin 2, PTH/PTH-related peptide (PTHRP), thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), and V_2 vasopressin.

d. **Ligand-responsive transcription regulators** are represented by low-abundance intracellular androgen receptor (AR) proteins, which are related to the retinoic acid, thyroid hormone, and vitamin D receptors.

e. **Nuclear receptor subfamily 3C** consists of glucocorticoid, mineralocorticoid, progesterone, and ARs.

f. **Transmembrane serine/threonine kinase receptors** are of three subtypes. They mediate responses to peptide growth/differentiation factors, including transforming growth

factor *β*, activins, and anti-Müllerian hormone (AMH).

g. **Guanylate cyclase-coupled receptors** or **membrane-bound guanylyl cyclases** are single transmembrane proteins. An example is NPR-B. The ligand for NPR-B, C-type natriuretic peptide (CNP), occurs in a wide variety of tissues, including the hypertrophic zone of the growth plate where it promotes synthesis of cartilage matrix and stimulates chondrocyte proliferation and differentiation in an autocrine/paracrine manner. The gene encoding this receptor, *NPR2*, is located on chromosome 9p12–21. Biallelic loss-of-function mutations of *NPR2* result in acromesomelic dysplasia, Maroteaux type. Heterozygous mutations in NPR2 are responsible for nonsyndromic familial short stature. Achondroplasia, hypochondroplasia, and thanatophoric dysplasia are syndromes of short-limbed dwarfism caused by **activating mutations of fibroblast growth factor receptor 3 (FGFR-3)**. In these skeletal dysplasias, elevated circulating levels of pro-CNP products have been found.

D. Specificity spillover. In states of resistance to traditional hormone action, the serum hormone concentration becomes elevated, via **negative feedback**. In some cases, it is thought that these high serum hormone concentrations can effect certain unintended actions through a receptor–effector pathway homologous to the normal signaling mechanism. For example, in the insulin resistance model, the resultant hyperinsulinemia may induce hyperandrogenism and polycystic ovarian disease, the skin changes of acanthosis nigricans, and hypertrophic cardiomyopathy, all of which may be mediated by a functioning homologous type 1 IGF receptor–effector mechanism in these victimized tissues that responds to the high circulating concentrations of insulin. This phenomenon has also been implicated in certain hormone-*sensitive* states (e.g., insulin stimulates macrosomia in the infant of the diabetic mother through the type 1 IGF receptor, IGF-II secreted from certain nonislet tumors induces hypoglycemia through the insulin receptor, and excess GH in acromegaly produces galactorrhea through the prolactin receptor).

E. Epigenetics. The term **epigenetics** refers to heritable, but reversible, changes in gene function without changes in nucleotide sequence, and thus may result in a change in phenotype without a change in genotype. Epigenetic change is a normal occurrence, but can

also be modulated by several factors, including age, environment/lifestyle, and disease state. Epigenetic modifications can manifest as commonly as the manner in which cells terminally differentiate to end up as skin cells, liver cells, brain cells, and so on or can have more deleterious effects that can result in diseases like cancer. At least three mechanisms, including DNA methylation, histone modification, and micro-RNA–associated gene silencing, are currently considered to initiate and sustain epigenetic change. Epigenetic regulation is known to affect the action of peptide hormones, steroid hormones, thyroid hormones, retinoic acid, and calcitriol. This p. 14p. 15phenomenon is also known to occur in utero and thus contribute to fetal programming of future endocrinologic/metabolic events, such as insulin sensitivity, as well as to the timing of pubertal events. Epigenetic abnormalities have also been implicated in pseudohypoparathyroidism type 1B (PHP-1B). Lastly, endocrine disruptors in the environment may have significant effects on the epigenome.

II. SPECIFIC DISORDERS ASSOCIATED WITH HORMONE RESISTANCE: RECEPTORS CONTAINING INTRINSIC TYROSINE KINASE ACTIVITY

A. Insulin

1. **General.** Insulin exerts its actions mainly in the liver, muscle, and adipose tissue, following its binding to cell-surface insulin receptors. The insulin receptor gene is located on chromosome 19p13.3–13.2. Binding of insulin to the extracellular α subunit results in activation of the tyrosine kinase activity of the β subunit, which appears to be the first step of intracellular modifications leading to the actions of insulin. Two major pathways appear to be regulated by insulin, one involving the intracellular phosphorylation of proteins, including, but not limited to, reduced insulin signaling of the insulin receptor substrate (IRS)-1/phosphatidylinositol 3-kinase pathway, resulting in diminished glucose uptake and utilization in insulin target tissues, and the other involving second messengers, such as glycolipids or diacylglycerol. These pathways ultimately lead to activation of the insulin-dependent glucose transporter, GLUT-4, and also of multiple enzymes.

2. Insulin resistance of uncertain etiology

a. Obesity and type 2 diabetes. Whole-body insulin resistance is the earliest predictor of type 2 diabetes onset, and this mainly reflects muscle insulin resistance. Possible causes of the insulin resistance of obesity include elevated levels of circulating inflammatory factors derived from adipocytes, such as tumor necrosis factor α (TNF-α), IL-6, and/or free fatty acids, that inhibit insulin signaling and induce insulin resistance, and activate serine/threonine kinases that phosphorylate the IRS proteins and inhibit their function. Insulin deficiency develops later (presumably secondary to gluco- and/or lipotoxicity). In overt type 2 diabetes, there is resistance to the ability of insulin to inhibit hepatic glucose output and to stimulate the uptake and use of glucose by fat and muscle; this peripheral insulin resistance is greater in patients with type 2 diabetes than in those with obesity alone. A reduced number of insulin receptors does not account for the observed insulin resistance, but probably reflects physiologic downregulation, which occurs in the setting of concomitant hyperinsulinemia. When the circulating insulin concentration is normal or low in patients with type 2 diabetes, the number of insulin receptors is normal. Both patients with obesity and those with type 2 diabetes have a reversible defect in tyrosine kinase activity of their insulin receptors in skeletal muscle. Impaired insulin-stimulated glucose transport has been demonstrated in muscle and adipocytes of both obese patients and patients with type 2 diabetes. However, the number of insulin-responsive glucose transporters (GLUT-4) in skeletal muscle of patients with type 2 diabetes is normal. In the Mexican-American population, single-nucleotide polymorphisms in calpain 10 (*CAPN10*), a gene coding for the protein from a large family of cytoplasmic proteases, seem to be responsible for 40% of type 2 diabetes familial clustering. A genome-wide association study (GWAS) conducted in Europeans has identified a dozen susceptibility loci linked to type 2 diabetes, of which eight have been replicated across multiple ethnic groups: *TCF7L2, SLC30A8, HHEX, CDKAL1, IGF2BP2, CDKN2A/B, PPARG,* and *KCNJ11*. Many, although not all, of the variants identified in Europeans have been replicated in non-Europeans, but with

differences in allelic frequencies and effect sizes. Collectively, these results highlight similarity in genetic susceptibility as well as ethnic differences, indicating that genetic variability strongly influences magnitude of the effect of GWAS risk loci in different populations. Adding to the complexity, among close to 80 loci associated with type 2 diabetes risk other than *TCF7L2*, there is absence of any large single-gene effects.

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b. **Insulin resistance, hypertension, hyperlipidemia, and atherosclerosis (metabolic syndrome).** Originally described in adults in 1988 (and called “syndrome X”), the metabolic syndrome is now defined by a constellation of interrelated physiologic, biochemical, clinical, and metabolic factors that directly increase the risk of cardiovascular disease, type 2 diabetes mellitus, and all-cause mortality. Obesity, insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, nonalcoholic fatty liver disease, elevated blood pressure, hypercoagulability, and chronic stress are all considered part of the syndrome. Such chronic inflammation is associated with visceral obesity and insulin resistance with resultant overproduction of abnormal adipocytokines as noted above. More recently, a linkage of the gut microbiome to obesity and its downstream manifestations has been proposed.
c. **Polycystic ovarian syndrome (PCOS).** This condition is associated with hyperandrogenism and chronic anovulation in conjunction with insulin resistance. **The onset of PCOS may be linked to a history of premature adrenarche** (early development of pubic and axillary hair secondary to early adrenocortical activity) in childhood or to a failure to establish regular menstrual patterns beginning at menarche followed by the development of hirsutism and acne. Insulin resistance is found in both obese and lean women with PCOS, and is associated with a postbinding defect in receptor signaling likely caused by increased insulin receptor and IRS-1 serine phosphorylation that selectively affects metabolic, but not mitogenic, pathways in classical insulin-sensitive target tissues. The resultant hyperinsulinemia is thought to play a primary role

in the induction of ovarian (and, perhaps, adrenal) hyperandrogenism by an as yet incompletely defined mechanism. In vitro studies show a direct effect of insulin stimulation on ovarian thecal cell production of androgens, and in vivo studies aimed at reduction of circulating insulin concentrations (e.g., by administration of diazoxide) are associated with a corresponding decrease in circulating testosterone. GWAS shows the strongest loci in Europeans with PCOS containing genes for *DENND1A* and *THADA*, with additional associations in loci containing the *LHCGR* and *FSHR*, *YAP1* and *RAB5/SUOX*.

d. Other associations

i. A history of intrauterine growth retardation (which may predispose to future type 2 diabetes)

ii. Genetic syndromes (e.g., Turner, Klinefelter, and Prader–Willi syndromes, and progeria)

iii. Degenerative neuromuscular diseases (e.g., myotonic dystrophy [see later] and Friedreich ataxia)

e. Intrinsic (primary) cellular defects associated with insulin resistance

i. Type A syndrome of insulin resistance and acanthosis nigricans

a) Clinical features. Acanthosis nigricans and ovarian hyperandrogenism in women.

b) Mechanism. Insulin receptor gene mutations in many cases.

ii. Rabson–Mendenhall syndrome

a) Clinical features. Similar to those of the type A syndrome of insulin resistance and acanthosis nigricans, along with dental and nail dysplasia, pineal hyperplasia, precocious pseudopuberty, and accelerated linear growth.

b) Mechanism. Insulin receptor gene mutations in all cases.

iii. Leprechaunism (Donohue syndrome)

a) Clinical features. Autosomal recessive inheritance, product of consanguineous parents, intrauterine and postnatal growth retardation, dysmorphic facies, lipoatrophy, muscle wasting, acanthosis nigricans,

ovarian hyperandrogenism in females, precocious puberty, hypertrophic cardiomyopathy, and early death.

b) **Mechanism.** Insulin receptor gene mutations (homozygous or compound heterozygous in all cases).

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iv. **Congenital generalized lipodystrophy (Berardinelli-Seip)**

a) **Clinical features.** Fat loss beginning at birth, with other features similar to those of the type A syndrome of insulin resistance and acanthosis nigricans, along with fatty liver infiltration leading, in some cases, to cirrhosis, hypertrophic cardiomyopathy, acromegaloidism, and hypertriglyceridemia.

b) **Mechanism.** This syndrome results from mutations in either *AGPAT2* (encoding 1-acylglycerol-3-phosphate O-acyltransferase) at 9q34, causing increased production of the cytokines, IL-6, and TNF-*α*; or *BSCL2* (encoding seipin) at 11q13, which functions as a transmembrane protein.

v. **Partial lipodystrophy (Dunnigan)**

a) **Clinical features.** Fat tissue affected by lipoatrophy or lipohypertrophy, usually beginning during puberty, with other features similar to those of the type A syndrome of insulin resistance and acanthosis nigricans, along with hepatosplenomegaly, hypertrophic cardiomyopathy, acromegaloidism, and hypertriglyceridemia.

b) **Mechanism.** Results from mutations of *LMNA* (encoding nuclear lamin) at 1q21–22 or *PPARG* (encoding peroxisome proliferator-activated receptor-*γ*) at 3p25 or 7q11.23-q21.11.

vi. **Myotonic dystrophy type 1**

a) **Clinical features.** Unusual form of insulin resistance characterized by weakness and wasting, myotonia, cataracts, and often by cardiac conduction abnormalities; adults may become physically disabled and may have a shortened life span, and a congenital form may be fatal.

b) **Mechanism.** Caused by a cytosine-thymine-guanine trinucleotide expansion in the 3′-untranslated region of

the DM1 protein kinase gene.

f. **Extrinsic (secondary) cellular defects associated with insulin resistance**

i. **Physiologic states.** Gender (female > male), race (African American, Hispanic, and Native American > Caucasian), puberty (perhaps secondary to increased GH secretion), pregnancy, and old age.

ii. **Abnormal physiologic states.** Infection (including HIV), drugs (e.g., glucocorticoids and GH), stress, starvation, uremia, cirrhosis, and ketoacidosis.

iii. **Endocrinologic causes.** Glucocorticoids (Cushing syndrome), GH (acromegaly), catecholamines (pheochromocytoma), glucagon (glucagonoma), hyperthyroidism, hypothyroidism, and hyperparathyroidism.

iv. **Antibodies blocking the insulin receptor** occur in the setting of a generalized autoimmune diathesis in patients with the **type B syndrome of insulin resistance and acanthosis nigricans** and in patients with **ataxia telangiectasia.**

B. Insulin-like growth factor I

1. **General.** Traditional dogma has taught that IGF-I, secreted from the liver, is the major effector of GH action in a classical endocrinologic sense. However, IGF-I, IGF-I–binding proteins, and type 1 IGF receptors are expressed by many different tissues, suggesting that autocrine–paracrine activity may be more physiologically relevant, a finding supported by the observation of normal growth in mice in which their hepatic type 1 IGF receptor gene has been knocked out. IGF-I and IGF-II bind and stimulate the type 1 IGF receptor, the type 2 IGF receptor (IGF-II/mannose 6-phosphate receptor), and, to a lesser extent, the insulin receptor. The type 1 IGF receptor, coded for by a gene located on chromosome 15q25–q26, is homologous to the insulin receptor and is composed of two entirely extracellular α subunits containing cysteine-rich domains and two transmembrane β subunits containing a tyrosine kinase domain in their cytoplasmic portion.

2. **Intrinsic defects**

a. **African Efe Pygmies**

i. **Clinical features.** Significant short stature in this

population is assumed to be adaptive in nature as a means of survival in the dense low-lying vegetation and high humidity of the jungle; intermittent periods of poor nutrition may also play a role. Depending on nutritional status, random p. 17p. 18GH levels may be normal or slightly elevated, and IGF-I and **GH-binding protein (GHBP)** levels normal or low.

ii. **Mechanism.** Although early studies suggested that GH resistance was responsible for the short stature of African Pygmies, more recent work has demonstrated genetically regulated IGF-I resistance (with superimposed GH resistance) in African Efe Pygmies. The underlying variation appears to be IGF-I resistance with secondary GH resistance. Neighboring Lese Africans, whose gene pool is intermingled with that of the Efe, show stature intermediate between that of the Efe and non-Pygmy Africans, as well as intermediate in vitro responses (between Efe and controls) to both GH and IGF-I.

b. Atleast five families have now been described consisting of 12 individuals with heterozygous mutations of the *type 1 IGF receptor* gene who presented with moderate-to-severe postnatal short stature (−1.6 to −5.0 standard deviations below the mean). Seventeen different mutations have been reported to the international collaborative known as the Growth Genetics Consortium. In addition, serum IGF-I levels were elevated to varying degrees in affected individuals.

c. Molecular defects of the type 1 IGF receptor gene are rare in humans. Intrauterine and postnatal growth retardation, microcephaly, and elevated IGF-I levels for age are consistent findings in these patients, although IGF-I levels can be low initially because of feeding problems. It has been hypothesized that at least 2.5% of children born small for gestational age may have type 1 IGF receptor gene defects.

3. Extrinsic defects

a. HIV infection is associated with in vitro and in vivo evidence of acquired combined IGF-I and GH resistance in both symptomatic adults and children. Such resistance may contribute to the growth disturbances seen in symptomatic HIV-

infected children and to the wasting syndrome seen in both children and adults with AIDS.

b. Malnutrition is associated with reversible IGF-I deficiency.

c. The growth delay of **chronic renal failure** stems in part from elevations of IGFBPs, leading to IGF-I resistance, which can be overridden with high-dose GH treatment.

d. Catabolic states are associated with IGF-I resistance.

C. FGFR-1

1. **General.** FGFR-1 contains an extracellular domain that has three immunoglobulin-like domains (D1, D2, and D3), including a single transmembrane helix and an intracellular domain with tyrosine kinase activity that dictates receptor affinity and ligand specificity. In the presence of heparin sulfate, fibroblast growth factor binds. FGFR-1 is a member of the tyrosine kinase superfamily of receptors. FGF-1 binds to the FGFR-1 with high affinity, stimulating receptor dimerization and transautophosphorylation of tyrosine residues in the intracellular domain. These steps result in activation of downstream signaling most importantly involving the MAP kinase pathway. FGFR-1 signaling through this pathway regulates neuronal migration, differentiation, and survival, as well as cell proliferation during embryonic development.
2. **Intrinsic defects.** Mutations of FGFR-1 lead to resistance to FGF-1, resulting clinically in an autosomal dominant form of **Kallmann syndrome** (hypogonadotropic hypogonadism) usually cocharacterized by failed morphogenesis of the olfactory bulbs, cleft palate, and dental agenesis, and, in some cases, split hand/foot malformation. Mutations in *FGFR1* account for approximately 10% of Kallmann cases and have been reported in patients with or without anosmia, the latter termed normosmic idiopathic hypogonadotropic hypogonadism.

III. SPECIFIC DISORDERS ASSOCIATED WITH HORMONE RESISTANCE: CLASS 1 CYTOKINE RECEPTORS

A. Growth hormone

1. **General.** The human GH receptor gene is located on chromosome 5p13-p12. The amino-terminal sequence of the circulating GHBP appears to be the proteolytic p. 18p. 19product of the

extracellular binding domain of the GH receptor. GH action is mediated by GH-induced dimerization of the GH receptor, followed by activation of receptor-associated JAK2 tyrosine kinase and cytoplasmic Stat proteins.

2. **Intrinsic defects**
   a. **Severe GH insensitivity syndrome (Laron dwarfism) (see Chapter 15)**
   b. **Noonan syndrome** (see Chapter 14)
   c. Mutations in the ***Stat5b* gene** have been reported in a few children with **severe short stature** and **immunodeficiency**, resulting in loss of GH-induced JAK2-dependent phosphorylation and nuclear localization of Stat5b. Immunodeficiency arises as Stat5b also plays a role in the IL-2 signaling pathway.
   d. Several cases of short stature and X-linked severe combined immunodeficiency has been described as a result of loss of the common cytokine receptor *γ* chain causing decreased GH-induced JAK2-dependent phosphorylation and nuclear localization of Stat5b.
   e. Genetic GH resistance has also been rarely reported in children with severe short stature on the basis of an **IGF-I gene deletion**.
   f. Several patients have been described with purported GH resistance on the basis of abnormalities in factors that interact with STAT5 pathway, including one with an IκB*α* mutation and another with a 17q21–25 duplication that is associated with dysregulation of the three classical GHR signaling pathways (STAT5B, MAPK, and PI3K).
3. **Extrinsic defects.** Reversible forms of GH resistance occur in the setting of **malnutrition**, **liver disease** (especially **Alagille syndrome**, which is characterized by intrahepatic bile duct paucity in association with cholestasis, cardiac disease, skeletal and ocular abnormalities, and a characteristic facies), poorly controlled **diabetes mellitus**, chronic renal failure, and the presence of GH-inhibiting antibodies (which develop in some children with *GH-1* gene deletions who are then treated with recombinant human GH).

B. Leptin

1. **General.** The leptin receptor contains extracellular binding,

transmembrane, and variable-length intracellular domains. The human leptin receptor gene has been localized to chromosome 1p31. Leptin is produced in adipose tissue, acts on specific receptors in the central nervous system, and is thought to function as an afferent satiety signal in a feedback loop that apparently regulates the appetite and satiety centers in the hypothalamus. Leptin also appears to have a stimulatory role in gonadotropin secretion and fertility.

2. **Intrinsic defects.** Mutations of the leptin receptor gene have been estimated to account for up to 3% of individuals with severe obesity and hyperphagia that begins in early childhood. Other features include delayed puberty as a result of hypogonadotropic hypogonadism, in association with consanguinity. Serum leptin levels are generally within the range predicted by the elevated fat mass in these patients. Their clinical features were less severe than those of patients with congenital leptin deficiency.
3. **Extrinsic defects.** Obese humans have higher serum leptin levels than do normal weight individuals, and these levels correlate with their degree of adiposity. In common obesity, a state of leptin resistance develops in which leptin loses its ability to inhibit energy intake and increase energy expenditure. Following weight loss, serum leptin levels fall.

IV. SPECIFIC DISORDERS ASSOCIATED WITH HORMONE RESISTANCE: GPCRs

A. Adrenocorticotropic hormone

1. **General.** The human ACTH receptor (preferentially known as *MC2R*) gene, along with that for the related melanocyte-stimulating hormone receptor, is located on chromosome 18p11.2. It is also one of a family of five related receptors (MC1R through MC5R). Mutations of MC1R cause various skin and hair abnormalities, along with increased susceptibility to melanoma and other skin cancers, and MC3R and MC4R cause early-onset severe obesity.

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2. **Intrinsic defects**

a. Familial glucocorticoid deficiency

i. Clinical. This rare familial disorder is characterized by

autosomal recessive inheritance, skin and mucosal hyperpigmentation, and signs of glucocorticoid insufficiency, but, in general, preserved mineralocorticoid function. Biochemically, this manifests as hypoglycemia and hyponatremia, without hyperkalemia.

ii. **Mechanism.** A genetic classification system has been developed that divides affected individuals into three subtypes: familial glucocorticoid deficiency (FGD) type 1 is caused by mutations of the *MC2R* gene, FGD type 2 localizes to 21q22.1 and is caused by mutations in melanocyte receptor accessory protein, whereas FGD type 3 appears to be linked to a locus on 8q. Other genes recently implicated in FGD include *NNT*, *MCM4*, and *TXNRD2*.

b. Triple A syndrome

i. **Clinical.** This is another rare, familial, autosomal recessive form of primary **adrenocortical insufficiency** with the clinical features of FGD, along with **achalasia** (an inability of the lower esophageal sphincter to relax, leading to difficulty in swallowing), **alacrima** (absence of tears), neuropathy (mixed upper and lower motor neuropathy, sensory impairment, autonomic neuropathy, and mental retardation), and, in some patients, hyperkeratosis of the palms and soles. Achalasia and alacrima presumably result from an underlying or associated autonomic neuropathy.

ii. **Mechanism.** The defective gene was found and dubbed ADRACALIN or AAAS (adrenal insufficiency, achalasia, alacrima, and neurologic disorder), which codes for ALADIN, a WD protein.

B. Antidiuretic hormone

1. **General.** The antidiuretic action of ADH or arginine vasopressin is mediated through V_2, cAMP-dependent receptors, whereas its vasoconstrictive action is mediated through V_1, phosphatidylinositol-dependent receptors. In response to ADH, intracellular vesicles, containing functional water channels, also known as aquaporin-2 proteins, are inserted into the normally watertight apical membrane of the collecting duct, thereby increasing water permeability. The aquaporin-2 gene is located on chromosome 12q12–q13.

2. **Intrinsic defects (see Chapter 10)**

C. Calcium sensor

1. **General.** The calcium-sensing receptor gene is located on chromosome 3q21–3q24 and encodes a cell-surface protein of 1 078 amino acids that is expressed in the parathyroid glands and in the kidneys. The receptor regulates the secretion of PTH and the reabsorption of calcium by the renal tubules in response to fluctuations in the serum calcium concentration.
2. **Intrinsic defects.** Loss-of-function mutations cause autosomal dominantly inherited **benign hypercalcemia**, also known as **familial hypocalciuric hypercalcemia**. Affected individuals are generally asymptomatic, have life-long mild-to-moderate elevations of serum calcium concentrations, and have low urinary excretion of calcium. More rarely, these mutations may cause severe **neonatal hyperparathyroidism** (presenting before 6 months of age) with marked symptomatic hypercalcemia; without parathyroidectomy, the condition may be lethal. When both are present in the same family, the former appears to represent heterozygous and the latter homozygous forms of the same genetic defect. Functionally, these mutations manifest as a failure to suppress PTH concentrations at expected levels of hypercalcemia as well as inappropriately high renal reabsorption of calcium despite hypercalcemia.

D. Corticotropin-releasing factor

1. **General.** Genes for the corticotropin-releasing factor (CRF) receptor are located on chromosomes 7p21-p15 and 17q12–q22. Activation of this receptor in pituitary corticotrophs by CRF regulates ACTH secretion.
2. **Intrinsic defects.** No disease-bearing mutations of the CRF receptor gene associated with resistance to CRF have been reported.

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3. **Extrinsic defects.** Patients with **depression** manifest a pseudo-Cushing state in which there is reversible dysfunction of the hypothalamic–pituitary–adrenal axis, elevation of basal serum cortisol levels, resistance to the negative feedback action of dexamethasone on cortisol secretion, and elevated levels of CRF in the cerebrospinal fluid. In addition, depressed individuals

manifested a blunted serum cortisol response to administered CRF, consistent with the presence of CRF resistance, the clinical significance of which is unclear. CRF resistance may also occur in females with hypothalamic amenorrhea.

E. Follicle-stimulating hormone

1. **General.** The gene for the FSH receptor is located on chromosome 2p21-p16 and consists of 10 exons, the last of which, as in the LH and TSH receptor genes, encodes the entire transmembrane and intracellular domains of the receptor. Activation of this receptor by FSH in the ovary stimulates follicular development and in the testis stimulates spermatogenesis by Sertoli cells.
2. **Intrinsic defects.** FSH receptor gene mutations are uncommon. Females harboring an inactivating mutation of the FSH receptor gene have a more severe phenotype than those with mutations of the LH receptor gene (i.e., they have unresponsive ovarian cells and almost completely absent female sex steroid production, resulting in underdeveloped secondary sexual characteristics, amenorrhea, and infertility—often referred to as the **"resistant ovary syndrome"**), in conjunction with elevated serum gonadotropin levels and arrested, but not absent, follicular maturation. Affected males are normally virilized and have small testes, indicating absent or poor spermatogenesis, in conjunction with moderately elevated serum FSH, normal or mildly elevated serum LH, and normal testosterone levels. Resistance to FSH also occurs to varying degrees in patients with PHP-IA.

F. Gonadotropin-releasing hormone

1. **General.** The human GnRH receptor gene is located on chromosome 4q21.2 and comprises three exons. Binding of GnRH to its receptor stimulates the activity of phospholipase C and intracellular calcium through G_q/G11 proteins. Activation of this receptor on pituitary gonadotrophs by GnRH stimulates both LH and FSH secretion.
2. **Intrinsic defects.** Loss-of-function mutations affecting the GnRH receptor are the most frequent cause of autosomal recessive, normosmic, isolated **hypogonadotropic hypogonadism**, accounting for 16% to 40% of cases. Most are compound heterozygous inactivating missense mutations inherited in an

autosomal recessive manner. Affected individuals present with either no evidence of puberty, incomplete pubertal development, small testes in males, amenorrhea in females, and/or infertility. As expected, treatment with pulsatile GnRH administration is ineffective, whereas treatment with gonadotropins can induce ovulation in females.

G. Growth hormone–releasing hormone (see Chapter 14)

1. **Intrinsic defects.** Initially, two perhaps related clusters of individuals from consanguineous kindreds in India and Sindh, Pakistan, and another from Brazil, were described with nondysmorphic, proportionate dwarfism; absence of microphallus and hypoglycemia; and microcephaly, in association with recessively inherited GH deficiency but a normal GH gene. These patients had a nonsense mutation of the GHRH receptor gene predicted to encode a severely truncated GHRH protein that lacks the spanning domains and the G-protein–binding site. No mutation of the GHRH receptor gene has been found in "typical" patients with GH deficiency.

H. Kisspeptin (KiSS-1)

1. **General.** Recent studies have uncovered a role for the GPR54 receptor (located on chromosome 19p13.3), an orphan receptor of the rhodopsin family, and kisspeptin, its cognate ligand, in pubertal activation, with their respective mRNAs colocalizing in the hypothalamus and GnRH neurons, GnRH-dependent activation of gonadotropins by kisspeptin, and increased hypothalamic KiSS-1 and GPR54 mRNAs at the time of puberty.
2. **Intrinsic defects.** Several large consanguineous families have been reported that harbor inactivating mutations of GPR54 that cause hypogonadotropic p. 21p. 22hypogonadism and low sex steroids, with resultant absence of spontaneous pubertal development in affected individuals.

I. Luteinizing hormone

1. **General.** The gene for the LH/chorionic gonadotropin (CG) receptor is located on chromosome 2p21. Activation of this receptor by LH stimulates gonadal steroid production by ovarian follicles and by Leydig cells of the testis.
2. **Intrinsic defects.** Inactivating mutations of the LH receptor gene are rare and may present in males either as 46,XY male

pseudohermaphroditism (secondary to an inability of fetal LH/human CG [hCG] to induce adequate fetal virilization) in conjunction with Leydig cell hypoplasia or as a milder phenotype characterized by undervirilization and micropenis. Affected females present with primary amenorrhea. Resistance to LH has also been noted in patients with PHP-IA.

J. Parathyroid hormone

1. **General.** A common receptor for PTH and the PTHRP, also known as the type 1 PTH/PTHRP receptor, has been localized to chromosome 3p22-p21.1. Activation of PTH receptors mobilizes calcium from bone and increases calcium reabsorption by the kidney.
2. **Intrinsic defects**
   a. **Pseudohypoparathyroidism (PHP)** is defined as resistance to PTH and is most commonly inherited in an autosomal dominant manner. Affected patients have hypocalcemia, hyperphosphatemia, and elevated PTH levels, and no increase in urinary cAMP or phosphaturia in response to injected PTH.
      i. **PHP type IA**
         a) **Clinical.** Affected patients have reduced expression or function of α-Gs in the setting of PTH and multihormone resistance (TSH, glucagon, etc.). These patients also have a characteristic phenotype **(Albright hereditary osteodystrophy [AHO])** characterized by short stature, obesity, round facies, short neck, shortened metacarpals and metatarsals, heterotopic subcutaneous calcification or ossification, and mental dullness.
         b) **Mechanism.** In most patients with PHP-IA, heterozygous germline loss-of-function paternally imprinted mutations in the α-Gs gene have been identified.
      ii. **PHP type IB**
         a) **Clinical.** Affected patients lack features of AHO, have normal expression of α-Gs protein in accessible tissues, and manifest hormonal resistance limited to PTH target tissues. PTH resistance may be limited to the kidney, with PTH responsiveness preserved in the bone, as evidenced by the hyperparathyroid skeletal lesions observed in these patients.

b) **Mechanism.** PHP-IB is characterized by renal resistance to PTH, absence of the AHO phenotype, lack of resistance to other hormones and typically no resistance to other hormones (although there occasionally may be mild resistance to TSH). There is also minimal cAMP production after PTH administration. PHP-IB is due to changes in the methylation pattern of the *GNAS* locus. It can be inherited in an autosomal dominant pattern although most of the cases are sporadic. The autosomal dominant form is typically characterized by an isolated loss of methylation at exon A/B, associated with microdeletions in the *STX16* gene.

iii. **PHP type IC**

a) **Clinical.** Affected patients have normal α-Gs activity, occasional evidence of the AHO phenotype, and features of multihormone resistance.

b) **Mechanism.** It is unclear whether patients with PHP-IC represent a subgroup of PHP-IA patients with *GNAS* mutations that affect receptor coupling or whether they constitute a distinct group in whom the genetic defect lies downstream of receptor-activated cAMP generation.

iv. **Blomstrand lethal osteochondrodysplasia.** This rare, fatal, short-limbed skeletal dysplasia, characterized by accelerated endochondral and p. 22p. 23intramembranous ossification, has been found to be caused by an inactivating mutation of the type 1 PTH/PTHRP receptor gene.

K. Thyrotropin-releasing hormone

1. **General.** The TRH receptor gene is located on chromosome 8q23. Activation of these receptors on pituitary thyrotrophs by TRH results in TSH secretion.
2. **Intrinsic defects.** Several patients have been described with central hypothyroidism in whom there was complete absence of TSH and prolactin responses following administration of synthetic TRH. Molecular analyses of the TRH receptor gene in these

subjects revealed mutations affecting TRH cellular binding and downstream signaling.

L. Thyroid-stimulating hormone

1. **General.** The TSH receptor gene has been mapped to chromosome 14q31 and has two segments. The TSH receptor is mainly coupled to α-Gs, leading to stimulation of the cAMP pathway, which mediates the effects of TSH on thyroid gland growth and thyroid hormone secretion.
2. **Intrinsic defects.** A large number of heterozygous or homozygous loss-of-function mutations of the TSH receptor gene have been reported. The presenting phenotype ranges from euthyroid hyperthyrotropinemia to, despite development of the thyroid anlage and its normal migration to the mid-neck, congenital hypothyroidism with profound thyroid gland hypoplasia. The mode of inheritance is autosomal recessive. Resistance to TSH occurs in patients with PHO-1A and rarely in those with PHP-1B

V. SPECIFIC DISORDERS ASSOCIATED WITH HORMONE RESISTANCE: STEROID HORMONES

A. Aldosterone (mineralocorticoid)

1. **General.** The gene for the human mineralocorticoid receptor has been mapped to chromosome 4q31.1. Aldosterone binds to mineralocorticoid receptors located in the distal renal tubule, sweat and salivary glands, and colonic mucosa, stimulating sodium retention and potassium excretion. Secretion of aldosterone is physiologically regulated by the renin–angiotensin system.
2. **Intrinsic defects**
   a. **Type 1 pseudohypoaldosteronism (PHAI)**
      i. **Clinical.** This form is characterized by salt-wasting in infancy, failure to thrive, hyponatremia, and hyperkalemia, and is responsive to supplemental sodium treatment, but not to mineralocorticoid therapy. This disorder is inherited either in an autosomal dominant manner, affecting only the kidneys, or in an autosomal recessive manner associated with multifocal target organ unresponsiveness to mineralocorticoids involving the kidneys, colon, sweat and salivary glands, and lungs. Markedly, elevated serum aldosterone levels are present in all cases, and the plasma

renin activity is usually increased. Salt supplementation can often be discontinued after infancy despite persistent absence of aldosterone receptors into adulthood in the autosomal dominant form. Thus, it is presumed that in this form, there must be progressive maturation of proximal tubular sodium-conserving mechanisms. Spontaneous remission does not occur in the recessive form.

ii. **Mechanism.** The autosomal dominant variant of pseudohypoaldosteronism is caused by mutations in the mineralocorticoid receptor gene. The autosomal recessive form has been linked to mutations in the gene encoding the amiloride-sensitive epithelial sodium channel located on chromosome 16p12.2–13.1.

b. Type 2 pseudohypoaldosteronism (PHAII)

i. **Clinical.** This form is associated with partial unresponsiveness of the renal tubules to aldosterone, leading to inadequate potassium excretion, metabolic acidosis, hypertension, no renal salt-wasting, low plasma renin p. 23p. 24activity, and normal or slightly elevated serum aldosterone concentrations. This form of pseudohypoaldosteronism is characterized by chronic mineralocorticoid-resistant hyperkalemia and hypertension.

ii. **Mechanism.** PHAII is the result of mutations in a family of serine-threonine kinases called with-no-lysine kinases (WNK)1 and WNK4.

3. Extrinsic defects

a. Infants with congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency, and ***without*** **associated mineralocorticoid deficiency, often still present with salt-losing crises and hyponatremia**, and with mild hyperkalemia. In the untreated state, elevated serum levels of 17α-hydroxyprogesterone and other steroid precursors antagonize mineralocorticoid action and may have a significant role in the salt-wasting state in affected infants.

b. Mineralocorticoid resistance may occur in infants and children with obstructive uropathy, urinary tract infection, tubulointerstitial nephritis, sickle cell nephropathy, systemic lupus erythematosus, amyloidosis, neonatal medullary necrosis,

and after unilateral renal vein thrombosis presumably secondary to renal tubular injury.

c. Drugs such as spironolactone block the effects of aldosterone by directly closing the sodium channel in the luminal membrane of the collecting tubular cell.

B. Androgen

1. **General.** The human AR gene spans more than 90 kb and has been mapped to Xq11.2–q12. It comprises 8 exons that code for a protein containing 910 amino acids. Activation of the AR is required to mediate the biologic actions of testosterone and dihydrotestosterone.
2. **Intrinsic defects**
   a. **Clinical.** In its full form, also known historically as **testicular feminization** and today as **complete androgen insensitivity syndrome**, this disorder causes 46,XY sex reversal and presents in the adolescent age range as primary amenorrhea, little or no pubic and axillary hair, and normal breasts (secondary to peripheral androgen-to-estrogen conversion) in a phenotypically normal female. This condition occasionally presents in the younger child because of the presence of testis-containing inguinal hernias in otherwise normal-appearing girls. Partial resistance to androgen usually presents clinically with ambiguous external genitalia, including perineoscrotal hypospadias, micropenis, and a bifid scrotum, usually in conjunction with undescended testes, in the newborn period and is becoming increasingly referred to as a **disorder of sex development**. The condition may also present later with pubertal breast development and azoospermia in a male or with a predominant female phenotype with partial labial fusion, clitoromegaly, and normal breast and pubic hair development. Isolated hypospadias may be considered as an expression of androgen resistance, whereas idiopathic micropenis is not. With either presentation, there is a blind-ending vagina, and there are no internal genital ducts (because of normal fetal AMH production and action causing regression of Müllerian derivatives, and resistance to local androgen action preventing Wolffian duct formation). The testes contain a normal or increased number of Leydig cells and seminiferous tubules, but there is no spermatogenesis. Because of the risk of gonadal

tumor development (and carcinoma in situ in the prepubertal testis), **prophylactic orchiectomies** are indicated, the optimal timing for which is controversial. Typically, affected infants and postpubertal patients have elevated serum levels of LH, testosterone, and estradiol.

b. Mechanism. Defects of the AR function fall into two categories. The first uniformly causes complete androgen resistance and includes mutations that disrupt the primary sequence of the receptor. The second and more common cause is associated with a variable phenotype.

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C. 1,25-Dihydroxyvitamin D_3

1. **General.** The human vitamin D receptor is the product of a single gene on chromosome 12q12–q14. Activation of this receptor by 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] increases intestinal calcium absorption and increases bone osteoid formation, with other effects on cellular differentiation and immune function.
2. **Intrinsic defects—hereditary vitamin D–resistant rickets (formerly known as vitamin D–dependent rickets, type II)**
   a. **Clinical.** Affected patients with this rare form of rickets present with a constellation of symptoms including early-onset rickets, growth retardation, hypocalcemia, hypophosphatemia, elevated alkaline phosphatase, secondary hyperparathyroidism, and **elevated serum levels of $1,25(OH)_2D_3$**. In addition, severe dental caries, dental hypoplasia, and, in most but not all cases, sparse hair or even total scalp and body **alopecia** frequently occur. The disease can occur in multiple family members of both sexes with a high incidence of parental consanguinity, suggesting autosomal recessive inheritance. Affected patients usually fail to respond to treatment with $1,25(OH)_2D_3$ even at supraphysiologic doses. Therapy with high-dose oral calcium overcomes the receptor defect, normalizes serum calcium, and maintains bone remodeling and mineral apposition. Spontaneous improvement with age also occurs in some affected children.
   b. **Mechanism.** More than 100 mutations of the $1,25(OH)_2D_3$-receptor gene have been described. These molecular defects

typically affect either the hormone-binding or DNA-binding zinc-finger regions, with mutation hot spots identified at conserved sequences among the steroid/nuclear receptor superfamily of ligand-activated transcription factors.

D. Estrogen

1. **General.** Two genes for the human estrogen receptor (ESR) have been cloned, ESRα (ESR1) and ESRβ (ESR2). Activation of the ESR effects estrogen actions on the female reproductive system and on bone.
2. **Intrinsic defects**
   a. **Clinical.** The first case of **estrogen resistance** as a result of a proven mutation in the ESR gene was described in a 28-year-old man (product of a consanguineous marriage) with very tall stature, incomplete epiphysial closure, decreased bone mineral density, and otherwise normal pubertal development. Serum estradiol, estrone, LH, and FSH levels were all increased, whereas serum testosterone concentrations were normal. The patient had no detectable physical or biochemical response to estrogen administration, despite a 10-fold increase in the serum free estradiol concentration. An 18-year-old woman without breast development and with markedly elevated serum levels of estrogens and bilateral multicystic ovaries has been reported and found to have estrogen resistance.
   b. **Mechanism.** In the preceding male case, direct sequencing of exon 2 revealed a cystine-to-thymidine transition at codon 157 of both alleles, resulting in a premature stop codon. The patient's parents are heterozygous carriers of this mutation. The affected female was found to have a homozygous loss-of-function ESR1 mutation in a completely conserved residue that interferes with estrogen signaling.

E. Glucocorticoid

1. **General.** The cDNAs encoding the human glucocorticoid receptor (GR) predict two protein forms of 777 (GRα) and 742 (GRβ) amino acids. GRα has a widespread distribution and is responsible for the induction and repression of target genes, whereas GRβ can act as a dominant-negative inhibitor of GRα-mediated transactivation and transrepression. Activation of the GR is required to effect the actions of glucocorticoids.
2. **Physiologic glucocorticoid resistance.** In the distal

nephrons of the kidney, cortisol resistance occurs. More specifically, the human mineralocorticoid receptor can be activated by cortisol, serum concentrations of which exceed those of p. 25p. 26aldosterone, the natural ligand, by as much as 1 000-fold. To avoid continuous activation of the mineralocorticoid receptor by cortisol, it is converted in the kidney by the enzyme 11 β-hydroxylase to cortisone, which does not activate the mineralocorticoid receptor. This localized resistance to cortisol prevents the development of cortisol-mediated hypertension and hypokalemia in normal subjects.

3. **Intrinsic defects**
   a. **Clinical features. Generalized inherited cortisol resistance** is a rare (usually) autosomal dominant disorder (but occasionally sporadic) that has been reported in several families in which affected members present with hypercortisolemia, but without Cushingoid features. Pituitary and peripheral resistance are balanced so that no features of hypercortisolism or hypocortisolism emerge. Clinical characteristics result from, in females, increased circulating adrenal androgens, which manifest as hirsutism, male pattern baldness, menstrual irregularities, infertility, and masculinization; in boys, sexual precocity; and in both sexes, increased serum levels of deoxycorticosterone, which cause hypertension and hypokalemia, and perhaps as a result of relative GR deficiency, fatigue. These clinical features respond to dexamethasone therapy.
   b. **Mechanism.** May or may not be associated with abnormalities of the human GR, including decreased receptor number, affinity, stability, and/or translocation into the nucleus.
4. **Extrinsic defects**
   a. **Psychiatric disorders**, including depression, anorexia nervosa, and certain types of psychoses, are associated with serum cortisol concentrations as high as those occurring in patients with Cushing syndrome, yet these patients have none of the physical features associated with Cushing syndrome, suggesting a state of glucocorticoid resistance.

b. **HIV.** Elevated serum cortisol levels with clinical evidence of glucocorticoid insufficiency have been described in some adults with acquired HIV, in whom wasting, diarrhea, and hyperkalemia are suggestive of adrenal insufficiency.

c. **Cushing disease.** Pituitary Cushing disease may be caused by glucocorticoid resistance localized to the hypothalamus and/or pituitary. Ectopic Cushing disease frequently is associated with ACTH production that is not suppressed by glucocorticoids.

d. **Inflammatory diseases.** Reported autoimmune/inflammatory/allergic diseases associated with glucocorticoid resistance include rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, Crohn disease, ulcerative colitis, septic shock/respiratory distress syndrome, and bronchial asthma. This effect may be initiated by inflammatory signals, such as IL-2, IL-4, IL-13, and TNF-α.

F. Thyroid hormones

1. **General.** There are two thyroid hormone (T_3) receptor genes, designated α and β, which are located on chromosomes 17q11.2 and 3p24.3, respectively. There are developmental and tissue-specific patterns of expression of T_3 receptor mRNA. Activation of this receptor effects the various metabolic actions of thyroid hormones.

2. **Intrinsic defects**

   a. **Clinical.** Until recently, patients thought to have thyroid hormone resistance were classified as having either generalized or selective pituitary resistance depending on the absence or presence of symptoms of hyperthyroidism. The term **generalized thyroid hormone resistance** has been applied to a syndrome characterized by elevated serum levels of free thyroid hormones, resistance to thyroid hormone action, and inappropriately normal or elevated and TRH-responsive serum TSH levels. Affected patients may also have attention deficit disorder (60%), stippled epiphyses, short stature, and multiple somatic abnormalities. Whereas patients with generalized thyroid hormone resistance are clinically euthyroid or even hypothyroid, those with the rarer **selective pituitary resistance to thyroid hormones** are clinically

hyperthyroid. This variant tends to be inherited in an autosomal dominant manner and is also associated with inappropriately normal and TRH-responsive serum TSH levels. The somewhat arbitrary classification of patients into generalized and p. 26p. 27pituitary forms of thyroid hormone resistance implies that clinical examination and routine biochemical measurements together allow clear-cut distinction between the presence and absence of hyperthyroidism. However, it is clear that in both forms, there can be variable refractoriness to thyroid hormone action in different tissues, including the bone, brain (reflected as degrees of permanent mental deficit), liver, heart, and pituitary gland.

b. Mechanism. These syndromes are usually transmitted in an autosomal dominant manner. In multiple kindreds with thyroid hormone resistance, an intrinsic heterozygous mutation of the T_3-receptor β gene, involving its ligand-binding domain, has been identified. These mutations fall into the class of **dominant-negative mutations** where the mutant form is coexpressed with a normal receptor but disrupts the activity of the normal receptor. This dominant-negative inhibition by mutant receptors may be corrected in certain tissues by a compensatory increase in the levels of circulating thyroid hormones. More than 1 000 patients with thyroid hormone resistance have been reported.

VI. SPECIFIC DISORDERS ASSOCIATED WITH HORMONE RESISTANCE: PEPTIDE GROWTH/DIFFERENTIATION FACTORS THAT ACT VIA TRANSMEMBRANE SERINE/THREONINE KINASE RECEPTORS

A. Anti-Müllerian hormone

1. General. The AMH receptor gene is located on chromosome 12q13. AMH, also known as Müllerian-inhibiting substance or Müllerian-inhibiting factor, is a hormone produced by immature Sertoli cells, the main action of which prevents development of the fallopian tubes, uterus, and upper vagina in male fetuses prior to 10 weeks' gestation. Postnatal ovarian granulosa cells also produce

AMH, although a distinct function has not been recognized in females.

2. **Intrinsic defects**
   a. **Clinical.** The **persistent Müllerian duct syndrome** is a rare form of male pseudohermaphroditism characterized by the presence of a uterus and fallopian tubes in an otherwise normally virilized male. The condition is most often discovered incidentally during repair of an inguinal hernia, at which time the hernia sac is found to contain Müllerian remnants.
   b. **Mechanism.** Some boys with this condition have no detectable immunoreactive or bioactive AMH in their serum in conjunction with a mutation in their AMH gene. In contrast, other affected boys who express normal amounts of AMH in their serum have been found to have mutations in their AMH receptor gene.

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3 Genetics of Endocrinology

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Genetic diseases can be divided into four areas: cytogenetic disorders (i.e., autosomal and sex chromosome abnormalities), single-gene disorders, multifactorial disorders, and conditions with nontraditional inheritance.

I. CYTOGENETICS. Approximately 0.7% of live-borns, 5% of stillborns, and 50% of spontaneously aborted fetuses have a chromosomal abnormality. The modal number of chromosomes in humans is 46, including 22 pairs of autosomes and an XX or XY sex chromosome complement. A wide variety of cytogenetic aberrations have been described, many with an associated endocrine dysfunction (Table 3-1). Chromosomal abnormalities can be numeric, structural, or dysfunctional and can involve either the autosomes or the sex chromosomes. An individual with two or more chromosomally distinct cell lines is termed a **mosaic**, a situation often involving the sex chromosomes. The International System for Human Cytogenetic Nomenclature (2005) allows precise descriptions of each heterogeneously stained chromosome according to its number, arm (**p** designating short arm; **q** designating long arm), region, band, and even subband. For example, the notation **2p12** refers to chromosome number 2, short arm, region 1, band 2.

A. Banding techniques. A number of staining procedures are available to produce a specific pattern of bands along the length of each chromosome. The patterns of homologous (paired) chromosomes are identical, with the exception of specific p. 29p. 30regions in which inherited variants or polymorphisms occur in the normal population, without known clinical significance.

TABLE 3-1 Endocrine Abnormalities in Chromosomal Disorders

Chromosomal Disorder[a]	Endocrine Abnormality
Down syndrome	Hypogonadism, hyperthyroidism or hypothyroidism
Turner syndrome (45,X and variants)	Hypogonadism, hypothyroidism, diabetes

	mellitus
Klinefelter syndrome (XXY and variants)	Hypogonadism, diabetes mellitus
Trisomy 13	Hypopituitarism, hypogonadism
Trisomy 18	Occasional thyroid or adrenal hypoplasia
Triploidy	Adrenal hypoplasia
del(4p) or Wolf–Hirschhorn syndrome	Hypogonadism
del(18p)	Holoprosencephaly, hypopituitarism
del(7q11.23)—Williams syndrome	Hypercalcemia in infancy
del(11p13)—Aniridia–Wilms tumor association	Ambiguous genitalia, gonadoblastoma
del(15q11q13)—Prader–Willi syndrome[b]	Hypogonadism, diabetes mellitus
del(22q11.2)—Velocardiofacial syndrome	DiGeorge sequence

del, deletion.
[a]A number of rare partial trisomies or monosomies have been associated with hypogonadism with or without a genital anomaly.
[b]Prader–Willi syndrome is also caused by maternal *UPD15* and methylation defects in this region.

1. **G banding**, the most popular staining technique, involving the use of Giemsa (hence the "G"), is helpful in identifying small structural abnormalities and marker chromosomes (those not obviously matching the banding pattern of a normal chromosome) and defining the breakpoints of structural rearrangements. Dark-staining (G-positive) bands generally contain fewer coding regions (active genes) than light-staining (G-negative) regions. Therefore, small structural abnormalities of G-negative bands may have more profound phenotypic effects than similar abnormalities of dark bands.

B. Culture techniques. Variation in the growth media, cell culture time, and use of specific additives to synchronize cell cycle or to inhibit specific metabolic processes greatly influences the resultant cytogenetic evaluation.

1. **Metaphase analysis.** Most routine cytogenetic analyses require 72- to 96-hour cultures of phytohemagglutinin-stimulated peripheral blood lymphocytes. An excellent-quality metaphase preparation should yield at least 500 to 550 bands per haploid set. When more rapid results are needed, a 48-hour culture of lymphocytes or direct preparation of bone marrow is requested. Both of these techniques are adequate for identification of numeric

abnormalities, but neither is generally sensitive enough to distinguish small structural abnormalities.

2. **High-resolution analysis.** By using cell synchronization techniques and varying the culture time, one can visualize early metaphase or late prophase chromosomes, which are more elongated and have more bands than standard preparations. Although this technique is quite sensitive, revealing 800 or more bands per haploid set, high-resolution analysis should be reserved for situations in which a structural defect or nonhomology has already been found or for a diagnosis in which a very small structural change has been noted.
3. **Other techniques** helpful to the endocrinologist include the following:
   - **a.** Breakage studies, in which the culture is exposed to a clastogen and a large number of cells, are scored for chromosomal breakage and rearrangement.
   - **b.** Cell culture in the presence of folic acid inhibitors or other inducers to elucidate chromosomal fragile sites. These techniques are not used widely in the clinical setting.
   - **c.** Culture of skin or other solid tissues, which may be particularly helpful in the evaluation of sex chromosome anomalies.

C. Molecular cytogenetics. New technology has allowed the implementation of techniques for visualization of specific chromosomes or parts of chromosomes by means of molecular probes.

1. **Fluorescence in situ hybridization (FISH).** Oligonucleotide probes, which are complementary to a repetitive or unique DNA sequence, can be hybridized to interphase or metaphase chromosomes. The probes are bound to a fluorescent dye, which allows visualization of a bright fluorescent spot representing each chromosomal region to which the probe has hybridized. This is particularly useful for the detection of aneuploidy in interphase cells, for rapid sex determination or confirmation of trisomy (including prenatal diagnosis), and in cancer cytogenetics.
2. **Chromosome painting.** A set of probes for various markers along the length of a chromosome can be applied to the cells using the FISH technique. The probes “paint” a specific chromosome regardless of its position in the cell or its structural integrity. This technique is especially useful in confirming the origin of small translocations and marker chromosomes.

3. **Single-copy probes.** Molecular probes that hybridize to a specific unique DNA sequence can be used to detect known mutations associated with a defined phenotype. This technique is particularly helpful in detecting **submicroscopic deletions** such as those underlying most cases of **Williams syndrome, Prader–Willi syndrome,** and **velocardiofacial syndrome**. The probe signal is visualized by fluorescent microscopy.
4. **Multiplex FISH (M-FISH).** M-FISH techniques allow visualization of all or parts of all of the chromosomes simultaneously. M-FISH using a subtelomeric probe p. 30p. 31set is useful in detecting submicroscopic deletions in children with otherwise undiagnosable mental retardation. Recent data suggest that at least 6% of mentally retarded children have subtelomeric deletions that are detectable by M-FISH.
5. **Chromosomal microarray (CMA).** CMA has become a major clinical diagnostic tool because it allows for high-resolution scanning of the entire genome. Two types of microarrays, comparative genomic hybridization (CGH) and single-nucleotide polymorphism (SNP) arrays, have been used in genetic testing to detect chromosomal defects. Array CGH uses direct comparison of the test genomic DNA (patient) to a standard reference control. Hybridization of these two samples, labeled with different fluorescent dyes, to an array of cloned genomic DNA fragments (80 to 200 kbs) or oligos (60 bps) allows visualization of gain or loss of specific chromosomal regions by measuring the ratio of two fluorescent dyes. In SNP arrays, a single, fluorescently labeled DNA sample is hybridized to an array of synthetic oligonucleotides representative of the genome, and the relative intensities of the test sample are compared to those of a pool of control samples available on the web. Owing to uneven distribution of SNPs throughout the genome, SNP arrays initially did not have a uniform coverage; however, inclusion of additional oligonucleotide probes allowed for an increased genomic coverage. Recently, manufacturers combined these techniques, which now allow for detection of copy number variations as well as regions of heterozygosity and homozygosity. However, the main limitation of

CMA is that the techniques cannot detect balanced structural rearrangements, such as translocations and inversions.

II. AUTOSOMAL DISORDERS. Complete monosomy for an autosome is generally lethal, most commonly recognized in spontaneously aborted fetuses. In live-borns, the effect of trisomy can be devastating. Mosaicism for an autosomal abnormality generally results in a milder phenotype and can be associated with survival in otherwise lethal conditions. With development of the molecular chromosomal techniques, small deletions and duplications have been recognized with increasing frequency. Parental studies should be performed with appropriate cytogenetic or FISH techniques to exclude balanced rearrangement whenever a structural abnormality is found.

A. Down syndrome occurs with an incidence of 1 in 670 births and is the most common disorder producing malformation and mental retardation. In nearly 97% of cases, the cause is trisomy 21 (including nearly 3% with mosaicism for a normal cell line). The remainder results from sporadic or inherited translocations involving chromosome number 21, most commonly occurring as the result of fusion of the centromere of the 21 and another acrocentric chromosome. Many of the phenotypic findings of Down syndrome have been attributed to trisomy of the distal portion of the long arm, segment 21q22. Recurrence risk is approximately 1% for trisomy 21 and significantly higher for carriers of a balanced translocation. Advanced maternal age is the only risk factor clearly associated with occurrence of trisomy 21. **Endocrine abnormalities** in Down syndrome include hypogonadism (100% in males), athyrotic and acquired hypothyroidism, and thyroid hyperfunction.

B. Trisomy 18 is variously reported to occur in about 1 in 3 300 to 1 in 10 000 live births. Affected females exceed males by a ratio of at least 3:1; gestational timing is frequently altered (including prematurity and postmaturity). The phenotype in trisomy 18 is more severe than in Down syndrome; only 50% survive to age 2 months, and 10% survive for 1 year. In addition to a characteristic pattern of major and minor malformations, trisomy 18 survivors are profoundly mentally and physically retarded. Aside from deficient growth and hypoplasia of subcutaneous adipose tissue, endocrine abnormalities are relatively uncommon, with thyroid or adrenal hypoplasia occurring in <10% of patients.

C. Trisomy 13 occurs in about 1 in 5 000 live births and is usually associated with a wide spectrum of malformations, many of which are midline defects. Typical facial features include microphthalmia, along with cleft lip and palate or agenesis of the premaxilla, which is the usual concomitant of holoprosencephaly. A number of **endocrine abnormalities** can occur, including hypopituitarism, ectopic pancreas, and gonadal hypoplasia.

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D. Other autosomal abnormalities, such as **triploidy** (modal number = 69), **Wolf–Hirschhorn syndrome** (4 short arm deletion), and **18 short arm deletion**, have been associated with increased likelihood of endocrine dysfunction. Of particular note are several well-defined syndromes associated with very small deletions, often requiring high-resolution or molecular studies for demonstration of the defect. These include the **Prader–Willi syndrome** of hypotonia, obesity, small hands and feet, and hypogonadism, in which region 15q11–13 is deleted in approximately 70% of affected individuals. Etiology of Prader–Willi syndrome is diverse. These 70% have a usually cryptic deletion, 25% have maternal uniparental disomy (UPD), which means that there are two copies of chromosome 15, but they both came from the mother. The remaining 5% have a variety of causes, all related to the same chromosome region, including atypical (usually smaller) deletions and rearrangements, imprinting defects, and, possibly, mutation in a gene called SNRPN. **Multiple endocrine neoplasia type 2** (MEN2a; see Chapter 79), which generally segregates as an autosomal dominant in affected families, presents with **medullary carcinoma of the thyroid, pheochromocytoma,** and **variable parathyroid involvement**. A small interstitial deletion of 20p has been described in members of several affected kindreds. The **DiGeorge sequence** has also been described in association with the **velocardiofacial syndrome**, which is usually a result of submicroscopic deletion of 22q11.2. Some patients with the **Aniridia–Wilms tumor** association (Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation) have a deletion of band 11p13. Mental retardation, ambiguous genitalia, streak gonads, other forms of hypogonadism, and gonadoblastoma also occur in this condition. A Wilms tumor locus maps to this region and is mutated in patients with **Drash syndrome** (XY gonadal dysgenesis, chronic glomerulopathy,

and Wilms tumor). Finally, the **Williams syndrome** of mental retardation, small stature, elfin facies, supravalvular aortic stenosis, and persistent hypercalcemia is caused by a deletion in chromosome 7q11.23. It is important to request cytogenetic analysis in patients suspected of having one of these disorders and to seek molecular studies (FISH) in clinically suggestive cases when chromosome analysis is normal.

III. SEX CHROMOSOME ABNORMALITIES. Monosomy or trisomy of the sex chromosomes is significantly more benign than autosomal abnormalities and may be associated with normal phenotype, as in some trisomy X females. Phenotypic findings are limited, and some sex chromosome abnormalities can be diagnosed only with failure of normal onset of puberty, recognition of aberrant secondary sexual development, or evaluation for infertility or fetal wastage. Screening procedures such as sex-chromatin determination (buccal smear) can be misleading. This is particularly important when there is a **Y-bearing cell line in dysgenetic gonads**, which implies an increased risk for development of **gonadoblastoma**. If sex chromosome aneuploidy is suspected, cytogenetic analysis must be performed with evaluation of an adequate number of cells to exclude the possibility of low-frequency mosaicism. In cases where there is a high index of suspicion for a sex chromosome disorder and peripheral blood lymphocyte analysis is normal, evaluation of a second tissue such as skin fibroblasts should be considered. FISH evaluation of a buccal smear may detect mosaicism without need for an invasive biopsy and tissue culture.

A. Turner syndrome, most commonly associated with karyotype 45,X (monosomy X), occurs in 1 in 5 000 live births (1:2 500 females) and produces a variable pattern of craniofacial and visceral malformations. Although the phenotype can be distinguished on the basis of dysmorphic facies, web neck, broad chest, cubitus valgus, and other stigmata, the most consistent and important findings are short stature and gonadal dysgenesis. Despite the relatively mild phenotype in live-born infants, 98% of 45,X concepti are spontaneously aborted.

1. More than 50% of patients with Turner syndrome have karyotype 45,X. The missing X chromosome is generally paternal in origin; there is no maternal age effect. Various cytogenetic findings are associated with Turner phenotype, including mosaicism for 46,XX, 46,XY, polysomy X, or a cell line with a structurally abnormal X

or Y. The phenotype is modified by the presence of another cell line p. 32p. 33as well as by the occasional findings of X-autosome translocation. When a Y chromosome is present, sexual ambiguity can occur. Structural abnormalities of the X chromosome include isochromosome of the long arm [i(Xq)], rare isochromosome of the short arm [i(Xp)], deletion of the long arm [del(Xq)], deletion of the short arm [del(Xp)], terminal rearrangement [46,X,ter rea(X;X)], and ring (r)X [46X,r(X)]. In most cases, inactivation of the abnormal X chromosome results in some degree of gene dosage compensation. Mosaicism for a 45,X cell line is a common associate of a structural anomaly. In the case of an X-autosome rearrangement, the karyotype can be balanced or unbalanced. Even when the exchange appears to be balanced, malformation or mental retardation occurs with increased frequency. The normal X is generally inactivated in X-autosome rearrangement. Turner syndrome may occur in association with a structurally abnormal Y chromosome, with or without a 45,X cell line, or with 45,X/46,XY mosaicism. Recurrence risk is generally low, except in the situation of inherited X-autosome translocation and, potentially, in offspring of mothers with a 45,X cell line.

2. Turner syndrome should be suspected in any newborn with typical stigmata and is often heralded by striking lymphedema or congenital heart disease (~20% have a cardiac defect; 75% of these are ventricular septal defects or aortic coarctation). Any girl with unexplained short stature should be evaluated even in the absence of other stigmata. Finally, girls with failure of normal secondary sexual development, amenorrhea, persistently erratic menses, unexplained infertility, recurrent fetal wastage (three or more episodes), or premature menopause should also be studied. Although gonadotropin levels can be evaluated in early childhood and during the prepubertal age range, the only definitive studies are cytogenetic analysis and CGH. Cytogenetic analysis should include evaluation of at least 30 to 50 cells.
3. **Management** of the young Turner syndrome patient includes careful evaluation for associated conditions (especially cardiac, gastrointestinal, or renal malformation, and hearing loss) and appropriate specific therapy as needed. **Autoimmune disorders** are most commonly associated with isochromosome Xq but occur

in 45,X individuals as well. Autoimmune thyroiditis, inflammatory bowel disease, diabetes mellitus, and arterial hypertension are common in older children and adults and require long-term treatment. Sudden death from aortic dissection has been reported. Administration of **growth hormone** results in accelerated growth rate and somewhat increased adult height. Such treatment can be initiated as early as 2 years of age and should be considered when growth falls below the 5th percentile. Carbohydrate metabolism should be evaluated periodically, especially during growth hormone treatment. Low-dose **estrogen replacement** should begin when epiphysial closure is documented, earlier when the psychological state of the patient necessitates institution of pubertal changes. Hormonal replacement should generally begin by age 14 years. Secondary sexual development often remains incomplete. Although infertility is likely, rare Turner syndrome patients achieve spontaneous ovulation and pregnancy. The possibility of fertility is suggested by the spontaneous onset of menses or normal gonadotropin levels before cyclic replacement therapy is started. Limited data suggest an increased likelihood of malformation in the offspring of fertile Turner syndrome patients. Such patients should be counseled carefully about the increased risk of miscarriage and early menopause and should be offered prenatal diagnosis. Finally, as in other situations with a dysgenetic Y chromosome–bearing gonad, Turner syndrome patients with a mosaic or nonmosaic cell line containing a Y chromosome should undergo removal of the streak ovaries because of the increased risk of gonadoblastoma.

B. Trisomy X (47,XXX) occurs in about 1 in 1 000 female live-borns, is commonly associated with a phenotype in the normal range, and is diagnosed only rarely in early childhood.

1. Although data from prospective, longitudinal studies are limited, the XXX female has a tendency toward tall stature, epilepsy, dull-normal intelligence, delayed language acquisition, menstrual dysfunction, and infertility. Advanced maternal age is well established in association with triple-X populations. Of p. 33p. 34note, offspring of fertile trisomy X women are

unlikely to have chromosomal aneuploidy, suggesting a protective mechanism against development or survival of the aneuploid gamete or zygote.

2. When polysomy X occurs with **more than three X chromosomes** (e.g., 48,XXXX and 49,XXXXX), there is an increasing likelihood of significant mental retardation, dysmorphic features, and visceral or skeletal malformation. These syndromes are rare and generally sporadic.

C. Klinefelter syndrome is usually associated with karyotype 47,XXY and is found in approximately 1 in 700 males. Rarer karyotypes, often associated with polysomy X or Y (with or without mosaicism), also occur. The syndrome of at least two X chromosomes and one Y chromosome constitutes the **most common cause of male hypogonadism**.

1. **Mosaicism** occurs in approximately 10% of Klinefelter males and is most commonly associated with karyotype 46,XY/47,XXY. Because the normal cell line can alter the phenotype significantly, 46,XY/47,XXY mosaics can have normal gonadal function and fertility. The additional X chromosome is often maternally derived (60%) and is associated with advanced maternal age. In patients whose additional X chromosome is paternally derived, paternal age distribution is normal.
2. **Phenotypic variability** is typical of Klinefelter syndrome. The most common features are mild **increase in stature** as a result of disproportionate growth of the lower extremities, and **small testes** (usually <2 cm) without evidence of abnormal Wolffian development. Testicular biopsy might be normal in childhood but becomes progressively more abnormal near or after puberty. Typical findings include tubular hyalinization, Leydig cell hyperplasia, decreased or absent Sertoli cells, and absent or rare spermatogenesis. Even when evidence of spermatogenesis is present, **fertility is rare**. Secondary sexual characteristics are frequently abnormal, with sparse facial hair, gynecomastia, and a female pattern of fat and hair distribution. As in the 47,XXX patient, **intelligence is often normal**. Cognitive ability is decreased in comparison with siblings, although the degree of intellectual involvement is mild. Auditory processing and expressive **language abilities are especially impaired**. Behavior disorders occur more frequently, as do

electroencephalographic abnormalities or frank seizure disorders. Other conditions associated with Klinefelter syndrome include varicose veins, thromboembolic disease, chronic respiratory disease, osteoporosis, diabetes mellitus, thyroid dysfunction, and, rarely, growth hormone deficiency or central precocious puberty. There is an increased incidence of extragonadal midline (mediastinal) germ-cell tumors, which usually present in the second to fourth decade. Although the relative frequency of breast cancer is increased compared to normal males, the absolute risk is low, probably about 1 in 5 000.

3. At present, there is no viable treatment for infertility in Klinefelter syndrome, though rare patients have fathered children through assisted reproductive techniques (testicular aspiration followed by in vitro fertilization and intracytoplasmic sperm injection). Testosterone replacement can be implemented between 11 and 14 years of age and is particularly helpful in achieving more complete virilization in the androgen-deficient patient. Adult patients report increased libido after institution of testosterone therapy. Gynecomastia might require surgical attention. Psychological counseling helps to achieve a normal adjustment in Klinefelter patients as well as in other individuals with sex chromosome abnormalities.

D. Of all the sex chromosome abnormalities, the **47,XYY karyotype** has raised the most controversy and public interest.

1. Occurring in 1 in 800 males, this cytogenetic finding is often accompanied by a completely normal phenotype and is rarely ascertained in childhood. The origin of the additional Y chromosome is generally a result of malsegregation at paternal meiosis II. Paternal age is not advanced.
2. Prospective data are limited but support the finding of tall stature with relatively early to mid-childhood growth spurt. Minor malformations can occur with increased frequency, but association of a major malformation is not established. Similarly, electrocardiographic abnormalities, severe cystic acne, and varicose veins p. 34p. 35have been described, but increased risk for these is unconfirmed. **Intelligence is generally within the normal range**, with a downward shift in comparison with siblings and the general population. Language

acquisition is particularly affected. Aberrant psychosocial development and behavior disorders occur with increased frequency, as does ordinary **criminal behavior** (i.e., not solely highly aggressive acts). Although gonadal development and function are normal in most XYY males, occurrence of small testes, subfertility, or infertility is known.

3. No specific treatment is indicated in 47,XYY males. Realistic and thorough counseling should be offered when the XYY karyotype is discovered or at the time of prenatal diagnosis. Adults who are newly diagnosed as XYY should be given reassurance and counseling support. Although prenatal diagnosis can be offered to partners of XYY males, their offspring generally have a normal chromosome complement.

IV. SINGLE-GENE DISORDERS

A. Table 3-2 lists a number of multisystem unifactorial (Mendelian) disorders in which endocrine abnormalities are common. Although the terms were initially used to describe the genotype (full complement of genes carried by the 46 chromosomes), the concept of dominant and recessive inheritance is now best applied to the phenotype. In addition to overlap with environmental, multifactorial, and chromosomal disorders, unifactorial disorders often exhibit considerable genetic heterogeneity. For example, both isolated **growth hormone deficiency** and **panhypopituitarism** can be inherited on an autosomal dominant, autosomal recessive, or X-linked recessive (XR) basis. Perhaps the best example of genetic heterogeneity occurs in the numerous disorders associated with **insulin-dependent diabetes mellitus (type 1)** and **non–insulin-dependent diabetes mellitus (type 2).** Although both **type 1** and **type 2** diabetes occur in association with specific Mendelian disorders, and at least one presentation of type 2 diabetes—**maturity-onset diabetes of the young**—occurs as an autosomal dominant disorder, both **isolated type 1** and **type 2 diabetes** appear to be highly heterogeneous, with autosomal recessive and multifactorial (including two or more gene loci) modes proposed.

TABLE 3-2 Selected Multisystem Unifactorial Disorders with Endocrine Abnormalities

Acanthosis nigricans (insulin-resistant diabetes mellitus)

Achondroplasia (relative glucose intolerance)
Acrodysostosis (hypogonadism)
Albright hereditary osteodystrophy (hypocalcemia, hypothyroidism, hypogonadism)
Ataxia telangiectasia (hypogonadism)
Beckwith–Wiedemann syndrome (hypoglycemia)
De Sanctis–Cacchione syndrome (hypothalamic dysfunction, hypogonadism)
Johanson–Blizzard syndrome (hypothyroidism)
Kenny syndrome (transient infantile hypocalcemia)
Laurence–Moon–Biedl syndrome (hypogonadism, diabetes insipidus)
Lysosomal storage disorders (short stature, hirsutism may prompt referral)
McCune–Albright syndrome (precocious puberty)
Multiple lentigines syndrome (hypogonadism)
Myotonic muscular dystrophy (diabetes mellitus, thyroid dysfunction)
Neurofibromatosis (precocious puberty, acromegaly)
Noonan syndrome (hypogonadism)
Robinow syndrome (hypogonadism)
Russell–Silver syndrome (fasting hypoglycemia in infancy)
Smith–Lemli–Opitz syndrome (hypogonadism, sex reversal, adrenal hypertrophy, giant islet cells)
Tuberous sclerosis (precocious puberty, hypothyroidism, thyroid adenomas)
Werner syndrome (diabetes mellitus, hypogonadism, hyperthyroidism, adrenal atrophy)

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1. A gene is considered **dominant** if one copy of it is sufficient to result in manifestation of the trait or disorder; the gene is **recessive** if two copies are required for expression of the phenotype. Examples of **codominance** are known, particularly in the inheritance of the blood groups. For example, the genes for hemoglobin S and hemoglobin A are codominant, but clinical expression of sickle cell anemia is recessive.
2. A gene can be autosomal or X-linked with resultant differences in the inheritance pattern. Fewer than 30 Y-linked conditions are known, including several related to gender development and fertility.
3. Chromosomes, and their constituent genes, occur in pairs. If an individual has an identical gene at the same locus on each of two paired chromosomes, he or she is **homozygous** for the trait determined by that gene. If the individual has two alternative forms of the gene at the same locus on paired chromosomes, he or she is

heterozygous for the trait. Such alternative forms, termed **alleles**, can result in normal polymorphism or in a variation of an abnormal phenotype. Because males normally have only one X chromosome, they are **hemizygous** for most X-linked genes.

B. Autosomal dominant inheritance has been implicated in **more than 5 000 disorders**, most of which result from the action of a rare mutant gene.

1. In general, dominant disorders include abnormalities of structural protein or of gene regulation.
2. **Autosomal dominant disorders** affect both sexes equally, except in sex-influenced or sex-limited conditions (e.g., Opitz syndrome and Opitz-Frias syndrome, both of which are ascertained largely because of the finding of hypospadias).
3. **Dominant disorders** are characterized by variation in expression (clinical phenotype) even within families. Occasional individuals who carry the gene might have no phenotypic findings, in which case the gene is **nonpenetrant**. Although penetrance is generally used as a population genetics concept, both nonpenetrance and minimal expression can result in an apparent "skip generation" or mimic a new mutation in a particular kindred.
4. A **new mutation** for a dominant gene generally results in expression of the trait. Therefore, mutation is important in the genesis of dominant disorders. Paternal age effect has been demonstrated in some dominant disorders, implying that increased paternal age is a predisposing factor for new mutation.
5. Dominant disorders generally follow a vertical pattern within families, except in the case of actual or genetic lethals (those disorders in which fertility is greatly reduced or absent). The risk of transmission of the gene from an affected individual to his or her offspring is 50%, regardless of the sex of the child or the degree of severity in the parent. Similarly, the parental phenotype does not predict the degree of severity in the offspring. Recurrence risk for apparently unaffected parents of a child with a known dominant disorder is generally low.
6. Disorders of endocrine hyperplasia and neoplasia, as well as other familial cancer syndromes, generally occur as autosomal dominant conditions. Thus, the multiple endocrine neoplasia syndromes (MEN1, MEN2A, and MENIIIB), the phakomatoses, and Gorlin syndrome (basal cell nevus syndrome) are inherited as autosomal

dominant traits.

C. Autosomal recessive inheritance is established **in >1 800 disorders**. Expression of a recessive disorder requires absence of the normal allele; the affected individual must be homozygous for the trait or heterozygous for two copies of the mutant genes. Deleterious recessive genes occur rarely in the population.

1. **Recessive disorders** generally involve genes that determine enzymatic protein and include the classic **inborn errors of metabolism**.
2. Either sex can be affected, although sex limitation does occur occasionally.
3. Decreased penetrance and extremely variable expression within a family occur much less commonly than in dominant conditions.
4. Although a new mutation can play a role in the occurrence of autosomal recessive disorders, such mutations are demonstrable only when specific heterozygote testing is available. If specific testing is not possible, parents of an affected child are considered **obligate heterozygotes**.

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5. Pedigrees of families with autosomal recessive disorders generally show a **horizontal relationship** among affected members. Affected siblings generally have **normal parents and normal offspring**. Consanguinity can increase the possibility that the parents share the same rare recessive allele. Recurrence risk to obligate heterozygote parents is 25%. Approximately two thirds of their normal offspring will be carriers of the mutation. Except in the case of a consanguineous union or a relatively common mutant gene (e.g., cystic fibrosis or phenylketonuria), recurrence risk to offspring of an affected parent is quite low; such offspring are obligate heterozygotes (carriers).
6. The majority of endocrine deficiency disorders, inborn errors of protein metabolism and glycogenesis, and lysosomal storage disorders occur as autosomal recessive conditions. The **inborn errors** of thyroid biosynthesis and the group of disorders that produce congenital adrenal hyperplasia are **examples of recessive (largely autosomal) disorders** in which glandular hyperplasia occurs as a secondary event as a result of interruption of a normal feedback inhibition loop. Specific therapy, if any,

depends on accurate diagnosis. Heterozygote (carrier) testing and prenatal diagnosis are available for most of these disorders.

D. Sex-linked disorders are usually equated with mutation of X-linked genes. Although genes associated with testicular development, sperm production, and height are known to be Y-linked, the range of functions of most Y chromosome genes has not been characterized definitively. The testis-determining factor **(SRY)** has been mapped to region 1a on the Y chromosome short arm (Yp). The gene, which has been highly conserved throughout mammalian evolution, consists of 900 base pairs (bp). It encodes a DNA-binding protein that initiates the developmental cascade involved in testis formation from the undifferentiated gonad. **Autosomal genes (e.g., *SOX9*) have a role in male gonadal development** as well. Visible or submicroscopic Y chromosome deletions in approximately 10% to 20% of males have been implicated as a major cause of azoospermia and subfertility. The deleted region contains azoospermia factor AZF locus located in the Yq11, specifically the Deleted in Azoospermia (DAZ) gene family is reported to be the most frequent deletion within the AZF locus. DAZ genes are explicitly transcribed in spermatogonia and primary spermatocytes. At least 495 known or suspected X-linked disorders have been cataloged. In general, X-linked disorders affect males who are related to each other through relatively unaffected (in the case of XR) or more mildly affected (X-linked dominant [XD]) females. Because the male is hemizygous for most X-linked genes, the relationship of gender to severity is expected. **Absence of male-to-male transmission is the hallmark of an X-linked disorder**, because an affected man must pass his Y chromosome to every son.

1. **XR disorders** vary in severity from genetic lethals (e.g., **Lesch–Nyhan syndrome**), in which affected males cannot reproduce, to relatively benign conditions (e.g., male pattern baldness). One third of genetically lethal cases arise as the result of a new mutation, a fact that complicates counseling of women with an apparently negative family history. Lethal XR disorders for which the gene has not been mapped to the X chromosome by cytogenetic, biochemical, or molecular techniques cannot be distinguished from autosomal dominant disorders with male sex limitation (e.g., **testicular feminization**). On average, half the daughters of heterozygous (carrier) females are also carriers, and half the sons are affected. Fertile males affected with an XR disorder have only

carrier daughters and normal sons. Examples of **XR endocrine disorders include adrenal leukodystrophy** (a peroxisomal disorder that demonstrates surprising clinical variability), **familial panhypopituitarism**, rare forms of **vasopressin deficiency**, nonsyndromic **hypoparathyroidism**, **adrenocortical hypoplasia**, and complete or partial **androgen insensitivity**.

2. **XD disorders** are relatively rare and can be lethal prenatally in hemizygous males. Such an effect has been proposed in several disorders, including **incontinentia pigmenti** and **focal dermal hypoplasia**, in which increased spontaneous miscarriages and a paucity of live-born males are well documented. In nonlethal XD disorders, there remains an excess of affected females, because a heterozygous p. 37p. 38female will pass the gene to half of her offspring of either sex, whereas a hemizygous male will pass the gene to all of his daughters and none of his sons. Examples of **XD disorders with endocrine manifestations** include **nephrogenic diabetes insipidus** and Albright hereditary osteodystrophy (**pseudohypoparathyroidism**).
3. **Specific treatment modalities**, heterozygote detection, and prenatal diagnosis are available for some X-linked disorders. When specific prenatal testing is unavailable, prenatal diagnosis is limited to sex determination or linkage analysis. In the first case, couples at risk for an XR disorder must opt to continue or terminate pregnancy solely on the basis of the 50% risk that a male fetus will be affected. In the latter situation, molecular markers are used to determine which maternal X carries the defective gene and whether that X or its homolog has been passed to the fetus. Linkage analysis is also useful in diagnosing autosomal dominant conditions.

V. SINGLE-GENE TESTING TECHNIQUES

A. The current trend of genetic diagnostic approach for patients presenting in clinic with abnormal features is to search for additional phenotypic and metabolic information through imaging studies and endocrine tests. This type of approach helps clinicians select candidate genes for testing that could explain the patient’s phenotype. This is usually inefficient as phenotypes frequently overlap and not all disease-causing genes have been identified. The single-gene testing

approach is often costly and time-consuming, because often several single genes must be tested sequentially.

1. **Sanger sequencing** is by far the most common sequencing method for DNA fragments of up to 1 000 bp. This method utilizes fluorescently labeled chain-terminating dideoxynucleotides for DNA synthesis and sequence readout. Most of the clinically available single-gene testing use Sanger sequencing to identify mutations in the gene of interest.
2. **Gene panels** are widely used in clinical practice for genetic diagnosis. Many disease-specific gene panels have been developed with varying number of test genes. Although Sanger sequencing can be used for panels with a limited number of genes, panel sequencing is often accomplished by capture of targeted exons from genomic DNA using biotinylated oligonucleotide probes followed by next-generation sequencing (NGS). Additional Sanger sequencing ("fill-in") may be performed for genes with missing or insufficient read depth coverage to detect heterozygous variants.
3. **Exome sequencing/genome sequencing** (ES/GS) has transformed the clinical genetic diagnostic capabilities for undiagnosed complex disorders. ES covers approximately 95% of the RefSeq protein-coding regions of the genome, which currently harbor 80% to 90% of known disease-causing variants. The sequencing method is similar to those used in gene panels, exon capture followed by NGS, and validation of low-quality mutations via Sanger. The primary advantage of this approach is that all genes known to be involved in the disease of interest are sequenced and analyzed simultaneously with a potential for discovery of a novel pathogenic gene variant. It is most effective to perform ES as a trio (proband and two parents), which may increase the diagnostic capabilities by almost 10% when compared to proband-only analysis. Several clinical ES laboratories around the United States have reported greater diagnostic yields when using ES rather than traditional molecular diagnostic methods, such as single-gene testing or panels.

VI. MULTIFACTORIAL INHERITANCE

A. General principles. A number of disorders demonstrate **familial aggregation without a clear pattern of Mendelian inheritance.** Analysis of data from twins studies and population

surveys reveals twins concordance or familial recurrence risk higher than expected by chance alone, but lower than predicted for a unifactorial trait, even one with reduced penetrance. The multifactorial model is a mathematical construct that predicts that two or more independent (nonallelic and unlinked) genes will interact in an additive way to create a genetic liability for expression of p. 38p. 39a specific trait. Interaction of the susceptible genotype with specific environmental effects can then exceed a threshold, resulting in expression of the trait. Although the threshold can be viewed in an all-or-none manner, severity of expression is variable and can be modified by other genetic risk factors, environmental factors, or both.

1. Multifactorial traits often demonstrate an altered sex ratio.
2. Recurrence risk varies with the sex of the affected individual, with the severity of the defect, between families because one family may have a greater genetic liability than another, with the number of affected family members, and with the incidence of the trait in the population.

B. Multifactorial inheritance has been implicated in a number of common malformations, including **cleft lip** (with or without cleft palate), isolated **cleft palate**, and the **myelomeningocele–anencephaly sequence**. The relative roles of genotype and environment in the pathogenesis of septo-optic dysplasia, holoprosencephaly, caudal regression, and athyrotic hypothyroidism are less clear, despite progress in identifying genes involved in the pathogenesis of these conditions (especially holoprosencephaly). The latter conditions generally occur as sporadic events in an otherwise normal family, and the recurrence risk appears to be less than that observed for the common multifactorial malformations. However, affected siblings or parents are occasionally described, underscoring the need for careful examination of close relatives of affected individuals. Familial aggregation is well known in the **autoimmune endocrinopathies**. **Graves disease** and **Hashimoto thyroiditis** are particularly **associated with clustering of symptomatic and asymptomatic family members** with positive antibodies.

C. Environmental disorders with endocrine manifestations are well known. **Rubella embryopathy** can be associated with hypopituitarism, isolated growth hormone deficiency, diabetes mellitus, and hypothyroidism. **Fetal hydantoin syndrome** can

result in hypogenitalism or ambiguity. Hydantoins, retinoids, and alcohol exposure are associated with prenatal and postnatal growth deficiency. Endocrine-acting agents that have a direct adverse effect on fetal outcome include sex hormones and antithyroid agents, such as iodides, iodine-131, propylthiouracil (PTU, which may be safer than methimazole), and methimazole. One report comparing the relative safety, suggests that PTU should be the first-line choice of treatment in pregnancy, with methimazole reserved for cases that do not respond. **Methimazole** is thought to cause a set of dysmorphic features including **scalp defects**, and has been associated with increased **risk of choanal atresia**, **esophageal atresia**, and at least one case with a limb defect—though the data are not as yet very good. Finally, maternal metabolic disorders, such as hyperparathyroidism and adrenal or thyroid hyperfunction or hypofunction, can seriously influence fetal viability or neonatal homeostasis. **Maternal diabetes mellitus** (type 1) is a well-known cause of fetal wastage and increases the risk for specific major malformation. Central nervous system and cardiac malformations, first and second branchial arch defects, caudal regression, and the myelomeningocele–anencephaly sequence are particularly prominent in offspring of diabetic mothers.

VII. NONTRADITIONAL INHERITANCE

A. Mosaicism. Both chromosomal and single-gene mutations can be distributed in a subset of cells in all body tissues, in tissues derived from a single embryonic layer, or in germ cells only **(gonadal mosaicism)**. Expression of the abnormality depends on the number and distribution of cells in the mosaic cell line.

1. **X inactivation**, which occurs very early in embryonic development, provides gene dosage compensation for most X-linked genes. Females have mosaic expression of all X-linked genes except those that escape X inactivation primarily in the pseudoautosomal region of Xp.
2. **Chromosomal mosaicism** is especially common in the sex chromosome disorders and usually produces a milder phenotype. Asymmetric growth or variable pigmentation is a marker for chromosome mosaicism, particularly when an autosome is involved. Evaluation of cultured skin fibroblasts or interphase cells from a buccal smear is helpful in confirming such diagnoses.

Confined placental p. 39p. 40mosaicism may account for intrauterine growth retardation in chromosomally normal fetuses.

3. **Somatic mutation** with resultant generalized or tissue-specific mosaicism at a single locus can account for patchy distribution of a dysfunctional gene and nonuniform expression of the condition (e.g., segmental neurofibromatosis). An apparent new dominant mutation can recur despite normal parental phenotypes because of **gonadal mosaicism** in one parent.

B. In **UPD**, both copies of a particular chromosome pair derive from one parent (i.e., the other parent's contribution is lost). Such cases can occur when a trisomic conceptus loses the extra chromosome (called trisomy rescue) but excludes the single copy of the chromosome derived from the normal gamete.

1. UPD has been described in **cystic fibrosis**, in which both mutations were inherited from the same parent, thus mimicking autosomal recessive inheritance.
2. In 25% to 30% of **Prader–Willi syndrome** patients with normal cytogenetic and FISH studies, maternal disomy 15 has been demonstrated by molecular techniques. Molecular analysis demonstrates two maternal chromosomes 15 and no copy of a paternally derived 15.
3. UPD for chromosome 7 has been associated with a clinical phenotype that overlaps the **Russell–Silver syndrome**, although UPD7 accounts for only 6% to 10% of the cases.
4. UPD is also a suggested cause of nonspecific intrauterine growth restriction, mental retardation, and microcephaly, although additional data are needed to confirm this concept and evaluate the extent to which it contributes to these conditions.

C. Genomic imprinting. Some genes or regions of chromosomes can be modified at meiosis such that the expression of a trait is altered and depends on the parental derivation of the gene or chromosomal region.

1. **Chromosomal deletion** syndromes can show effects of imprinting. In Prader–Willi syndrome, the 15q11–q13 deletion is always seen in the paternal chromosome 15. Deletion of a similar region of the maternal chromosome 15 produces Angelman syndrome, which can easily be distinguished from Prader–Willi syndrome despite some overlap in phenotype.
2. **Unequal gene expression** from the homologous chromosomes

may result in genetic "silence" or abnormal expression at a particular locus if the normal allele is not expressed and the homologous allele is defective. For example, in addition to deletion or paternal UPD15, mutation in the maternal copy of the ubiquitin 3A gene (*UBE3A*) on chromosome 15q11–13 results in Angelman syndrome because the normal gene is not expressed from the paternally inherited chromosome 15.

D. Other mechanisms account for some nontraditional inheritance.

1. **Mitochondrial** inheritance accounts for some rare conditions that are variable within kindreds, affect males and females, but are always maternally derived. Examples include **Leber hereditary optic atrophy** and the **mitochondrial encephalomyopathies**. A number of kindreds demonstrate maternal transmission of some combination of **diabetes**, sensorineural hearing loss, myopathy, central nervous system dysfunction, and retinopathy on the basis of mitochondrial mutation.
2. **Triplet-repeat disorders** occur because of expansion of an unstable triplet repeat that interrupts functioning of the gene. Expression of these conditions can depend on which parent transmitted the gene (e.g., juvenile-onset **Huntington disease** occurs only in offspring of **affected fathers**, whereas **congenital myotonic dystrophy** is limited to the offspring of **affected mothers**) because some of the triplet repeats are unstable in male meiosis, whereas others are unstable during meiosis in the female. Also, these conditions demonstrate anticipation, in which the phenotype becomes more severe and/or the age of onset is earlier in later generations within a kindred.

VIII. PRENATAL DIAGNOSIS

A. General principles. Prenatal diagnostic techniques now allow diagnosis of most chromosomal abnormalities and many specific genetic disorders. The use p. 40p. 41of ultrasound before and during amniocentesis has greatly reduced the risk of the procedure. **Chorionic villus sampling (CVS)** provides access to fetal tissue during the late first trimester/early midtrimester. This procedure is particularly useful when the fetus is at high risk for a genetic condition that is diagnosable by cytogenetic, biochemical, or molecular

techniques. Targeted ultrasound has also been increasingly useful in the evaluation of fetal morphology and growth parameters. Overall risk of major complications following ultrasound-directed amniocentesis is <1 in 200. Risks associated with CVS are not significantly higher in experienced hands. **Amniocentesis** is no longer recommended before week 13 of gestation, because of an increased risk of spontaneous rupture of membranes, as well as of clubfoot in surviving fetuses. **Noninvasive prenatal testing (NIPT) or noninvasive prenatal screening** relying on cell-free DNA circulating in maternal blood has advanced rapidly to capture the prenatal testing market. NIPT is extremely beneficial in a clinical setting because it avoids risks associated with early invasive methods, such as miscarriage in CVS. NIPT can accurately detect the status of inherited conditions or other birth defects due to monosomies, trisomies and has a potential of detecting acquired gene mutations.

B. Indications for amniocentesis or CVS vary among prenatal diagnosis programs but generally include the following:

1. Advanced maternal age (35 years at term).
2. Previous child with a chromosomal abnormality.
3. Previous child or parent affected with a neural tube defect.
4. Parent who is a carrier of a balanced chromosomal rearrangement.
5. Parent who is affected with a chromosomal abnormality.
6. Family history of nondisjunction.
7. Parents who are heterozygous for a detectable autosomal recessive disorder, or a parent who is affected by a detectable dominant disorder.
8. Mother who is a carrier of a detectable X-linked disorder or a nondetectable X-linked disorder (fetal sexing).
9. Abnormal ultrasound.
10. Significant history of fetal wastage (at least three episodes) or a previous child with unexplained multiple congenital anomalies.
11. Abnormal maternal analyte screen (most commonly α-fetoprotein, unconjugated estriol, β-human chorionic gonadotropin, inhibin, or pregnancy-associated plasma protein A).
12. Increased fetal nuchal translucency (neck skinfold thickness) on ultrasound assessment in the late first trimester or early midtrimester.

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4 The Growth Plate

Francesco De Luca, Ola Nilsson, and Jeffrey Baron

Longitudinal bone growth takes place at the growth plate (GP) through a two-step process called endochondral ossification. The GP is morphologically organized into three distinct layers, the resting, the proliferative, and the hypertrophic zones (Fig. 4-1). In the resting zone (the GP zone closest to the epiphysis), chondrocytes are small and rounded, irregularly arranged in a bed of cartilage matrix and proliferate rarely. Farther toward the metaphysis, in the proliferative zone, the chondrocytes are flat and are arranged in columns. Proliferative chondrocytes express types II, IX, and XI collagen and proteoglycans, such as aggrecan. After having divided for a finite number of cell cycles, the proliferative chondrocytes at the bottom of each column stop replicating and enlarge to become hypertrophic chondrocytes. Hypertrophic chondrocytes differentiate and begin to express alkaline phosphatase and type X collagen. These terminally differentiated cells, which form a layer adjacent to the metaphysis termed the hypertrophic zone, eventually undergo apoptosis. GP chondrocyte proliferation and hypertrophy, along with the extracellular matrix secreted by chondrocytes, lead to continued formation of new cartilage (chondrogenesis). While new cartilage is formed, the hypertrophic chondrocytes release a variety of signaling molecules, such as Indian hedgehog (IHH), vascular endothelial growth factor (VEGF) and enzymes, such as matrix metalloproteinases (MMPs). IHH promotes differentiation of osteoblasts in the nearby perichondrium and metaphysis; VEGF induces blood vessel invasion from the metaphysis. MMPs contribute to the degradation of the extracellular matrix. Along with blood vessels, the GP is invaded by endothelial cells, osteoclasts, and osteoblast precursors. The remodeling of the cartilaginous hypertrophic zone into bone tissue carried out by these cells is known as ossification.

Chondrogenesis and ossification are tightly coupled so that, although the width of the GP remains relatively constant, the long bone elongates through the continuous formation of new bone at the junction of the GP and the metaphyseal bone.

The rates of GP chondrogenesis and longitudinal bone growth decrease progressively over time. This decrease appears to result from mechanisms

intrinsic to the GP rather than a hormonal or other systemic mechanism.

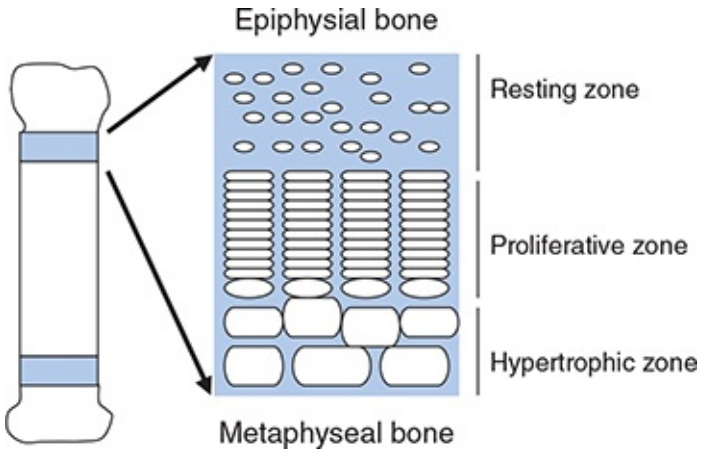

Figure 4-1. Histology of the growth plate.

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The decline in the rates of chondrogenesis and longitudinal bone growth is primarily caused by a decline in the proliferation rate of GP chondrocytes, which leads to a reduced number of proliferative and hypertrophic chondrocytes per column. As a result, the overall height of the human GP progressively decreases during childhood. The human GP cartilage is completely replaced by bone at the completion of puberty. This event, termed **epiphyseal fusion**, seems to occur when the proliferative capacity of the GP chondrocytes is finally exhausted. Evidence suggests that the decline in proliferation rate of GP chondrocytes is due to the fact that chondrocytes in the resting zone have a finite proliferative capacity that is gradually exhausted. The combination of progressive loss-of-function and progressive structural involution of the GP has been termed **GP senescence**. There is evidence that the developmental program of senescence is driven not by time per se but instead by growth.

The molecular mechanisms that slow growth in vivo are not well understood. However, recent studies in rodents suggest that change in expression of a set of genes in GP chondrocytes may contribute to the occurrence of GP senescence.

For example, insulin-like growth factor-2 (*Igf2*), a growth-promoting gene, is downregulated almost 1 000-fold during senescence. Other pathways involving fibroblast growth factors (FGFs), wingless-related integration sites (WNTs), eicosanoids, p38-MAPK, and vitamin D receptor signaling may be involved. Further research is required to determine whether these genes' expression changes are causally related to the cellular events representing GP senescence.

I. REGULATION OF GP CHONDROGENESIS AND LONGITUDINAL BONE GROWTH

The rates of GP chondrogenesis and, in turn, of longitudinal bone growth are regulated by multiple systemic (endocrine) factors. In addition, the underlying cellular processes of proliferation, differentiation, and ossification appear to be regulated by a network of local (paracrine) factors, expressed in the GP. The activity of these paracrine factors is also influenced by a number of molecules expressed in the cartilage matrix. Lastly, both endocrine and paracrine growth factors modulate GP function by activating or inhibiting a multitude of intracellular factors.

A. Endocrine factors (Fig. 4-2)

1. **Growth hormone and IGFs.** Growth hormone (GH) and IGF-1 are potent stimulators of longitudinal bone growth.

   GH deficiency or insensitivity caused by GH receptor (GHR) or postreceptor mutations leads to a significant reduction of postnatal growth in mammals. **GH deficiency and insensitivity do not impair prenatal growth.** In contrast, mice lacking either the *Igf-1* or *Igf-2* genes, and humans with **IGF-I deficiency** p. 44p. 45caused by a mutation in the *IGF-1* gene, or with **IGF-I resistance** caused by mutations in the type I IGF receptor gene, **show intrauterine growth retardation and postnatal growth deficit**. According to the original somatomedin hypothesis, GH induces bone growth by stimulating hepatic production of IGF-1 (previously known as somatomedin) which, in turn, stimulates longitudinal bone growth at the GP. This evidence, along with the detection of IGF-1 and IGF-2 expression not only in the liver but also in other tissues, supported a revised somatomedin hypothesis, according to which GH modulates longitudinal bone growth via IGF-1 expressed in extrahepatic tissues. Furthermore, the somatomedin hypothesis was subsequently challenged by studies demonstrating a direct growth-promoting effect of GH when injected in a rat tibial GP, with this effect limited only to the injected bone. Further studies confirmed a direct effect of GH on longitudinal bone growth, indicating that **GH acts, at least in part, by inducing the expression and the action of IGF-1 locally in the GP**.

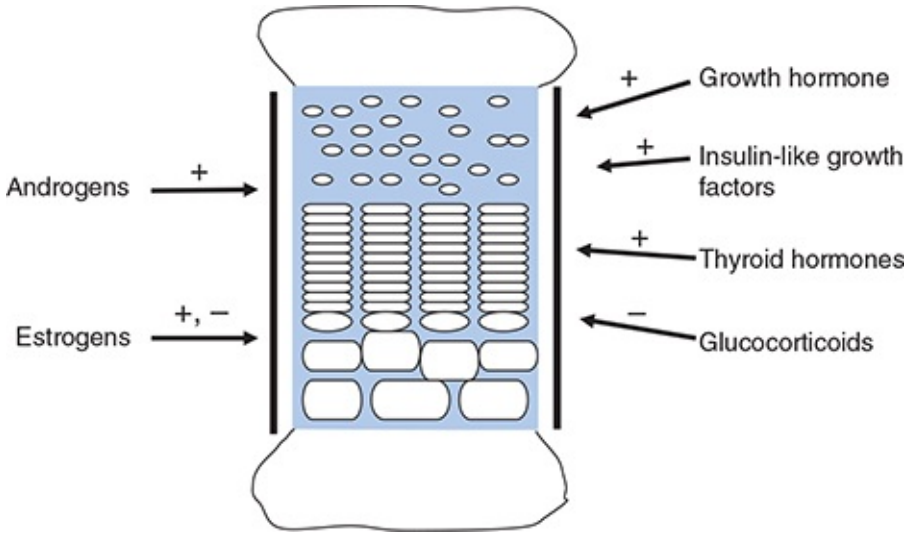

Figure 4-2. Endocrine regulation of growth plate chondrogenesis. +, stimulation of chondrogenesis; −, inhibition of chondrogenesis.

In mice, genetic manipulations that severely reduce circulating levels of IGF-1 modestly impair bone growth, suggesting that IGF-1 acts only in part by an endocrine mechanism. In another study, targeted disruption of IGF-1 expression in mouse chondrocytes led to reduced bone length. These findings suggested that IGF-1 expressed in the GP acting in a paracrine manner contributes to the GH-dependent effects on longitudinal bone growth.

On the other hand, further evidence suggests that GH may have IGF-1-independent effects on bone growth. In one study, it was demonstrated that tibial growth rate is reduced more in *Ghr* null mice than in *Igf1* null mice. In another study, the authors demonstrated that the body size of mutant mice lacking both *Ghr* and *Igf1* was smaller than that of mice lacking *Igf1* or *Ghr*. However, in the *Igf1* null mice, IGF-2 expression in the GP is significantly increased; thus, it is **possible that the IGF-1-independent effects of GH on GP chondrogenesis and longitudinal bone growth may be mediated by IGF-2**.

Lastly, it has been shown that postnatal ablation of IGF-1 receptor (*Igf1r*) (which is activated by both IGF-1 and IGF-2) in the mouse GP results in diminished body and tibial growth. Despite the lack of *Igf1r* expression in the GP, postnatal systemic administration of GH induces body and tibial growth, as well as cartilage formation in the GP. As a result, these findings indicate

that **GH may promote longitudinal bone growth through IGF-independent mechanisms**.

It is not entirely clear which specific cellular events of GP chondrogenesis are modulated by GH and IGFs.

According to the *dual effector hypothesis*, it was previously thought that GH acts locally at the GP to recruit resting chondrocytes into a proliferative state, as well as to stimulate local IGF-1 production, which then stimulates proliferation of proliferative zone chondrocytes. However, subsequent in vivo labeling experiments suggest that IGF-I, like GH, can stimulate proliferation of resting zone chondrocytes as well as chondrocyte hypertrophy. In contrast, studies in IGF-I-deficient mice suggest that IGF-I acts primarily to increase hypertrophic cell height, with little effect on proliferation.

Mice with a postnatal ablation of *Igf1r* in the GP exhibit a reduced tibial GP height, which is due to reduced height of all three zones (epiphyseal, proliferative, and hypertrophic). In addition, the systemic injection of GH in these mice leads to an increase of the GP height, with such effect resulting from the increased height of the epiphyseal, proliferative, and hypertrophic zones. In cultured chondrocytes transfected with IGF-1R siRNA, the addition of GH stimulates both thymidine incorporation (marker of cell proliferation) and collagen X mRNA expression (marker of chondrocyte differentiation/hypertrophy). Thus, these findings suggest that both GH and IGFs may regulate both chondrocyte proliferation and differentiation.

2. Glucocorticoids

Systemic administration of high-dose glucocorticoids often leads to growth failure, which in mammals reflects impaired longitudinal bone growth. p. 45p. 46Glucocorticoids **inhibit longitudinal bone growth, in part, through a direct effect on the GP**. A direct effect of glucocorticoids in the GP has been shown by a study in which local infusion of dexamethasone into a rabbit tibial GP caused a decreased growth rate of the treated tibia compared with the contralateral untreated one. Consistent with a direct effect of glucocorticoids on the GP, the expression of the glucocorticoid receptor has been demonstrated in GP chondrocytes. In vitro exposure to glucocorticoids leads to

inhibition of GP chondrocyte proliferation, decreased cartilage matrix synthesis, and increased chondrocyte apoptosis.

The apoptotic effect of glucocorticoids in the GP is also confirmed by the observed increased expression of apoptotic proteins, caspase-3 and Bax, and decreased expression of Bcl-2 and Bcl-x, antiapoptotic proteins. Regarding the molecular mechanisms underlying decreased chondrocyte proliferation and increased apoptosis, short-term systemic administration of glucocorticoids in rodents decreases IGF-I expression in the GP, whereas long-term treatment (1 month) increases it. In cultured rat GP chondrocytes, glucocorticoids can downregulate expression of GHR and IGF1R. However, other studies suggest that glucocorticoids increase the expression of IGF1R mRNA in porcine-cultured chondrocytes, whereas growth-suppressive doses of dexamethasone given to rabbits increase GHR mRNA expression in the GP.

In conclusion, a large body of data consistently indicates that **glucocorticoids suppress statural growth by inhibiting GP chondrogenesis.** In contrast, conflicting experimental evidence exists on the molecular mechanisms underlying the glucocorticoid-mediated suppression of GP function.

Discontinuation of glucocorticoid treatment is followed by catch-up growth, which is caused, at least in part, by a mechanism intrinsic to the GP. Catch-up growth may occur because the decreased cell proliferation during glucocorticoid treatment conserves the proliferative capacity of the chondrocytes, thus slowing GP senescence. Following discontinuation of the glucocorticoid treatment, the GPs are less senescent; thus, they grow more rapidly and for a longer period of time, resulting in catch-up growth.

3. Thyroid hormones

Adequate thyroid hormone synthesis and action supports normal skeletal growth and maturation. **Hypothyroidism in mammals reduces longitudinal bone growth, whereas hyperthyroidism accelerates it**. Hypothyroid animals exhibit a decrease in the heights of the GP proliferative and hypertrophic zones, and a decrease in chondrocyte proliferation, chondrocyte hypertrophy, and vascular/bone cell invasion. Some of the skeletal effects of thyroid hormone appear to be caused by a direct action

on the GP. In fetal mouse tibia organ culture, thyroid hormone promotes longitudinal growth with the largest effect seen in the hypertrophic zone. In cell culture, thyroid hormone stimulates hypertrophic differentiation, but often diminishes proliferation.

Local conversion of T_4 to T_3 by thyroid hormone deiodinase 2 in the GP may contribute to its local effects. GP chondrocytes express thyroid hormone receptor (TR) isoforms TR-α1, TR-α2, and TR-β1. Knocking out TR-β isoforms in mice has little effect on the skeleton. In contrast, ablation of TR-α impairs longitudinal bone growth and endochondral ossification. In humans, one family with homozygous deletion of TR-β showed some delayed skeletal maturation but normal growth, suggesting that TR-β mediates some of the effects of thyroid hormone on human skeletal development. Thus, deletion of TR-β affects skeletal development in humans, but has little effect in mice. Most cases of thyroid hormone resistance in humans are caused by dominant-negative mutations of the TR-β gene and show variable skeletal effects. In children, heterozygous mutations in TR-α also slow bone growth and skeletal maturation. In addition to its local action on the GP, thyroid hormone may have indirect effects on the GP, mediated by GH and IGF-I. In hypothyroid humans and mice, GH and IGF-I levels are reduced. Replacing GH in hypothyroid rats, or in mice lacking TR-α improves longitudinal bone growth. However, GH does not normalize GP chondrogenesis.

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4. Estrogens

Estradiol (E2) affects longitudinal bone growth and GP function. Increased secretion/action of E2 during early and mid-puberty induces an acceleration of longitudinal bone growth (pubertal growth spurt), whereas **high E2 levels in late puberty result in GP fusion** and thereby cessation of longitudinal bone growth in humans. The cause–effect relationship linking estrogen, pubertal growth spurt, and GP closure is supported by experiments of nature in humans.

Individuals with estrogen deficiency caused by mutations in the aromatase gene, and with estrogen resistance secondary to mutations of the ER-α, all exhibited lack of pubertal growth

acceleration and GP fusion. The effects of a mutated ER-α in humans indicate that it is ER-α that mediates the estrogen action on human growth and GP. The mechanisms of action for these two opposite effects of estrogens on longitudinal bone growth remain only partially understood.

The growth-accelerating effects of E2 are in part due to its modulation of the GH/IGF-I axis. **Low-dose E2 treatment raises serum GH and IGF-I levels**, whereas estrogen receptor blockade downregulates the GH/IGF-I axis. In addition to its effect on the GH–IGF axis, E2 may directly modulate the function of the GP. Three lines of evidence support this hypothesis. First, both ER-α and ER-β are expressed in the GP. Second, estrogen inhibits longitudinal bone growth of hypophysectomized and castrated female rats. Third, some evidence suggests that human GP chondrocytes placed in primary culture may be stimulated by estrogen.

Experimental evidence in rabbits suggests that epiphyseal fusion occurs when the proliferative capacity of the GP chondrocytes is exhausted and that **estrogen acts by advancing GP senescence**, causing earlier proliferative exhaustion, and thus earlier fusion.

It was previously thought that in mice, unlike humans, the effects of estrogen on the GP are mediated primarily by ER-β rather than ER-α. However, recent evidence indicates that high E2 levels, both in humans and mice, inhibit bone growth and cause its cessation through a direct effect on ER-α in the GP.

5. Androgen

Androgen can directly stimulate longitudinal bone growth and GP function. In boys, dihydrotestosterone, a nonaromatizable androgen, can accelerate linear growth. In addition, androgen receptor expression has been detected in rat and human GP cartilage. In vitro dihydrotestosterone can stimulate proliferation and proteoglycan synthesis in GP chondrocytes.

In puberty, increased androgen secretion contributes to the acceleration of statural growth. However, some of the effects elicited by endogenous androgen may depend on the conversion (because of aromatization) of androgens to estrogens in various tissues, including the GP. Indeed, aromatase is expressed in GP cartilage. Local administration of testosterone reportedly increases

unilateral rat tibial epiphyseal GP width. Furthermore, testosterone, and to a lesser extent, dihydrotestosterone stimulate chondrocyte proliferation in the mouse mandibular condyle, an organ culture model of endochondral ossification.

B. Paracrine factors (Fig. 4-3)

1. **Parathyroid hormone–related protein (PTHrP).** Inactivation by genetic recombination of the gene encoding either PTHrP or its receptor (PTH1R) in the mouse resulted in neonatal death and short-limb dwarfism caused by premature hypertrophy of chondrocytes. Conversely, overexpression of PTHrP or PTH1R in chondrocytes markedly delayed chondrocyte hypertrophy, resulting in a completely cartilaginous endochondral skeleton at birth. Similarly in humans, inactivating mutations in PTH1R cause **Blomstrand chondrodysplasia**, characterized by advanced skeletal maturation with shortened long bones and increased bone density, whereas gain-of-function mutations in PTH1R cause **Jansen metaphyseal chondrodysplasia**. Lastly, heterozygous mutations in the gene that encodes PTHrP result in short stature and short fingers in individuals with brachydactyly, type E2. All this evidence indicates that PTH signaling suppresses chondrocyte hypertrophy in the GP.

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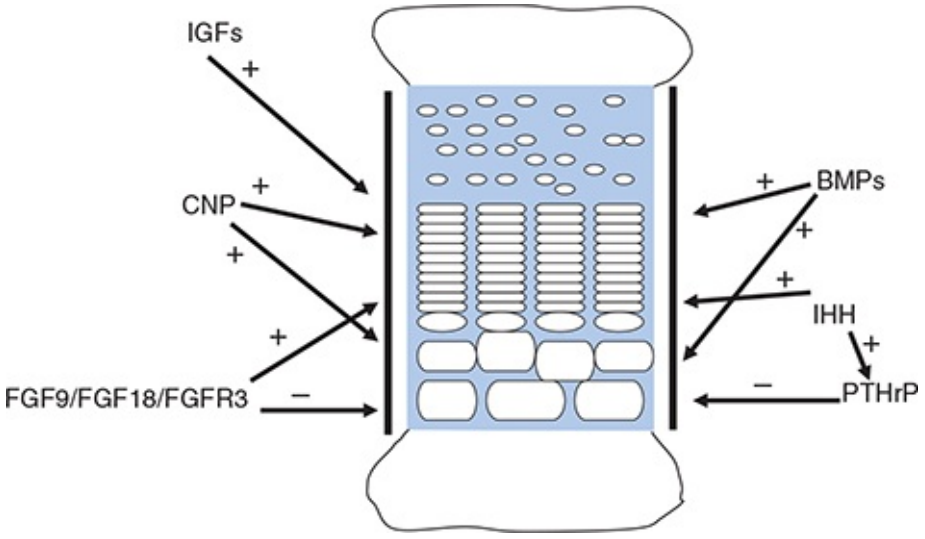

Figure 4-3. Paracrine regulation of growth plate chondrogenesis. IGFs, insulin-like growth factors; CNP, C-type natriuretic peptide; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; BMPs, bone morphogenetic proteins; IHH, Indian hedgehog; PTHrP, PTH-related

peptide; +, stimulation of chondrogenesis; −, inhibition of chondrogenesis.

2. **IHH.** In the developing cartilage, **IHH** is primarily expressed by chondrocytes immediately before hypertrophy (prehypertrophic chondrocytes) and also by early hypertrophic chondrocytes. The IHH binds to Patch (PTCH), and its signal is transduced through Smoothened (SMO), a seven-pass transmembrane domain protein.

   Mouse embryos with a targeted deletion of IHH exhibited a severe reduction in chondrocyte proliferation and premature hypertrophy of chondrocytes. Subsequent genetic manipulation of SMO in chondrocytes revealed that direct IHH input was required for the regulations of chondrocyte proliferation, but not for the regulation of chondrocyte hypertrophy. PTHrP and IHH interact in the GP through a negative feedback loop within the GP that regulates chondrocyte hypertrophy and proliferation. Overexpression of IHH in chick embryos induces PTHrP expression in the periarticular perichondrium of the GP. Conversely, PTHrP expression is absent from the GP in IHH-deficient mice. Exogenous IHH inhibits chondrocyte hypertrophy in the mouse GP, with such effect being prevented by the concomitant deletion of either PTHrP or PTH1R. The expression of constitutively active Pth1r in the GP of $IHH^{-/-}$ mice reverses premature chondrocyte hypertrophy but fails to rescue decreased chondrocyte proliferation. These findings suggest that IHH controls chondrocyte proliferation via a PTHrP-independent pathway and chondrocyte hypertrophy via a PTHrP-dependent pathway.

3. **Fibroblast growth factors**

   In addition to the IHH/PTHrP system, FGF signaling controls GP development.

   Conditional inactivation of Fgfr1 in chondrocytes delayed maturation of hypertrophic chondrocytes, whereas $Fgfr3^{-/-}$ mice have increased levels of chondrocyte proliferation and an expanded hypertrophic zone. In contrast, overexpression of activated FGFR3 in the GP of transgenic mice reduced chondrocyte proliferation and resulted in decreased numbers of cells in the prehypertrophic and hypertrophic zones. Thus, FGFR3 signaling negatively regulates chondrogenesis by inhibiting chondrocyte proliferation, accelerating chondrocyte hypertrophy and decreasing the size of

hypertrophic chondrocytes, and reducing the synthesis of cartilage matrix.

Activating **mutations of *FGFR3* are responsible for reduced longitudinal bone growth in humans with achondroplasia, hypochondroplasia**, and p. 48p. 49**thanatophoric dysplasia**. A recent report suggests that activating mutations of FGFR3 may also cause proportionate short stature. On the other hand, inactivating mutations of FGFR3 have been detected in humans with tall stature.

The main FGF ligand(s) for FGFR3 in the GP remain to be identified. However, FGF9 and FGF18 are good candidates. They are expressed in the GP and in the perichondrium and are known to activate FGFR3 in vitro. Fgf9-deficient mice exhibit bone shortening, decreased proliferation, and delayed chondrocyte hypertrophy. At a late stage of embryonic development (E16.5 to E18.5), $Fgf18^{-/-}$ mice display an increase in proliferating and hypertrophic zone thickness and an enlarged GP, indicating that, at this stage of development, Fgf18 signaling negatively regulates proliferation and maturation of GP chondrocytes. In addition, loss-of-function studies in mice suggest that FGF18 inhibits proliferation and accelerates maturation. FGF21 is also expressed in the GP, and it appears to exert an important role in fasting-induced growth inhibition. FGF21 expression is induced by fasting. Fgf21 knockout mice exposed to food restriction experience greater linear growth and GP thickness when compared with wild-type mice, indicating that the growth suppression induced by fasting is elicited by Fgf21. Decreased GHR and IGF-1 expressions in the liver and in the GP, which occur in a fasting animal, are prevented by Fgf21 deletion. As a result, fgf21 knockout mice exhibit spared linear growth and GP chondrogenesis. In vitro studies in cultured GP chondrocytes indicate that FGF21 may suppress chondrogenesis and GH action locally at the GP acting both as an endocrine and a paracrine factor. Recent evidence suggests that FGF21 may also be implicated in regulating bone growth in humans.

4. Bone morphogenetic proteins

Bone morphogenetic proteins (BMPs) are involved in the regulation of proliferation and differentiation in the GP. Evidence suggests that BMP2 may have an important regulatory role among other BMPs. In mice, targeted ablation of BMP2 causes defective chondrocyte proliferation and differentiation. In cultured whole mouse fetal metatarsals, BMP2 stimulates resting zone chondrocytes to proliferate and stimulates proliferative zone chondrocytes to hypertrophy.

While mice completely lacking two BMP receptor subtypes, Bmpr1a and Bmpr1b, in chondrogenic progenitors fail to form many cartilage elements, those carrying one Bmpr1b allele developed all cartilage elements, but exhibit reduced chondrocyte proliferation and hypertrophy. In mice lacking either Bmpr1a or Bmpr1b, IHH expression and activity is reduced, and FGF signaling is increased in their GP. In contrast, the expression of Bmp4 is suppressed in GP chondrocytes of mice overexpressing activated FGFR3. These findings support an antagonism between BMP and FGF signaling; thus, balancing of BMP and FGF signaling may be necessary for proper GP function.

In humans, **mutations** in the genes that encode several BMPs, their receptors, and antagonists **lead to skeletal dysplasias**, including brachydactyly, type A2 (*BMP2* or *BMPR1B*), brachydactyly, type A1 and brachydactyly, type C (*GDF5*), chondrodysplasia, Grebe type (*GDF5*), **Klippel-Feil syndrome 1** (*GDF6*), and proximal symphalangism 1A (*NOG*).

5. **C-type natriuretic peptide**

C-type natriuretic peptide (CNP) is expressed in the GP and acts primarily by activating the receptor NPR2. Knockout mice lacking the expression of CNP or NPR2 have short bones, whereas mice overexpressing NPR2 exhibit longer bones compared to wild type, and *Npr2*-null mice display a similar phenotype to *CNP* knockout mice. In humans, homozygous loss-of-function mutations in the *NPR2* gene cause **acromesomelic dysplasia**, type Maroteaux, characterized by severe growth retardation, whereas heterozygous mutations of NPR2 are associated with short stature. In contrast, a gain-of-function mutation of the same gene has been found in a family with skeletal overgrowth. In light of these skeletal features described in mice and humans, it is believed that CNP regulates chondrogenesis by stimulating chondrocyte proliferation and

hypertrophy and by increasing the synthesis of cartilage extracellular matrix.

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6. **Wingless-type MMTV integration site family members (WNTs)**

   Some members of the WNT family may regulate GP chondrocyte function, although the underlying mechanisms of such regulation are not clear yet. WNT5A and WNT5B are expressed by chondrocytes. $Wnt5a^{-/-}$ mice exhibited a marked delay in chondrocyte hypertrophy. On the other hand, overexpression of either WNT5A or WNT5B in chondrocytes also delayed hypertrophy in both mouse and chicken embryos.

7. **NOTCH**

   NOTCH signaling modulates development of the GP chondrocytes. Deletion of both NOTCH1 and NOTCH2 in the limb mesenchyme before chondrogenesis reduced chondrocyte proliferation and delayed chondrocyte hypertrophy in the mouse embryo. Conversely, overexpression of the intracellular domain of Notch1 in differentiated chondrocytes accelerated hypertrophy. Thus, Notch signaling within the GP is critical for normal proliferation and maturation of chondrocytes.

C. Cartilage extracellular matrix

Proteoglycans (collagenous and noncollagenous proteins) are expressed by GP chondrocytes and secreted into the extracellular space. They are necessary to maintain a normal physical structure of the cartilaginous GP and, at the same time, interact functionally with a number of paracrine growth factors regulating GP function.

Mutations of the gene-encoding collagen X (*COL10A*) cause short stature secondary to a skeletal dysplasia known as **metaphyseal chondrodysplasia**, Schmid type.

Mutations of the gene-encoding aggrecan (*ACAN*), a proteoglycan secreted by GP chondrocytes, lead to short stature and skeletal deformities of varying severity. Homozygous mutations cause a severe skeletal dysplasia called spondyloepimetaphyseal dysplasia aggrecan type. Heterozygous mutations are responsible for a more subtle skeletal dysplasia (spondyloepiphyseal dysplasia, Kimberley type) or short stature. Individuals with short stature caused by mutations of the

aggrecan gene often present with advanced skeletal maturation. The GP of mice lacking aggrecan exhibits decreased chondrocyte proliferation and accelerated hypertrophic chondrocyte differentiation, associated with altered IHH, FGF, and BMP signaling.

Biglycan, a noncollagenous protein of the cartilage matrix, appears to modulate GP function and bone formation by interacting with transforming growth factor *β*, as demonstrated by the growth retardation and osteoporosis detected in mice lacking biglycan.

D. Intracellular factors (Table 4-1)

1. SOXs

SOX9 is a member of the Sox family of **transcription factors** characterized by a high-mobility-group-box DNA-binding motif **related to that of the sex-determining factor SRY**. Evidence provided by mouse models and by human disorders has revealed that Sox9 is an essential **regulator of chondrogenesis**. Haploinsufficiency of SOX9 results in chondrodysplasia in the mouse, and complete loss of SOX9 in prechondrogenic limb mesenchyme abolishes chondrogenesis altogether. Along with its role in early chondrogenesis, SOX9 cooperates with SOX5 and SOX6 in regulating GP chondrocyte differentiation and activating genes-encoding cartilage matrix components, such as collagen II and aggrecan. In humans, heterozygous mutations within and around the Sox9 gene cause **campomelic dysplasia**, a severe human chondrodysplasia.

2. SHOX

SHOX is another **transcription factor** expressed in the GP, especially in the terminally differentiated chondrocytes. Homozygous inactivating mutations of SHOX cause a severe skeletal dysplasia called **Langer mesomelic dysplasia**. Heterozygous inactivating mutations, or deletions of *SHOX*, are responsible for a skeletal dysplasia called **Leri–Weill dyschondrosteosis**, which is characterized by wrist deformities and short stature. Some heterozygous mutations have also been detected in idiopathic short stature without any obvious skeletal malformations. In addition, **haploinsufficiency of SHOX causes growth failure in subjects with Turner syndrome**. The histology of radial GPs surgically excised from patients with SHOX deficiency revealed a disrupted columnar arrangement of

chondrocytes, with expansion of the p. 50p. 51hypertrophic zone and reduced height of the proliferative zone. Although these findings suggest the involvement of SHOX in chondrocyte differentiation, and, possibly, apoptosis, its exact function in the GP remains to be fully elucidated.

TABLE 4-1 Effects of Intracellular Factors on the Specific Processes of GP Chondrogenesis

	GP CHONDROGENESIS			
	Proliferation	Differentiation/hypertrophy	Cartilage matrix	Apoptosis
SOXs		+	+	
SHOX		**?**		+
RUNX2/RUNX3		+		
HDAC4		−		
MEF2C		+		
FoxA2/FoxA3		+		
HIFs		+		+
Ras/MAPK	+	−		
NF-κBs	+	+		−

+, stimulation of chondrogenesis; −, inhibition of chondrogenesis; GP, growth plate; FoxA, forkhead box A; HDAC4, histone deacetylase 4; HIFs, hypoxia-inducible factors; Ras–MAPK, retrovirus-associated DNA sequences mitogen-activated protein kinase; RUNX, runt-related transcription factor; SOX9, sex-determining region Y-box 9; SHOX, short stature homeobox; MEF2C, myocyte enhancer factor-2C; NF-κBs, nuclear factors κB.

3. RUNX

Runt domain family transcription factors Runx2 and Runx3 are involved in the regulation of GP chondrocyte differentiation. Runx2$^{-/-}$ mice lack hypertrophic chondrocytes, whereas overexpression of RUNX2 in chondrocytes leads to premature chondrocyte hypertrophy, and also corrects the defective chondrocyte hypertrophy observed in Runx2$^{-/-}$ mice. Similar effects on chondrocyte hypertrophy are induced by Runx3: *Runx2/Runx3*-double knockout exhibits a more severe defective chondrocyte hypertrophy compared to that observed in Runx2

knockout mice. It has been shown that Runx2 activates the transcription of *Ihh*, Col X, and *MMP13*. Recently, it has also been shown that Sox9 suppresses the expression of Runx2, leading to inhibition of chondrocyte hypertrophy.

4. **Histone deacetylase 4**
   Histone deacetylase 4 (HDAC4) is a member of the **class II histone deacetylases** and is expressed in hypertrophic chondrocytes. Genetic deletion of HDAC4 leads to premature chondrocyte hypertrophy. Conversely, overexpression of HDAC4 in all chondrocytes inhibited hypertrophy. From a molecular standpoint, its activity depends on its interaction with RUNX2, preventing its binding to DNA. Thus, HDAC4 prevents premature hypertrophy of chondrocytes in part by directly suppressing RUNX2 activity.
5. **Myocyte enhancer factor-2C**
   Myocyte enhancer factor-2C (MEF2C) is a member of the **myocyte enhancer factor family**, and is expressed by hypertrophic chondrocytes. Decreased expression of MEF2C in chondrocytes impairs hypertrophy, whereas an activated form induces premature chondrocyte hypertrophy. MEF2C stimulates hypertrophy partly by increasing RUNX2 expression. HDAC4 inhibits chondrocyte hypertrophy by suppressing the activity of MEF2C.

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6. **FoxAs**
   FoxA2 and FoxA3, two **transcription factors members of the forkhead family**, are expressed in the developing skeleton. Mice lacking both FoxA2 and FoxA3 expression in cartilage exhibit growth retardation, primarily because of impaired chondrocyte hypertrophy. In the GP of these mice, the expression of markers of chondrocyte hypertrophy and differentiation (collagen X, MMP13, and alkaline phosphatase) is markedly diminished.
7. **Hypoxia-inducible factors**
   The **hypoxia-inducible factors** (HIFs) are proteins involved in mediating cellular responses under hypoxic conditions. HIF-1a is known to regulate cartilage development. In addition, it has been recently shown that HIF-2a is implicated in controlling

chondrocyte hypertrophy, cartilage degradation, and vascularization. Overexpression of HIF-2a in mouse chondrocytes markedly increased the number of apoptotic chondrocytes.

8. **Retrovirus-associated DNA sequences mitogen-activated protein kinase**

   The retrovirus-associated DNA sequences mitogen-activated protein kinase (Ras–MAPK) **signaling pathway mediates the action of a number of growth factors**, **such as FGFs, CNP,** and epidermal growth factor. Increased activation of this pathway results in a number of genetic syndromes characterized by growth failure, including **Noonan syndrome, LEOPARD syndrome, Costello syndrome, cardiofaciocutaneous syndrome,** and **neurofibromatosis–Noonan syndrome**. Conversely, tall stature associated with **Sotos syndrome** may be related to the decreased activity of the Ras–MAPK pathway.

9. **Nuclear factors *κ*Bs**

   Skeletal growth is also regulated by **nuclear factor *κ*B (NF-*κ*B)** and a group of seven transcription factors participating in the regulation of cell proliferation, migration, and apoptosis. In GP chondrocytes, NF-*κ*B–p65 helps to mediate the stimulatory effects of GH and IGF-1 on chondrogenesis. In humans, heterozygous loss-of-function mutations in the gene that encodes I*κ*B*α*, an essential component of the NF-*κ*B pathway, result in GH insensitivity and growth failure, as well as ectodermal dysplasia and immunodeficiency.

E. Summary

Statural growth in children is driven by endochondral ossification at the GP, which involves chondrocyte proliferation, hypertrophy, cartilage matrix secretion, and ossification. This process is highly regulated by multiple endocrine signals, paracrine signals, extracellular matrix factors, and intracellular factors. Abnormalities at all of these different levels result in childhood growth disorders, which range from severe short stature and malformed bones to idiopathic short stature to tall stature.

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SECTION 2

Hypothalamic-Pituitary Dysfunction

5

Anterior Pituitary Diseases

Harold E. Carlson

I. NORMAL ANTERIOR PITUITARY PHYSIOLOGY

A. Anterior pituitary hormones. The normal anterior pituitary gland secretes six well-characterized major hormones.

1. Adrenocorticotropic hormone (ACTH). ACTH has moderate melanocyte-stimulating activity and may account for most of the hyperpigmentation seen in Nelson syndrome and Addison disease
2. Thyrotropin (thyroid-stimulating hormone [TSH])
3. Luteinizing hormone (LH)
4. Follicle-stimulating hormone (FSH)
5. Growth hormone (GH)
6. Prolactin (Prl)
7. A seventh hormone, **β-lipotropin**, is synthesized along with ACTH in corticotropes as part of a large precursor molecule called **proopiomelanocortin**. The physiology of β-lipotropin is still poorly understood

B. Feedback system. TSH, ACTH, and the two gonadotropins, LH and FSH, stimulate end-organ target glands to secrete hormones, which in turn exert a restraining negative feedback effect on their respective pituitary tropic cells. Thus, ACTH secretion is largely controlled by the inhibitory feedback effects of circulating cortisol on the pituitary; similar relationships hold for TSH and thyroid hormones,

and for LH–FSH and gonadal steroids. FSH secretion is also inhibited in both genders by a gonadal peptide called **inhibin**. Insulin-like growth factor I (IGF-I, produced in the liver; also known as somatomedin C), a GH-dependent growth-promoting peptide, can inhibit GH secretion. In contrast, Prl has no well-defined peripheral product that exerts a feedback effect.

C. Hypothalamic-releasing hormones. In addition to the feedback system, the hypothalamus contributes to pituitary regulation by means of releasing and inhibiting hormones secreted into the hypothalamic-pituitary portal circulation. Several such hormones have been identified.

End-organ hormones exert their feedback effects on the hypothalamus as well as directly on the pituitary, although the direct effects on the pituitary are probably more important.

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1. Protirelin, or thyrotropin-releasing hormone (TRH), releases TSH and Prl from the pituitary.
2. Gonadotropin-releasing hormone (GnRH) releases both LH and FSH.
3. Corticotropin-releasing hormone stimulates ACTH and lipotropin secretion.
4. Growth hormone–releasing hormone stimulates GH release.
5. Somatostatin inhibits GH and, to some extent, TSH secretion.
6. Dopamine, a potent inhibitor of Prl release, is probably the main factor that physiologically regulates this hormone. In the absence of dopamine, Prl secretion increases.

II. HYPOPITUITARISM

A. General principles. Hypofunction of the pituitary can result from disease of the pituitary itself or of the hypothalamus (Table 5-1). In either case, there is decreased secretion of the pituitary hormones, with consequent effects on the function of the p. 55p. 56remainder of the organism. Thus, TSH deficiency causes hypothyroidism without goiter; LH and FSH deficiencies cause hypogonadism; ACTH deficiency leads to hypoadrenalism and poor tanning of the skin; Prl deficiency results in failure of postpartum

lactation; and GH deficiency causes short stature and, occasionally, fasting hypoglycemia in children; in adults, GH deficiency may lead to increased abdominal fat, poor energy, reduced muscle mass and strength, dyslipidemia, and impaired psychological well-being. Both GH deficiency and hypogonadism may contribute to fine facial wrinkling.

TABLE 5-1 Causes of Hypopituitarism

- Infarction
  - Postpartum necrosis (Sheehan syndrome)
  - Vascular disease (in diabetes mellitus)
  - Following pituitary stimulation testing (e.g., GnRH)
  - Head trauma
  - Subarachnoid hemorrhage
- Infections
  - Tuberculosis
  - Fungi
  - Pyogenic
  - Syphilis
  - Toxoplasmosis
- Granulomas
  - Sarcoidosis
  - Langerhans cell histiocytosis
- Autoimmune lymphocytic hypophysitis
- Spontaneous, often pregnancy related
- Drug induced (ipilimumab, interferon-α)
- Neoplasms involving pituitary
  - Pituitary adenoma
  - Craniopharyngioma
  - Metastatic or primary carcinoma (rare)
- Aneurysm of internal carotid artery
- Hemochromatosis
- Idiopathic or genetic disorders
  - Deficient production of pituitary hormone
  - Synthesis of abnormal hormone
- Primary hypothalamic disorders
  - Tumors (e.g., craniopharyngioma, glioma)
  - Granulomas (sarcoidosis, Langerhans cell histiocytosis)
  - Midline central nervous system structural anomalies of the hypothalamus
  - Genetic or idiopathic releasing hormone deficiency
  - Head trauma
- Iatrogenic factors
  - Stalk section
  - Radiation
  - Hypophysectomy

GnRH, gonadotropin-releasing hormone.

B. Diagnosis. With some hormones (ACTH, TSH, LH, and FSH), the diagnosis of secondary (i.e., as a result of hypothalamic-pituitary causes) end-organ hypofunction can easily be established by demonstration of low or inappropriately normal serum levels of the appropriate pituitary hormone concurrent with low levels of the target-organ hormone. Thus, the finding of low or normal serum gonadotropins in the presence of clinical hypogonadism with low serum levels of testosterone or estrogen suggests the diagnosis of secondary rather than primary hypogonadism. To separate hypothalamic from pituitary causes of hypofunction as well as to diagnose GH or Prl deficiency, specific pituitary stimulation tests are needed. However, in many cases, it is of no practical importance to distinguish hormonally between pituitary and hypothalamic disorders because the endocrine therapy is the same. Prl deficiency is usually of no therapeutic importance in adults; thus, Prl stimulation tests can often be omitted in the evaluation of hypopituitarism. However, documentation of diminished Prl reserve is occasionally useful in supporting the diagnosis of hypopituitarism in adults.

C. Pituitary stimulation testing (Table 5-2)

1. **GH.** Serum GH levels are normally low throughout most of the day in adults, rising during exercise, sleep, stress, and postprandially. The most useful stimulation tests are insulin-induced hypoglycemia and the intramuscular administration of glucagon. Consensus on the criteria for diagnosing GH deficiency in adults is incomplete. Different commercial GH assay kits may produce widely disparate p. 56p. 57results when the same serum sample is assayed, and GH responses to provocative tests are not entirely reproducible in individual subjects. Nevertheless, most normal adult subjects achieve peak serum GH values of at least 3 to 5 ng/mL in response to stimulation tests; insulin-induced hypoglycemia is probably the most consistent stimulus. In children, the diagnosis of GH deficiency relies on the combination of short stature (more than 2.5SD below the mean for age), slow growth velocity, delayed bone age, and **stimulated serum GH concentrations <10 ng/mL**. Serum IGF-I and

IGF–binding protein 3 levels are low in some, but not all, patients with GH deficiency and should not be used as the sole criterion of insufficient GH secretion. Hypothyroid or obese patients often have blunted responses to all provocative stimuli of GH.

TABLE 5-2 Pituitary Stimulation Tests

Hormone	Test Agent	Normal Response
GH	Insulin, 0.05–0.15 U/kg IV, or glucagon 1–1.5 mg IM	Serum GH >3–5 ng/mL at any time in adults; >10 ng/mL in children
Prl	Metoclopramide, 5–10 mg	Doubling of baseline level with peak >12 ng/mL
TSH	TRH, 500 µg IV (not currently available)	Peak value >5 µU/mL
LH and FSH	GnRH, 100 µg IV	Doubling of baseline LH, with peak >10 mIU/mL; 0%–30% rise in FSH
	Clomiphene, 100–200 mg/d PO for 5–10 d	50% rise in LH, 30% rise in FSH
ACTH	Insulin, 0.05–0.15 U/kg IV, or glucagon 1–1.5 mg IM	Peak serum cortisol > 18–20 µg/dL, with increment >10 µg/dL
	Metyrapone, 2–3 g PO at bedtime	Serum 11-deoxycortisol level > 7 µg/dL next morning
	Cosyntropin, 250 µg IV (indirect test)	Peak serum cortisol >18–20 µg/dL

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IM, intramuscular; IV, intravenous; LH, luteinizing hormone; Prl, prolactin; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

2. **Prl.** Prl secretion is normally low throughout much of the day, rising during sleep or stress and postprandially. A clinically useful provocative test of Prl release involves the administration of a dopamine antagonist such as metoclopramide, which blocks endogenous dopamine, the main Prl-inhibiting factor; a minimal normal Prl response consists of a doubling of the baseline value, with a peak of at least 12 ng/mL. Prl responsiveness is enhanced by estrogen administration and is, therefore, generally greater in women. Patients with hypopituitarism will have low baseline serum Prl levels that fail to rise appropriately following stimulation. In contrast, patients with pure hypothalamic disease will have basal hyperprolactinemia because the intact lactotropes

will have been freed from the tonic inhibitory effect of hypothalamic dopamine; Prl responses can be blunted or normal in such patients.

3. **TSH.** With pure pituitary disease (e.g., posthypophysectomy), serum TSH levels are low and do not rise following intravenous (IV) administration of TRH, which directly stimulates thyrotropes. Patients with pure hypothalamic disease may have low, normal, or even slightly elevated serum TSH in the presence of hypothyroidism, with a normal-sized but delayed TSH peak following TRH administration (see Chapters 36 and 38), presumably reflecting TRH deficiency. The apparent paradoxic occurrence of hypothyroidism despite normal or elevated serum TSH levels by radioimmunoassay is explained by the finding that serum TSH bioactivity is low in such patients; endogenous TRH appears to be needed to confer full bioactivity on the TSH molecule. Unfortunately, TRH is not currently available for administration to humans.
4. **Gonadotropins**
   a. **Synthetic GnRH,** a direct stimulator of gonadotropes, is injected IV, and LH and FSH responses are assessed. Patients with complete pituitary destruction show low baseline serum LH and FSH levels with no rise after GnRH injection. Subjects with hypothalamic disease generally respond to GnRH, although "priming" doses of GnRH might be needed (400 μg intramuscularly daily for 5 days) to fully demonstrate the response.
   b. **Gonadotropin reserve** can also be assessed by testing with oral clomiphene, a competitive estrogen receptor antagonist. In normal adult men and women, clomiphene administration produces a rise in both LH and FSH by blocking the inhibitory feedback effects of gonadal steroids on the hypothalamus. Although it is useful as a research tool, clomiphene testing occasionally has practical applications as well.
5. **ACTH.** The assessment of ACTH secretion has traditionally been indirect because of the difficulty and expense of plasma ACTH measurement.
   a. Recent advances in ACTH radioimmunoassay techniques have made the clinical use of plasma ACTH determinations much more widely available. Indirect assessments have utilized

measurements of plasma cortisol, which parallels plasma ACTH under most circumstances. In patients with obvious adrenal insufficiency, primary and secondary (hypothalamic-pituitary) adrenal failure can be distinguished by measuring plasma ACTH and cortisol in the morning (8 to 10 A.M.), when levels are normally highest. In the presence of low serum cortisol concentrations, plasma ACTH will be elevated in patients with primary adrenal failure, whereas low or low-normal levels are seen in patients with secondary adrenal insufficiency.

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b. Provocative testing with insulin-induced hypoglycemia or glucagon administration (as described for GH testing; see Section II.C.1) or metyrapone can be used to document lesser defects in ACTH reserve.

i. Following insulin-induced hypoglycemia or glucagon administration, plasma cortisol should normally rise to levels >18 to 20 μg/dL, generally with an increment of at least 10 μg/dL over baseline.

ii. The short overnight metyrapone test can be performed by giving oral metyrapone (3 g if body weight >60 kg; 2 g if <60 kg) at bedtime with a snack to avoid nausea and measuring serum 11-deoxycortisol at 8 A.M. the next morning. A normal response consists of a serum 11-deoxycortisol level of ≥7 μg/dL. If a subnormal rise in 11-deoxycortisol is seen, serum cortisol should be measured in the same sample to assess the adequacy of enzymatic blockade. A serum cortisol level >5 μg/dL suggests poor absorption of the metyrapone, and the test could be repeated with a higher dose of the drug or the response to hypoglycemia assessed.

c. Cosyntropin testing has been used to assess ACTH secretion indirectly; a **chronic** deficiency of ACTH secretion leads to adrenal atrophy and blunted serum cortisol responses at 30 and 60 minutes following the injection of cosyntropin (synthetic ACTH [amino acids 1–24], 250 μg IV bolus). Results of this test correlate reasonably well with those obtained using insulin-induced hypoglycemia, but the cosyntropin test is performed much more easily. Peak serum cortisol levels are >20 μg/dL in

normal subjects. Cosyntropin testing is not useful in evaluating **acute** ACTH deficiency because adrenal atrophy takes several weeks to develop.

6. **Clinical indications** for detailed pituitary stimulation testing include:
   - **a.** To assist in the diagnosis of otherwise obscure pituitary or hypothalamic disease.
   - **b.** To assess the need for GH replacement therapy.
   - **c.** Note that, with the exception of gonadotropins (for infertility) and GH therapy, the need for hormone replacement therapy is determined solely by clinical status and measurement of end-organ products (cortisol, thyroxine, and testosterone) rather than pituitary hormones.

D. Management of hypopituitarism

1. In most cases, the hormonal deficiencies of hypopituitarism are treated by supplying the needed end-organ hormones (Table 5-3). Prl replacement therapy is p. 58p. 59rarely needed and is unavailable in any case. **Women with secondary adrenal insufficiency may benefit from dehydroepiandrosterone replacement** in addition to cortisol supplementation.

TABLE 5-3 Management of Hypopituitarism

Deficient Hormone	Therapy
TSH	L-Thyroxine, 0.05–0.2 mg/d PO
ACTH	Oral glucocorticoid, e.g., prednisone, 2.5–5 mg in A.M., 0–2.5 mg in early evening, or hydrocortisone, 10–20 mg in A.M., 5–10 mg in early evening. Mineralocorticoid usually not needed. DHEA, 50 mg in A.M., may benefit adult women
LH and FSH	Men: Testosterone enanthate or cypionate, 200–300 mg IM q2–3 wk, or testosterone transdermal patch, 2.5–5 mg daily, or testosterone transdermal gel, 2.5–10 mg daily
	Women: Cyclic estrogen and progesterone, e.g., conjugated equine estrogens, 0.625 mg PO daily for days 1–25 of each calendar month with the addition of medroxyprogesterone acetate, 10 mg PO, on days 16–25. Alternatively, an oral contraceptive may be given
	For restoration of fertility in either sex, human FSH and either hCG or LH are given by injection, usually for periods of several months
GH	3–25 µg/kg SC daily in adults (see Chapter 14 for doses in children)

ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; FSH, follicle-stimulating hormone; GH, growth hormone; hCG, human chorionic gonadotropin; IM, intramuscular; LH, luteinizing hormone; PO, per os; SC, subcutaneous; TSH, thyroid-stimulating hormone.

2. Replacement pituitary hormones are given in only two circumstances.
   a. Human GH is given to GH-deficient pediatric or adult patients with clinical and chemical features of GH deficiency (see Chapters 12 and 14).
   b. Exogenous gonadotropins may be given to stimulate gonadal function in hypopituitary patients who desire fertility. In this situation, human chorionic gonadotropin may be used as a substitute for LH, or biosynthetic recombinant human LH can be given; FSH activity can be provided by either urofollitropin or biosynthetic recombinant human FSH preparations.
3. Patients with hypopituitarism should carry a card or wear a bracelet identifying their hormonal status. Both patients and their families should be capable of administering extra glucocorticoid, either parenterally or orally, in case of severe illness or injury.

III. PITUITARY TUMORS

A. General considerations

1. Types of tumors

a. **Pituitary tumors,** nearly always benign, occur in about 10% of adults; most of these tumors are small, incidental findings on radiologic studies. The appearance of a pituitary tumor on hematoxylin and eosin staining bears little relationship to its functional status.
b. **Prl-secreting tumors** are the single most common neoplasm, followed by **clinically nonfunctioning tumors** (Table 5-4).
c. **"Chromophobe" tumors** often secrete Prl, GH, or other hormones. Many clinically silent tumors, unassociated with any recognized state of hormone hypersecretion, actually contain or secrete small amounts of gonadotropins or their α and β subunits.

2. **Signs and symptoms.** Both secreting and nonsecreting tumors can produce signs and symptoms as a result of their space-occupying characteristics and their location. These features, such

as headache, visual impairment (typically bitemporal hemianopsia resulting from compression of the optic chiasm), extraocular palsy, hydrocephalus, seizures, and cerebrospinal fluid (CSF) rhinorrhea, are all more common with larger tumors (macroadenomas, >1 cm in diameter) and tumors with extrasellar extension than with intrasellar microadenomas (<1 cm in diameter). Hypopituitarism and diabetes insipidus are also more frequently encountered in patients with large destructive tumors.

Spontaneous hemorrhage into a pituitary tumor occurs in as many as 15% to 20% of patients; about one third of these are clinically recognizable (pituitary apoplexy) and present with headache, decreased vision, extraocular palsies, and p. 59p. 60other neurologic findings. Evacuation of the hematoma may be needed in severe cases, along with administration of fluids and glucocorticoid supplements.

TABLE 5-4 Frequency of Pituitary Tumors

Type of Tumor	Relative Frequency of Occurrence (%)
Prl secreting	25–30
Clinically nonfunctioning (most secrete gonadotropins or gonadotropin subunits)	25–30
ACTH secreting	15
GH secreting	15
Plurihormonal	12
TSH secreting	2

ACTH, adrenocorticotropic hormone; GH, growth hormone; Prl, prolactin; TSH, thyroid-stimulating hormone.

B. Radiology of pituitary tumors

1. **Magnetic resonance imaging (MRI)** is currently the procedure of choice in documenting the presence and extent of pituitary neoplasms; it is more sensitive than computed tomography (CT) in detecting small tumors. MRI, usually performed with and without contrast, is particularly useful in showing mass effects on the optic chiasm and extrasellar extension. A normal scan does not exclude the presence of a very small tumor (e.g., <2 mm in diameter).

C. Management of pituitary tumors

1. **General principles.** In some patients with small, asymptomatic pituitary tumors, no treatment other than observation and end-organ hormone replacement is indicated. However, many patients require specific therapy to diminish hormone hypersecretion, if present, and to correct or prevent the mass effects of the intracranial lesion. Table 5-5 lists the indications and contraindications for the various methods.

TABLE 5-5 Choice of Therapy for Pituitary Tumors

Radiation Therapy

Appropriate for:

- Small or medium tumors with minimal or modest suprasellar extension
- Patients in whom surgery is contraindicated or refused
- Postoperative adjunctive therapy in patients with invasive or incompletely removed tumors

Contraindicated as sole therapy in:

- Patients with large suprasellar extensions
- Patients with major visual-field defects
- Acromegaly patients with serum GH levels >50 ng/mL prior to treatment

Prolactinoma patients who wish to restore fertility

Surgery: Transfrontal Approach

Appropriate for:

- Large suprasellar extensions, especially if dumbbell shaped with a constriction at the diaphragma sellae, or with lateral suprasellar extension
- Patients in whom the transsphenoidal approach to the sella is relatively contraindicated (patients with chronic sinusitis or an incompletely pneumatized sphenoid sinus)

Contraindicated in:

- Not generally needed for small intrasellar tumors

Surgery: Transsphenoidal Approach

Appropriate for:

- Microadenomas (<1 cm in diameter)
- Tumors associated with extension into the sphenoid sinus or cerebrospinal fluid rhinorrhea
- Tumors associated with pituitary apoplexy
- Macroadenomas (>1 cm in diameter) with minimal or modest suprasellar extension

Contraindicated in:

- Tumors with large dumbbell-shaped or lateral suprasellar extensions
- Patients with chronic sinusitis or incompletely pneumatized sphenoid sinus (relative, not absolute contraindications)

Medical Therapy with Dopaminergic Agonists

Appropriate for:

- Primary treatment of prolactin-secreting tumors
- Rapid correction of neurologic sequelae of large prolactin-secreting tumors
- Shrinkage of prolactin-secreting tumors to facilitate ablative therapy
- Pregnant patients with prolactin-secreting tumors who experience gestational tumor growth
- Adjunctive therapy in patients with acromegaly or TSH-secreting tumors

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Contraindicated in:

- Nonfunctioning tumors (although a few patients may respond)
- Primary treatment of acromegaly, except when ablative therapy is refused

Medical Therapy with Somatostatin Analogs

Appropriate for:

- Adjunctive therapy in patients with acromegaly or TSH-secreting tumors
- Primary therapy in patients with acromegaly when ablative therapy is refused
- Adjunctive therapy in patients with ACTH-secreting tumors or when ablative therapy is refused

Contraindicated in:

- Other types of tumors

Medical Therapy with Pegvisomant

Appropriate for:

Patients who have persistent GH hypersecretion following ablative therapy and/or somatostatin analogs

ACTH, adrenocorticotropic hormone; GH, growth hormone; TSH, thyroid-stimulating hormone.

2. **Surgery.** In general, surgery has historically been preferred when serious anatomic complications exist (e.g., visual-field defects) or when immediate correction of hormone hypersecretion is desired. Surgery occasionally damages adjacent structures or results in hypopituitarism.
3. **Radiation.** Radiotherapy delivered as supervoltage photons from either cobalt-60 or linear accelerator devices, or as heavy particles (protons or α particles) has a slower onset of effect than surgery, generally taking 6 to 24 months for initial benefit to be seen, with progressive improvement over 2 to 10 years. Hypopituitarism is seen in up to 50% to 80% of patients 10 to 20 years after radiotherapy. Stereotactic or conformal radiotherapy using cobalt-60 (“gamma knife radiosurgery”) or a rotating linear accelerator beam is receiving increasing use; to date, it appears to be no more effective than standard methods, though it is generally given in a single treatment session, rather than multiple treatments over 5 to 6

weeks as are used for fractionated radiotherapy. The relatively large single treatment dose utilized in conformal therapy may result in greater radiation damage to nearby adjacent structures, such as the optic nerves or chiasm.

4. **Medical therapy.** Dopamine agonists, such as **bromocriptine** and **cabergoline**, have been shown to lower serum Prl and rapidly shrink many Prl-secreting adenomas; these drugs are often recommended as the sole or adjunctive therapy for such tumors (see Section V). Some patients with acromegaly or clinically nonfunctioning tumors also demonstrate tumor regression with cabergoline or bromocriptine therapy, and these drugs may also lower GH in some acromegalics. Octreotide and lanreotide, synthetic analogs of somatostatin, have been used successfully to reduce GH and TSH secretion from pituitary tumors that produce these hormones, and also frequently partially shrink such tumors. Another somatostatin analog, pasireotide, is used to reduce pituitary ACTH secretion in Cushing disease and GH secretion in acromegaly. Synthetic antagonists of GnRH have been used experimentally to inhibit LH–FSH secretion from gonadotropin-producing tumors.
5. **Preoperative evaluation.** Patients scheduled for hypothalamic-pituitary surgery should not be routinely subjected to an exhaustive preoperative hormonal evaluation because testing needs to be repeated postoperatively. Instead, measurements of serum-free thyroxine (T_4) or free T_4 index (because severe untreated hypothyroidism can increase the risks of general anesthesia), IGF-I, and Prl (to detect occult hypersecretion of GH and Prl) should be obtained. Rather than p. 61p. 62assess the ACTH reserve preoperatively, most physicians provide supplemental glucocorticoid in the perioperative period and during stressful diagnostic procedures and then evaluate cortisol secretion postoperatively. Alternatively, morning serum cortisol can be measured; a serum cortisol level >10 to 12 μg/dL suggests intact pituitary-adrenal function, whereas cortisol levels <4 to 5 μg/dL suggest the presence of adrenal insufficiency.
6. **Postoperative assessment.** In postoperative patients and those receiving radiation or medical therapy alone, the need for

hormone replacement should be evaluated by measuring serum testosterone (in men) and the serum-free T_4 or free T_4 index, and by assessing the pituitary-adrenal axis with a morning serum cortisol level, insulin-induced hypoglycemia or metyrapone, or indirectly with cosyntropin. Note that the **cosyntropin test may be normal in the immediate postoperative period, because adrenal atrophy takes several weeks to develop after ACTH secretion is lost.** The presence of regular menses in a premenopausal woman usually indicates relatively normal estrogen secretion, and further testing is not needed unless the patient is infertile. Children should have provocative tests of GH secretion (see Chapters 12 and 14), as should adults with symptoms of GH deficiency.

7. **Follow-up.** Following initial treatment, patients are seen every 3 or 4 months for 1 year, then every 6 to 12 months. During each visit, signs and symptoms of hormone deficiency or excess should be sought. Serum-free T_4 or free T_4 index and serum testosterone (in men) should be tested every 1 to 2 years and ACTH assessed every 2 to 3 years with a morning serum cortisol measurement or cosyntropin testing. Patients with pituitary tumors should have a follow-up MRI or CT scan within 6 months of treatment to assess early anatomic changes, and then every 1 to 3 years.

IV. ACROMEGALY AND GIGANTISM

A. Clinical features.

Hypersecretion of GH produces the typical appearance of acromegaly, with enlargement of the facial features, hands, and feet in most patients. The presence of GH excess prior to the closure of long-bone epiphyses in late puberty leads to increased stature; gigantism can result if the process begins in childhood. Other common symptoms include:

1. Excessive perspiration, perhaps caused by enlarged sweat glands or hypermetabolism.
2. Carpal tunnel syndrome, resulting from compression of the enlarged or edematous median nerve by the fibrocartilaginous tissue of the wrist.
3. Degenerative arthritis, secondary to bony overgrowth and deformity around large weight-bearing joints.
4. Hypertension, perhaps related to salt-retaining effects of GH.

5. Glucose intolerance or diabetes mellitus, reflecting the insulin-antagonistic properties of GH.
6. Hypercalciuria, perhaps secondary to stimulation of 1,25-dihydroxy-vitamin D_3 production by GH or IGF-I, in addition to GH effects on renal calcium excretion.
7. Galactorrhea, resulting either from the intrinsic lactogenic properties of GH or from the presence of a mixed adenoma that produces both GH and Prl.
8. Sleep apnea, both obstructive and central. Increased mortality in acromegaly is attributed to cerebrovascular, cardiovascular, and pulmonary diseases. Additionally, there is an increased incidence of colon polyps and, possibly, colon cancer in these patients.

B. Diagnosis of acromegaly. In a patient with a compatible clinical history and appearance, a diagnosis of acromegaly is usually easy to confirm.

1. In the absence of serious concurrent illness, serum levels of IGF-I are uniformly elevated in patients with active acromegaly.
2. The other well-established test involves the assessment of GH responses to oral glucose. In normal subjects, serum GH is suppressed to low levels (<1 ng/mL; often undetectable) 60 to 120 minutes following the oral ingestion of 75 to 100 g of glucose in solution. Nearly all patients with acromegaly fail to show such suppression, and some may demonstrate a rise in GH instead.

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3. In addition to dynamic testing, two or three random measurements of serum GH should be obtained to provide an average pretreatment baseline value.
4. Baseline serum Prl should also be measured in all patients with acromegaly, because up to 40% have a “mixed” pituitary adenoma, secreting both GH and Prl, usually from two separate cell types in the same tumor.
5. After a hormonal diagnosis has been made, patients with acromegaly should also undergo an anatomic evaluation of their sellar contents with MRI and may require a formal visual-field examination if the tumor appears to impinge on the optic chiasm.

C. Management of acromegaly

1. Pituitary surgery produces better long-term results than

radiotherapy, with about 50% to 60% of patients achieving serum GH values <2 ng/mL and normal serum IGF-I. Surgery also offers the advantage of an immediate lowering of GH, whereas radiation therapy slowly reduces serum GH over many years. In addition, patients with pretreatment serum GH values >50 ng/mL are often left with residual GH hypersecretion after radiotherapy and are probably best treated with surgery as the initial therapy. Factors such as visual-field defects and large extrasellar extensions can also influence the choice of treatment (Table 5-5).

2. Medical therapy is typically given to patients with persistent GH hypersecretion following pituitary surgery. Dopamine agonists, somatostatin analogs, and pegvisomant have been successfully used alone or in combination in many patients.
   a. **Dopamine agonists** significantly lower serum GH and IGF-I in a minority of patients (10% to 40%). Unfortunately, there is no means of predicting which patients will achieve significant GH suppression with dopamine agonist therapy. In addition, pituitary tumor shrinkage may occur in <5% of acromegalic patients who are given dopamine agonists. At present, dopamine agonists are used primarily as adjunctive treatment in acromegaly, following surgery or radiation. **Cabergoline** appears to be the most useful of the dopamine agonists and is usually begun at doses of 0.25 mg once or twice a week, with doses increased to 1 to 2 mg/week as needed. Rarely, additional benefit is gained by increasing the total daily dose to levels >3 mg/week. In some reports, patients with tumors that cosecreted Prl were more likely to have significant GH suppression on dopamine agonist therapy.
   b. **Octreotide, lanreotide, and pasireotide,** synthetic analogs of somatostatin, have **greater efficacy than dopamine agonists** in the management of acromegaly, although the requirement for injection makes them much less convenient. Long-acting depot forms of these drugs are available and are given as a monthly intramuscular or subcutaneous injection. Common side effects include abdominal cramps, loose stools, worsened glucose tolerance, and cholelithiasis. These drugs normalize serum GH and IGF-I in 50% to 70% of patients and produce partial shrinkage of GH-secreting adenomas in around 50%. All three drugs are quite expensive, in the range of

$20 000 to $40 000 per year.

c. Pegvisomant is a competitive antagonist of native GH at the cell-membrane GH receptor. It consists of biosynthetic human GH with nine amino acid substitutions that remove its ability to activate the GH receptor without impairing receptor binding; this modified GH molecule is then coupled to polyethylene glycol to prolong its serum half-life. When it is administered to patients with acromegaly, it **prevents the binding of native GH to the GH receptor**, thereby preventing GH action. IGF-I production falls, and the clinical signs and symptoms of acromegaly are ameliorated. Pegvisomant **does not cause shrinkage of the GH-secreting tumor** and, theoretically, could result in additional tumor growth by decreasing the effect of native GH to stimulate hypothalamic somatostatin production; for this same reason, it has been observed that secretion of native GH (as measured in specific assays) is increased during pegvisomant therapy.

Pegvisomant is given as a daily subcutaneous injection of 10 to 20 mg; between 60% and 90% of patients will achieve normal serum IGF-I levels. p. 63p. 64Pegvisomant is relatively free of serious side effects; pain at the injection site, nausea, or diarrhea are each seen in about 10% of patients. Abnormal serum concentrations of liver enzymes have been noted in 1% to 5% of patients; in some individuals, enzyme concentrations have normalized despite continuation of the drug. Frequent monitoring of serum liver enzyme concentrations and bilirubin is recommended during the first year of therapy; pegvisomant may need to be discontinued if severe and persistent elevations are found.

Pegvisomant is detected in routine commercial GH assays, so serum **GH measurements cannot be used to monitor disease activity. IGF-1 is measured instead.** Tumor size should continue to be monitored by MRI scan every 6 months for the first year of pegvisomant treatment and, if unchanged, yearly thereafter.

Pegvisomant is expensive (up to $100 000 per year) and is, therefore, not usually given as initial therapy in acromegaly.

d. Successful treatment of acromegaly restores serum GH and

IGF-I to normal and often results in regression of soft-tissue enlargement, improvement in carpal tunnel syndrome and glucose tolerance, increased energy, and diminution of excessive sweating. Bony changes and osteoarthritis usually do not improve but can stabilize.

3. **Follow-up.** Following treatment, patients with acromegaly should have serum GH and IGF-I measured in a random blood specimen every 6 months for 2 or 3 years and then at yearly intervals. Radiologic evaluation of the pituitary tumor and measurement of serum Prl (if previously elevated) should be performed at similar intervals. Serum-free T_4 or free T_4 index, testosterone (in men), and cortisol secretion should be tested every 1 to 2 years. Many patients, especially those with residual GH hypersecretion, require ongoing therapy for diabetes mellitus, hypertension, cardiovascular disease, and arthritis, and periodic surveillance for colon polyps and cancer.

V. PRL-SECRETING TUMORS

A. Clinical features.

Adenomas that secrete Prl (prolactinomas) are the **most common pituitary tumors**. Hyperprolactinemia in women commonly leads to amenorrhea, with or without galactorrhea. Occasionally, women with prolactinomas have spontaneous menses but manifest infertility or a short luteal phase of the menstrual cycle. Men usually manifest decreased libido and potency or symptoms linked to the intracranial-mass lesion. **Galactorrhea is uncommon in men**, perhaps because the male breast has not been "primed" with endogenous estrogen. The manifestations of hypogonadism in both sexes appear to result principally from the inhibition of GnRH release from the hypothalamus by Prl, with resultant decreased LH and FSH secretion. Some women with Prl-secreting tumors also manifest **hirsutism** and elevated serum androgens; the **evidence for Prl stimulation of adrenal androgen production is still controversial.** Oral contraceptive use does not appear to cause prolactinomas to develop or enlarge.

B. Diagnosis

1. **Etiology.** In addition to pituitary tumors, hyperprolactinemia occurs in a wide variety of other circumstances (Table 5-6). A careful drug history is of prime importance in the investigation of hyperprolactinemia. Hypothyroidism, pregnancy, and renal failure

can be excluded by examination and simple laboratory tests.

A substantial number (15% to 46%) of patients with elevated serum Prl levels are found to have macroprolactinemia, a generally harmless condition in which monomeric Prl is bound to a large serum protein, most often an immunoglobulin. This high-molecular-weight form of Prl has a prolonged serum half-life but low biologic activity in vivo, so patients usually have few or no symptoms related to their hyperprolactinemia. A useful screening test for macroprolactinemia, available in most laboratories, involves precipitating the high-molecular-weight complex with polyethylene glycol and then assaying the remaining supernatant for monomeric Prl. If the concentration of monomeric Prl exceeds the normal range for serum Prl, further evaluation of the patient is needed.

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TABLE 5-6 Causes of Hyperprolactinemia

Altered physiologic states
- Sleep
- Stress
- Postprandial, especially in women
- Coitus
- Pregnancy, including pseudocyesis
- Nursing or nipple stimulation
- Chest wall or thoracic spinal cord lesions
- Hypoglycemia
- Hypothyroidism
- Adrenal insufficiency
- Chronic renal failure
- Cirrhosis
- Seizure
- Polycystic ovary syndrome
- Presence of high-molecular-weight prolactin with reduced bioactivity (macroprolactinemia)

Medications
- Phenothiazines
- Butyrophenones (e.g., haloperidol)
- Thioxanthenes (e.g., thiothixene)
- Buspirone
- Olanzapine
- Risperidone and paliperidone
- Ziprasidone

- Asenapine
- Metoclopramide
- Domperidone
- Sulpiride
- Labetalol
- Monoamine oxidase inhibitors
- Amoxapine
- Reserpine
- *α*-Methyldopa
- Intravenous cimetidine
- Estrogens
- Opiates
- Verapamil

Decreased delivery of prolactin-inhibiting factor to pituitary

- Pressure on pituitary stalk by sellar or parasellar mass
- Stalk section
- Hypothalamic destruction

Prolactin-secreting pituitary tumors

Ectopic secretion of prolactin by nonpituitary tumors (rare)

Idiopathic

2. **Radiologic studies** are used to separate patients with pituitary or hypothalamic lesions from those with presumed "functional" hyperprolactinemia. MRI can reveal an intrasellar or a suprasellar mass.
3. **Laboratory studies.** It is useful to obtain three separate or pooled determinations of serum Prl to account for spontaneous or stress-induced fluctuations in the hormone level. A serum Prl level persistently >200 ng/mL is almost always associated with a pituitary tumor (normal male levels are <15 ng/mL in most laboratories, and normal female levels are <25 ng/mL). Because the serum Prl p. 65p. 66level is roughly proportional to the mass of the tumor, small tumors can cause mild elevations of serum Prl similar to values commonly seen with hyperprolactinemia from other causes (e.g., 30 to 50 ng/mL).

C. Treatment

1. **Medical therapy** with dopamine agonists is the treatment of choice for many patients with Prl-secreting tumors. Ergot derivatives, such as **bromocriptine** and **cabergoline**, are potent suppressors of Prl secretion; they promptly lower serum Prl,

abolish galactorrhea, and restore normal gonadal function in most patients with hyperprolactinemia from any cause. Bromocriptine and cabergoline also cause anatomic shrinkage of prolactinomas in 60% to 80% of patients, although often this is incomplete. These drugs can thus obviate the need for pituitary surgery or, by partially shrinking large tumors, make surgery easier.

2. **Ablative therapy,** either surgical or radiologic, is no longer the preferred primary mode of treatment for many patients. Because the beneficial effects of radiotherapy are gradual and can require years for full expression, this form of treatment has not been favored for the typical patient with a prolactinoma (i.e., a young woman desiring fertility). Although selective transsphenoidal adenomectomy can be achieved in many patients with microadenomas, a substantial number of such patients (~20%) experience recurrent hyperprolactinemia within 5 years postoperatively; even the initial "cure" rate is low in patients with macroadenoma (~30%).
3. Initial concerns regarding the effects of **bromocriptine** use during **pregnancy** have been resolved by the finding that to date, there has been **no evidence of an increase in spontaneous abortions, stillbirths, or fetal anomalies**. Although more limited experience suggests that cabergoline is also safe during pregnancy, bromocriptine is generally preferred because more extensive data support its use. Because bromocriptine is usually discontinued once pregnancy is confirmed, there is also the possibility of renewed tumor growth during gestation. Although increased estrogen production during pregnancy does induce pituitary lactotrope hyperplasia, the incidence of clinically significant growth of small prolactinomas during pregnancy appears to be low (~2% to 3%). However, patients with macroadenomas have a somewhat higher risk of complications; those who experience significant tumor growth during pregnancy, with headaches and visual-field problems, can be treated with early delivery or with reinstitution of bromocriptine during gestation, if necessary.

   Thus, women with microprolactinomas who wish to become pregnant can do so, as long as the patient has a clear understanding that there is a small but finite risk of significant tumor growth during pregnancy. The prophylactic use of pituitary radiotherapy

prior to conception does not seem warranted in patients with microadenomas but might be useful in patients with large tumors. Radiotherapy does not cause impairment of the subsequent response to bromocriptine.

4. **Bromocriptine** is usually begun at a low dosage (1.25 to 2.5 mg per day, usually at bedtime with a snack, to minimize nausea and orthostatic hypotension), with increments of 1.25 or 2.5 mg every 3 or 4 days until a total dosage of 5 to 10 mg per day is reached (given in two or three divided doses with meals) or serum Prl is normalized. Some patients require larger doses.

   Cabergoline is usually initiated at 0.25 mg once a week and increased as needed to 0.5 mg once or twice a week; higher doses may be given, if necessary.

   Dopamine agonist therapy should be cautiously reduced every 2 to 3 years to assess the need for continued therapy. Recent studies suggest that about 50% of patients appear to be cured of hyperprolactinemia after several years of treatment, particularly patients with microadenoma who show complete disappearance of the tumor on cabergoline therapy.
5. In men with prolactinomas or in women who do not desire fertility, either radiotherapy or surgery may also be used (Table 5-5). **In men, decreased libido and impotence resulting from hyperprolactinemia** may not be fully reversed by testosterone administration; these patients may also require lowering Prl to normal by medication or other modalities. Patients with Prl-secreting tumors should receive follow-up as outlined for acromegaly (see Section IV.C).

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VI. TSH-SECRETING TUMORS

TSH-secreting pituitary adenomas are uncommon, accounting for <2% of pituitary tumors. Typically, patients with such tumors demonstrate hyperthyroidism with detectable or elevated serum TSH. Serum TSH often shows little response to TRH (see Chapter 39); serum levels of glycoprotein hormone α subunit and the molar ratio of α subunit to TSH are often elevated. About one third of TSH-secreting tumors produce additional hormones, generally GH or Prl. Tumor ablation by **surgery or radiation** has been the preferred treatment; many patients respond to

octreotide or lanreotide with a decrease in serum TSH and some with tumor shrinkage, but only a **few respond to dopamine agonists**.

VII. GONADOTROPIN-SECRETING TUMORS

In recent years, it has been recognized that most clinically nonfunctioning pituitary tumors actually synthesize and secrete LH, FSH, or the subunits (α or β) of these glycoprotein hormones. These tumors are **usually large macroadenomas** when they are discovered; headaches, visual changes, and, occasionally, hypopituitarism are the typical presenting features. Testicular enlargement has been observed in a few men with FSH-secreting tumors. Serum FSH and, occasionally, LH concentrations are elevated in some cases but more often are normal; serum **LH can rise in response to IV TRH, a finding that is not observed in normal individuals**. The primary treatment is surgical, frequently with adjunctive radiotherapy. Gonadotropin hypersecretion has been suppressed by the administration of a GnRH antagonist (Nal-glu GnRH) in a few cases, but with no effect on tumor size. In a few patients, partial tumor shrinkage has been achieved with somatostatin analogs or dopamine agonist administration.

VIII. ACTH-SECRETING TUMORS

The majority of patients with pituitary-dependent Cushing syndrome (Cushing disease and bilateral adrenal hyperplasia) appear to have small (<10 mm) ACTH-secreting pituitary tumors as the cause of their hypercortisolism. Many are cured by selective transsphenoidal adenomectomy. In patients with Cushing disease, bilateral adrenalectomy without therapy directed at the pituitary can lead to progressive enlargement of the pituitary tumor, accompanied by intense hyperpigmentation (Nelson syndrome) in 5% to 10% of cases. This presumably occurs because physiologic doses of replacement glucocorticoids exert an inadequate restraining feedback effect on the preexisting tumor. The ACTH-secreting tumors of Nelson syndrome can behave aggressively and can be difficult to extirpate surgically. For this reason, the best treatment is prevention, consisting of therapy for Cushing disease directed primarily at the pituitary rather than the adrenal. The somatostatin analog, **pasireotide**, can be given to patients with Cushing disease, with about a 35% rate of normalization of cortisol production. Occasionally, patients with ACTH-secreting tumors respond to dopamine agonists or cyproheptadine.

IX. PITUITARY HYPERPLASIA

Patients with untreated primary endocrine end-organ failure (e.g., of the thyroid or gonads) manifest hypersecretion of the appropriate tropic hormone(s) (TSH, LH, and FSH). In some cases, long-standing hormonal hypersecretion is accompanied by sufficient hyperplasia of the corresponding pituitary cells to produce pituitary and sellar enlargement. It is important to recognize this condition to avoid unwarranted investigation and treatment for a presumed pituitary neoplasm. The elevated pituitary hormone level readily returns to normal following replacement of end-organ hormones (T_4 or gonadal steroid), and the pituitary will return to a normal size.

X. EMPTY SELLA SYNDROME

A. Pathogenesis. When the pituitary gland does not fill the sella turcica, the remaining space is often occupied by CSF, as an extension of the subarachnoid space; such a situation has been called an **empty sella**. The sella can also be enlarged. An empty sella can arise in two ways.

1. A secondary empty sella is found following infarction, shrinkage (e.g., by bromocriptine), or destruction (by disease, surgery, or radiation) of a hyperplastic p. 67p. 68or adenomatous pituitary. In this case, any sellar enlargement was presumably caused by initial expansion of the pituitary tumor. The remaining pituitary can function normally or show residual impairment related to the primary pathologic process or its therapy.
2. More often, an empty sella is found without evidence of preexisting tumor. In this situation, termed the **primary empty sella**, it is believed that a congenitally incomplete diaphragma sellae (seen in 10% to 40% of normal persons) allows CSF to enter the sella. Normal pulsatile CSF pressures then compress the pituitary and may gradually expand the sella turcica. If intracranial pressure is elevated (e.g., in pseudotumor cerebri), sellar enlargement is more likely to occur. The primary empty sella is most often found in obese, middle-aged women, perhaps because these individuals more commonly have increased CSF pressure.

   Pituitary function is usually normal in patients with the primary empty sella; a minority of patients demonstrates diminished secretion of gonadotropins, GH, or other pituitary

hormones, but decreased GH might be a result of obesity rather than pituitary dysfunction. Hypopituitarism and hyperprolactinemia can occur with the primary empty sella, probably caused by compression or kinking of the pituitary stalk or portal system capillaries with resultant decreased delivery of hypothalamic releasing hormones to the pituitary.

B. Diagnosis. Many cases of empty sella are now detected as an incidental finding during the performance of CT or MRI for other indications; in a few patients, an enlarged sella turcica is found on routine skull radiographs performed for sinusitis, head trauma, or other reasons. Demonstration of CSF within the sella is readily made on MRI or CT; the pituitary gland is usually seen compressed against the posterior or inferior wall of the sella. Endocrine investigation of patients with suspected primary empty sella should be kept to a minimum. In a patient with no endocrine signs or symptoms, measurement of serum Prl, free T_4 or free T_4 index, and testosterone (in men) should be sufficient; patients with endocrine symptoms or with a history suggesting a prior pituitary disorder may require a more detailed evaluation.

C. Treatment. Usually, no treatment other than reassurance is required for patients with a primary empty sella. Hormone replacement might occasionally be needed but is more commonly required in patients with a secondary empty sella related to a previous pituitary tumor.

Rarely, visual-field defects may occur in patients with the empty sella syndrome; although the cause is not always clear, it may sometimes be a result of herniation of the optic chiasm into the sella. CSF rhinorrhea facilitated by openings in bony sutures of the sellar floor may also occur. These two rare complications are the only indications for surgery in patients with a primary empty sella. Management of residual pituitary tumor may be necessary in patients with a secondary empty sella.

XI. CRANIOPHARYNGIOMA

Craniopharyngiomas are tumors of developmental origin, arising from the Rathke pouch, but may be clinically unrecognized for many years. There are two peaks of incidence: one in childhood and one in late middle-aged/elderly individuals. **About 55% to 60% of craniopharyngiomas are predominantly cystic**, 15% are solid, and 25% to 30% are combined. The tumor originates above the sella; as it

enlarges, pressure is exerted on the optic chiasm, the hypothalamus, and the pituitary, leading to elevated intracranial pressure, visual defects, endocrine hypofunction (e.g., GH deficiency in children), hyperprolactinemia, and mental changes. Routine skull radiographs can show enlargement or erosion of the sella; 80% of children and 40% of adults have grossly visible suprasellar or intrasellar calcification. The tumor is usually well defined on CT or MRI. Surgery is helpful in debulking the tumor and in relieving compression of adjacent structures. Radiation therapy permanently controls the tumor in 70% to 90% of patients; surgical and radiation therapies are often combined to achieve the best results. Hormone replacement is given as needed (Table 5-3).

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6 Hypopituitarism after Traumatic Brain Injury

Norman Lavin

This chapter presents data on the epidemiology of traumatic hypopituitarism, the underlying pathophysiology, and pertinent pathologic findings with a focus on the diagnosis and management of the associated neuroendocrine disorders.

I. INTRODUCTION

The increased incidence of traumatic brain injury (TBI), often referred to as a "concussion," has attracted media and public attention. TBI is a complex pathophysiologic process affecting the brain, induced by traumatic biochemical forces that include impairment of neurologic function, neuropathologic changes, possible loss of consciousness, and possible abnormalities on neuroimaging studies. Approximately 10% of the patients lose consciousness. The most common symptoms are headache and confusion, fogginess, nausea, vomiting, poor concentration, irritability, sadness, mood swings, difficulty in sleeping, balance problems, difficulty in remembering, visual problems, drowsiness, dizziness, and forgetfulness. Post-traumatic hypopituitarism (PTHP) was recognized more than 80 years ago, but it was thought to be a rare occurrence. However, recent clinical evidence has demonstrated that TBI may frequently cause associated hypopituitarism. Any or all of the pituitary hormones may become deficient, but growth hormone and gonadotropin deficiencies appear to be the most common and have been associated with increased morbidity in this population.

Hypopituitarism should be evaluated during the acute phase as well as during the rehabilitation phase of patients. Recent literature suggests that all patients with moderate-to-severe TBI require evaluation of pituitary function, but it is believed that evaluation should be instituted even with mild TBI. Changes in pituitary hormone secretion may be observed during the acute-phase post-TBI, but it can occur at any time after the traumatic event. It is believed that PTHP is observed in about 40% of patients with a history of TBI presenting either as an isolated

deficiency or, more rarely, a complete pituitary failure. Evaluation and long-term follow-up of at least a year of all TBI patients are necessary in order to detect the occurrence of PTHP. In order to improve outcome and quality of life for these patients, an adequate replacement of pituitary hormones is absolutely necessary.

II. EPIDEMIOLOGY

One study states that at least 2 million people with documented TBI in the United States are hospitalized annually. Many more patients not hospitalized are seen as outpatients or not evaluated at all. It is also estimated by some that approximately 52 000 patients die each year as a result of this disorder. The estimated burden of long-term disability is even greater. It is also likely that TBI is underreported or underdiagnosed, particularly in those who suffer repeated head trauma in sports. Of course, there may be limited access to health care in war zones, which may further contribute to underreporting of TBI.

III. PATIENT POPULATION

TBI is a common cause of death and disability in adults, young adults, teenagers, and children with consequences ranging from physical disabilities to long-term cognitive, behavioral, psychological, and social defects. Automobile accidents, bicycle–car encounters, falls, child abuse, violence, and of course, sports injuries are the most common causes of this type of trauma. In the military, blast injuries have been recently recognized as a cause of TBI-induced hypopituitarism. The most common groups at high risk include p. 70p. 71males, young adults, children less than 5 years of age, and elderly persons over 75 years of age. Estimates of the prevalence of hypopituitarism in patients with TBI range between 15% and 68%. In another study of 800 patients 5 months after the injury, growth hormone deficiency (GHD) and gonadotropin deficiency were most prevalent, each affecting approximately 12% of patients. Adrenocorticotropic hormone (ACTH) deficiency was reported in 8%, and thyroid-stimulating hormone (TSH) deficiency was present in 4% of patients. Multiple pituitary hormone deficiencies were present in at least 8%. In some cases, recovery of pituitary function occurred, but new pituitary hormone deficiencies developed during follow-up in several patients. There are very few studies regarding the natural history of hypopituitarism several years after TBI. In a more recently published

systematic review of 66 studies of approximately 6 000 patients, the prevalence of persistent anterior pituitary hormone deficiencies was approximately 30%. In a recent prospective study of children, the prevalence of newer endocrine dysfunction was 15% at 1 month, 75% at 6 months, and 29% at 12 months. One year after TBI, 14% of the children had precocious puberty, 9% had hypothyroidism, and 5% had GHD. Additionally, the death rate increased for those who needed hospitalization compared to those individuals who were seen as outpatients.

IV. IMMEDIATE EVALUATION

Generally, the most common alterations post-TBI appear to be gonadotropin and somatotropin deficiency, followed by corticotropin and thyrotropin deficiencies. Hyperprolactinemia or hypoprolactinemia may also be present. Diabetes insipidus (DI) may be seen frequently in the early acute-phase post-TBI, as can adrenal insufficiency. Therefore, immediate pituitary hormone evaluation is essential to prevent hormonal crisis and possibly, death. In order to improve outcome and quality of life for these patients, pituitary hormone therapy is of paramount importance. Immediate evaluation should focus on Addison disease and/or DI, which can lead to immediate death. Subsequent evaluation of all hormones needs to be measured as well.

V. LONG-TERM EVALUATION

GHD has been found in a large percentage of individuals with chronic moderate-to-severe TBIs. In one study by High et al., 83 subjects with chronic TBIs were screened for hypopituitarism, and 42 patients were found to have GHD and were treated with growth hormone replacement. Compared to a control group, improvement was seen on several tests, including the dominant hand finger tapping test, Wechsler Adult Intelligence Scale 3, Information Processing Speed Index, California Verbal Learning Test 2, and the Wisconsin Card Sorting Test. This study provides preliminary evidence that some of the cognitive impairments observed in persons who are growth hormone deficient after TBI may be partially reversed with appropriate growth hormone replacement therapy.

In a study by Lieberman et al., the majority of patients with TBI (49 months postinjury) had subnormal serum levels of TSH, free T4, insulin-like growth factor 1 (IGF-1), prolactin, testosterone (in males), and cortisol deficiency. In all, 14% had GHD, and 87% had both TSH and free

T4 below the mid-normal level. Basal morning cortisol was below normal in 46% of subjects, whereas cosyntropin stimulation levels were low in 7%. Hypogonadism and hyperprolactinemia were uncommon. GHD may compound the physical and psychological complications of TBI and interfere with rehabilitation.

VI. PATHOPHYSIOLOGY

The pathophysiology of hypopituitarism include necrosis, fibrosis, infarction, and hemorrhage in the pituitary gland. There are several mechanisms, including direct injury to the hypothalamohypophyseal unit and/or its blood supply, compression of the pituitary as a result of edema, hemorrhage, or elevated intracranial pressure, trauma-related anemia, and hypotensive and/or hypoxic insults. The portal vessels passing through the diaphragma sellae are particularly susceptible to mechanical injury, compression, local parasellar brain swelling, brain hemorrhage, raised intracranial pressure, and vasospasm.

A. Acute hypopituitarism

The most important considerations postinjury is central hypoadrenalism and DI. Up to 50% of hospitalized TBI patients may develop these abnormalities. Severe p. 71p. 72anemia, hypotension, hypoxia, and hyponatremia may superimpose these hormone deficiencies. Low serum cortisol levels have been associated with increased mortality in patients with moderate-to-severe TBI. It is important to note that in contrast to Addison disease, skin *hyper*pigmentation and *hyper*kalemia are absent in patients with TBI-induced hypopituitarism who lack both ACTH and cortisol, but maintain sufficient aldosterone secretion.

1. Adrenal insufficiency

Early morning serum cortisol levels of over 18 mcg/dL generally assure sufficient function of the hypothalamic–pituitary–adrenal axis. Serum cortisol levels, however, can be influenced by abnormalities in corticosteroid-binding globulin (CBG) levels. In women taking oral estrogen or during pregnancy, CBG levels can be elevated, and in patients with acute illness and malnutrition, CBG levels may be low. It is important to note that in the acute phase of injury, cortisol levels can also be significantly suppressed by commonly used medications, including Etomidate and metabolic suppressant agents such as Pentobarbital and Propofol.

Morning cortisol levels less than 3 mcg/dL are diagnostic of adrenal insufficiency. If the values are between 3.1 and 7.9 mcg/dL, hypoadrenalism should be considered for glucocorticoid replacement. It is also important to obtain an ACTH level, because if this is low, as well as the cortisol being low, there is greater confirmation of hypothalamic or pituitary deficiency. Some suggest that all hospitalized patients with a morning serum cortisol less than 10 mcg/dL be given glucocorticoid replacement.

2. **Posterior pituitary function testing (DI)**

   DI should be suspected if the patient has polyuria (urine output over 200 mL/hour for at least 2 hours or 40 mL/kg/24 hours over 3 L/24 hours in patients of average weight) and/or hypernatremia. If patient sensoriums are altered, dehydration can ensue because they may not take adequate amounts of water or they experience hypodipsia or adipsia. Unfortunately, the presence of DI has been associated with increased mortality. If the patients manifest hypernatremia and have not received diuretics or Mannitol, the presence of inappropriately dilute urine (<700 mmol/kg) is consistent with a diagnosis of DI. The water deprivation test can differentiate central DI from nephrogenic DI or primary polydipsia. A magnetic resonance imaging (MRI) reveals an absence of the "posterior bright spot" in unenhanced T1-weighted sequences in patients with central DI and may also show stalk disruption. Pituitary imaging additionally serves to exclude a sellar mass as the cause of DI.

3. **Syndrome of inappropriate antidiuretic hormone secretion**

   Hyponatremia is common in patients with TBI and is most frequently caused by the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Consider other causes, including adrenal insufficiency, hypothyroidism, hypovolemia, volume overload states, and side effects of some medications before attributing hyponatremia to SIADH.

B. Chronic hypopituitarism (days, weeks, or months post-TBI)

A patient with central hypoadrenalism may present with fatigue, weight loss, anorexia, dizziness, and joint aches. Dynamic testing of pituitary adrenal function may not be helpful during the acute phase, but certainly is helpful in establishing the diagnosis of central hypoadrenalism several weeks after injury. Although a blunted

response to the cosyntropin stimulation test is diagnostic of adrenal insufficiency, it may take 6 to 8 weeks after TBI for patients with central hypoadrenalism to show an abnormally low cortisol response. There are other dynamic tests that can be useful during the chronic phase, including the insulin-tolerance test or the metyrapone test, but it is not as helpful or practical or even safe in acutely ill patients.

1. **Hypothyroidism**

   Central hypothyroidism is not likely to present during the acute phase (owing to the long half-life of thyroxine). In a few weeks or months, hypothyroid symptoms can occur, including fatigue, weight gain, constipation, irregular menses, cold intolerance, neurocognitive dysfunction, depression, and hyponatremia, but there is no goiter evident in contrast to patients with Hashimoto thyroiditis.

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Laboratory testing in patients with central hypothyroidism demonstrates a low free T4 level with either low or inappropriately normal serum TSH levels. T3 levels are generally maintained in the normal range. Acutely ill hospitalized patients for any reason often show abnormalities in thyroid function tests (“euthyroid sick syndrome”), which can be difficult to distinguish from true central hypothyroidism. In patients with the euthyroid sick syndrome, T3 levels are usually low, and T4 levels may also decline in the presence of critical illness. It is suggested that evaluation of thyroid function be deferred for several weeks (4 to 6 weeks) after TBI.

2. **Hypogonadism**

   The evaluation of the pituitary–gonadal axis is appropriate only during the rehabilitation phase of TBI, because acute illness injury will generally result in suppression of gonadal function. Both men and women may present with sexual dysfunction, and women with amenorrhea and hot flashes. Loss of secondary hair and bone mass may also result. To examine central hypogonadism in men, a morning serum testosterone level should be measured. Abnormal results should be confirmed by repeat testing. In premenopausal women, assess menstrual history for evaluation of hypogonadism. In both sexes, the presence of low or inappropriately normal serum gonadotropins helps to establish the diagnosis of central

hypogonadism. Some medications can suppress the gonadal axis, such as opioids and glucocorticoids.

3. **Hyperprolactinemia**

   Hyperprolactinemia may also occur in approximately 12% of patients as a consequence of hypothalamic dysfunction, stalk interruption, and/or medication side effects, and can contribute to hypogonadism.

4. **Growth hormone deficiency**

   The growth hormone levels (IGF-1) are evaluated immediately and several months after TBI and after replacement of other pituitary deficiencies. Adult patients with GHD may present with poor stamina and exercise capacity, impaired quality of life, central adiposity, and may also develop dyslipidemia, insulin resistance, and low bone mass. Decreased memory, forgetfulness, and attention deficits are also noted. In children, there is a slowdown in growth, and TBI should be in the differential diagnosis for short stature in any child. Randomly measured serum growth hormone levels are of no diagnostic value in the assessment of hypopituitarism in children or adults. IGF-1 levels lack sensitivity in the diagnosis of GHD in adults. Unfortunately, a low IGF-1 level can also be present in patients taking oral estrogen and in those with liver disease or poorly controlled diabetes mellitus. In patients who have a low serum IGF-1 level and other pituitary hormone deficiencies, however, it is likely that they will be growth hormone deficient as well.

   a. **Growth hormone stimulation test**

      A growth hormone stimulation test is required to make the diagnosis of GHD. There are many medications used as a stimulant, including insulin, glucagon, growth hormone–releasing hormone (GhRH) plus arginine, clonidine plus arginine, arginine alone, or, occasionally, ghrelin mimetics. GhRH is not available currently, and ghrelin mimetics are not Food and Drug Administration approved. The insulin-tolerance test is contraindicated in many patients and requires close physician monitoring to ensure patient safety. The glucagon stimulation test has recently emerged as one of the preferred alternative tests to diagnose GHD in adults because of its availability, safety, lack of influence by gender, and hypothalamic cause of GHD. It is important to remember that

the glucagon stimulation test lacks specificity in the diagnosis of central hypoadrenalism in adults, because a cortisol response to glucagon administration is often low in patients without adrenal dysfunction.

5. **Pituitary imaging**

   Patients with evidence or a suspicion of hypopituitarism should undergo an MRI to exclude the presence of a sellar mass or other pituitary/hypothalamic abnormalities.

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6. **Periodic reassessment**

   a. **Adults**

      Periodic reassessment of pituitary function is recommended in patients with a history of TBI in order to detect continued deficiency, onset of new deficiency, or recovery of pituitary hormone deficiencies. It is suggested a reevaluation at 1 month, 6 months, and again at 12 months, and perhaps beyond. Long-term retesting of pituitary function may be indicated, but there are no official data to support this recommendation.

   b. **Children**

      Neuroendocrine dysfunction in children is common after TBI and can, like the adult, be persistent. Therefore, neuroendocrine evaluation should occur until at least 1 year after injury. Not all endocrine abnormalities resolve by 1 year after TBI.

VII. MEDICAL MANAGEMENT

A. Glucocorticoid (see Table 6-1)

Glucocorticoid replacement is critical in patients with known or suspected central hypoadrenalism. These patients should receive glucocorticoids in stress doses (such as hydrocortisone 100 mg intravenously [IV] every 6 to 8 hours) even without absolute evidence of the diagnosis. Alternatively, hydrocortisone 15 to 25 mg can be given daily in divided doses or prednisone 2.5 to 5 mg daily with titration based on clinical criteria. Because the aldosterone secretion is preserved, mineralocorticoid replacement is not indicated.

1. Stress doses of hydrocortisone should be given for fever >100.5°F, vomiting, diarrhea, physical trauma (e.g., broken bone, concussion, organ injury, etc.), and/or lethargy.
2. Signs of impending adrenal crisis include, but are not limited to,

weakness, dizziness, nausea, vomiting, hypotension, hypoglycemia, pallor, and/or lethargy.

B. Diabetes insipidus

Central DI can be treated with desmopressin. In patients who are hospitalized, desmopressin should be administered on demand (1 to 2 mcg subsequently or IV every 8 to 12 hours as needed) because central DI is often transient. Monitoring of fluid p. 74p. 75balance and serum sodium is required to avoid hyponatremia. If the patient is stable, he or she can be treated with oral or nasal desmopressin (10 to 20 mcg nasally or 100 to 400 mcg orally administered every 8 to 24 hours). The goal is comfortable sleep without polyuria or excessive thirst while maintaining eunatremia. Patients with adipsia or hypodipsia require careful monitoring of fluid balance and sodium levels, and generally need to drink fluids on schedule to avoid abnormalities of salt and water homeostasis.

TABLE 6-1 Adrenal Insufficiency

Immediate treatment after drawing STAT electrolytes, glucose, and point-of-care glucose should consist of:

1. Treatment of hypoglycemia, if present
2. IV fluids: D5 normal saline at 20 mL/kg for 1 hr and then continue fluid replacement
3. Solu-Cortef by IV bolus (or other parenteral hydrocortisone formulation) (as soon as IV is started)—can give IM if IV access is a problem:
   - 25 mg for children 0–3 yr of age
   - 50 mg for children >3–10 yr of age
   - 100 mg for children >10 yr of age, teens, and adults
4. Solu-Cortef (or other parenteral hydrocortisone formulation) should then be continued in the hospitalized patient either as a continuous IV drip or in 4 divided doses IV/IM for the duration of the stress:
   - 25 mg/d for children 0–3 yr
   - 50 mg/d for children >3–10 yr
   - 100 mg/d for children >10 yr, teens, and adults

This document was developed and approved by the Pediatric Endocrine Society Board of Directors, November 2015.
IM, intramuscular; IV, intravenous.

C. Central hypothyroidism

Begin treatment with Levothyroxine at a dose of approximately 1.6 mcg/kg/day. If the patient is older and/or has cardiovascular disease or mild hypothyroidism, start with a lower dose. To avoid precipitating adrenal crisis, Levothyroxine replacement should begin only after adrenal function has normalized. Free T4 levels (not TSH) should be monitored at 6 weeks after starting Levothyroxine replacement with a goal of maintaining the values in the middle of the normal range.

D. Central hypogonadism

In men, testosterone replacement can be administered as transdermal gels, patches, buccal mucosa system, subcutaneous pellets, or intramuscular injections. Women of premenopausal age who have central hypogonadism can receive estrogen and progestin replacement (if they have an intact uterus) or estrogen replacement only (after hysterectomy), if not contraindicated based on careful gynecologic evaluation and follow-up.

E. Growth hormone deficiency

Growth hormone replacement may be implemented in GHD patients after other pituitary hormone deficiencies have been addressed. The studies show a possible benefit of growth hormone replacement on cognition and quality of life in patients with TBI. It is not clear whether there is a full neurocognitive improvement in this population. Growth hormone replacement may also improve body composition (increasing muscle and bone mass and decreasing visceral adiposity), cardiovascular risk factors (including serum lipids and C-reactive protein), and exercise capacity. Serum IGF-1 levels are helpful to titrate growth hormone doses (targeting IGF-1 levels between 0 and +1 standard deviation score). Hyperglycemia may occur as a direct effect of the growth hormone and glucose homeostasis, particularly in obese patients. Therefore, glycemic monitoring is advisable in patients receiving growth hormone replacement. Once growth hormone replacement has been initiated, monitoring of latent hypoadrenalism, alteration of Levothyroxine dose, or a decrease in requirements for desmopressin is important.

VIII. CONCLUSION

It has been shown over the past several years that TBI-induced hypopituitarism is not uncommon and is associated with increased morbidity and mortality and that includes patients with even mild or repetitive TBI. A thorough systematic evaluation of pituitary function,

therefore, is advisable in patients with moderate-to-severe TBI as well as many patients with mild TBI. By replacing pituitary hormones, we can improve patient outcome, thereby improving quality of life. Once again, immediately following the TBI during hospitalization, the focus should be on monitoring for adrenal insufficiency, DI, and SIADH. In the chronic phase, the entire anterior and posterior pituitary function should be evaluated, including assessments for GHD and hypogonadism, which appear to be the most common, as well as assessments of adrenal and thyroid function.

Further studies are forthcoming, and hopefully improvement in evaluation and treatment is evident.

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7 Prolactin

Ignacio Bernabeu and Felipe F. Casanueva

I. PROLACTIN SECRETION

Prolactin (Prl) is a 198 amino acid protein (23 kDa) mainly secreted by the pituitary lactotrophs and involved in lactation, luteal function, and reproduction as well as multiple additional homeostatic roles. Estrogens, nipple stimulation during breastfeeding, and physical or psychological stress stimulate Prl secretion. Some hypothalamic factors (thyrotropin-releasing hormone, oxytocin, and neurotensin) promote Prl secretion; however, the **main hypothalamic influence over Prl secretion** is inhibitory and exerted by **dopamine**. Dopamine is produced in the arcuate nucleus of the hypothalamus and transported by the hypothalamic hypophysial portal system to the pituitary gland, which impinges on specific dopamine receptors (D_2) on lactotrophs cells inhibiting Prl secretion and release and reducing lactotroph proliferation.

II. HYPERPROLACTINEMIA

Hyperprolactinemia is diagnosed when serum Prl concentration is above the normal upper range (usually 20 ng/mL for most laboratories). Dynamic tests are not needed for diagnosis.

III. CAUSES OF HYPERPROLACTINEMIA

Major physiologic and pathologic causes of hyperprolactinemia are outlined in Table 7-1 and Figure 7-1 (columns A and B). According to the presence or absence of symptoms and with the degree of hyperprolactinemia, we can distinguish the following situations:

A. Asymptomatic patients with slight or mild hyperprolactinemia (20 to 40 ng/mL)

In these cases, once physiologic causes have been excluded, a traumatic venipuncture, pulsatile Prl secretion, and the presence of macroprolactinemia must be ruled out.

In the first two cases, venous sampling should be repeated on another day. A venous catheter should be inserted to obtain two or three blood samples at 15 to 20 minute intervals to avoid the effect of

venipuncture stress and Prl pulsatility.

Macroprolactin is a larger size (150 to 170 kDa) Prl with decreased clearance, producing pseudohyperprolactinemia without any clinical significance. To avoid this misdiagnosis and unnecessary studies and treatments, the patient's serum must be pretreated with polyethylene glycol to precipitate macroprolactin before performing a Prl immunoassay.

B. Symptomatic patients with mild or moderate hyperprolactinemia (20 to 100 ng/mL)

The most frequent causes of this degree of hyperprolactinemia are the use of some drugs (antipsychotics, oral contraceptives, antidepressants, gastric motility drugs, or antiemetics), the coexistence of chronic renal failure, or primary hypothyroidism.

Additionally, all sellar and parasellar masses may produce mild or moderate hyperprolactinemia by decreasing the dopamine-inhibitory effect over Prl secretion either by neuronal (dopaminergic) hypothalamic damage or by pituitary stalk compression.

C. Symptomatic patients with more severe hyperprolactinemia (>100 ng/mL)

This situation could be related to specific drugs (risperidone, phenothiazines, sulpiride, and metoclopramide) that can produce a greater increase in Prl level (even >200 ng/mL), with the coexistence of at least two of the previously described situations (i.e., chronic renal failure or antidepressants use) or may be produced by a lactotroph adenoma.

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TABLE 7-1 Causes of Hyperprolactinemia

I. Physiologic

Pregnancy, lactation, coitus, sleep, physical or psychological stress, exercise

II. Pathologic

a) Increase in hormonal and neural factor promoting Prl secretion

Thyrotropin-releasing hormone (TRH): Primary hypothyroidism

Estrogens: Oral contraceptives

Neural stimulus: Chest wall injuries (thoracic herpes zoster)

b) Loss of dopamine suppressive effect on Prl secretion

Dopamine deficiency

- Hypothalamic diseases: Tumors, cyst, vascular malformations, infiltrative and inflammatory processes, surgery, trauma (craniopharyngiomas, germinona, metastases, sarcoidosis, Rathke cyst)
- Drugs: α-Methyldopa, reserpine

Pituitary stalk disruption

- Sellar and parasellar masses distorting the pituitary stalk hampering the transport of dopamine to the pituitary (nonfunctioning pituitary adenomas, sellar and suprasellar masses, hypophysitis, empty sella syndrome)
- Pituitary stalk interruption syndrome (traumatic brain injury, irradiation, surgery)

Reduced lactotroph sensitivity to dopamine

- Drugs blocking dopamine receptors on lactotrophs cells (dopamine antagonist): Chlorpromazine, haloperidol, phenothiazines, risperidone, paliperidone, metoclopramide, domperidone, sulpiride

c) Prl-secreting pituitary adenoma

Pituitary micro- and macroprolactinoma (sporadic/isolated/familial)

d) Other causes

Decreased clearance of Prl: Chronic renal failure, macroprolactinemia

Other drugs acting by mechanism not well understood: Tricyclic antidepressants (clomipramine); selective serotonin reuptake inhibitors; antihypertensives (verapamil); opioid analgesics, methadone, morphine

Familial hyperprolactinemia (loss-of-function mutation in the prolactin receptor gene)

Idiopathic hyperprolactinemia

Prl, prolactin.

IV. LACTOTROPH ADENOMAS

Lactotroph adenomas or prolactinomas are a common type of pituitary adenoma affecting more women (60%) than men. Prolactinoma may be sporadic or familial; isolated or associated with other endocrine diseases in the context of a “familial-isolated pituitary adenoma” syndrome; or as a part of multiple endocrine neoplasia type I. In premenopausal women, prolactinomas are usually small tumors (microadenomas) with an indolent or a benign clinical course, good response to treatment, and a very low risk of tumor progression. By contrast, both men and postmenopausal women have larger tumors (macroadenomas) with more aggressive behavior and poorer response to treatments. Some specific molecular characteristics recently described, may explain these different clinical courses. Giant and malignant prolactinomas are very infrequent (Figs. 7-1D (top) and 7-2).

V. IDIOPATHIC HYPERPROLACTINEMIA

The term **“idiopathic hyperprolactinemia”** is used for those cases (in general with mild or moderate hyperprolactinemia) in which no specific cause can be found after a complete diagnostic evaluation. Probably, many patients with idiopathic hyperprolactinemia have nonvisible and nonprogressive microprolactinoma on magnetic resonance imaging (MRI).

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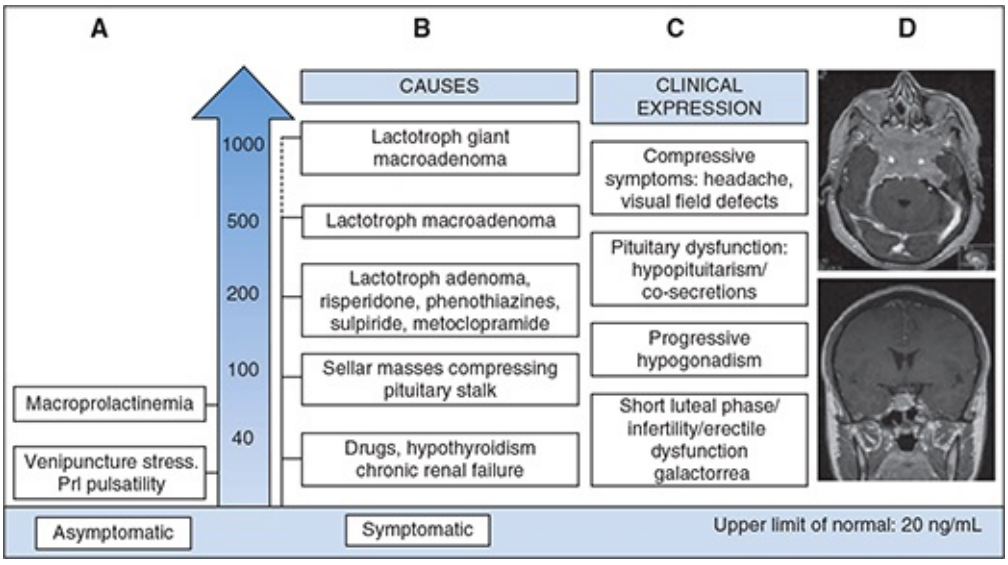

Figure 7-1. Representative diagram about causes and clinical expression of hyperprolactinemia. Asymptomatic patients with mild hyperprolactinemia **(A)**; symptomatic patient, most frequent causes according to prolactin level **(B)**; clinical expression **(C)**; and upper figure giant macroprolactinoma with wide skill base invasion **(D)**. Lower image shows noninvasive macroprolactinoma.

VI. CLINICAL PRESENTATION

Hyperprolactinemia may produce infertility, hypogonadism, and galactorrea. Additionally, in some cases of lactotroph macroadenoma, compressive symptoms and pituitary hormone deficiencies or cohypersecretion (Fig. 7-1C) may be evident.

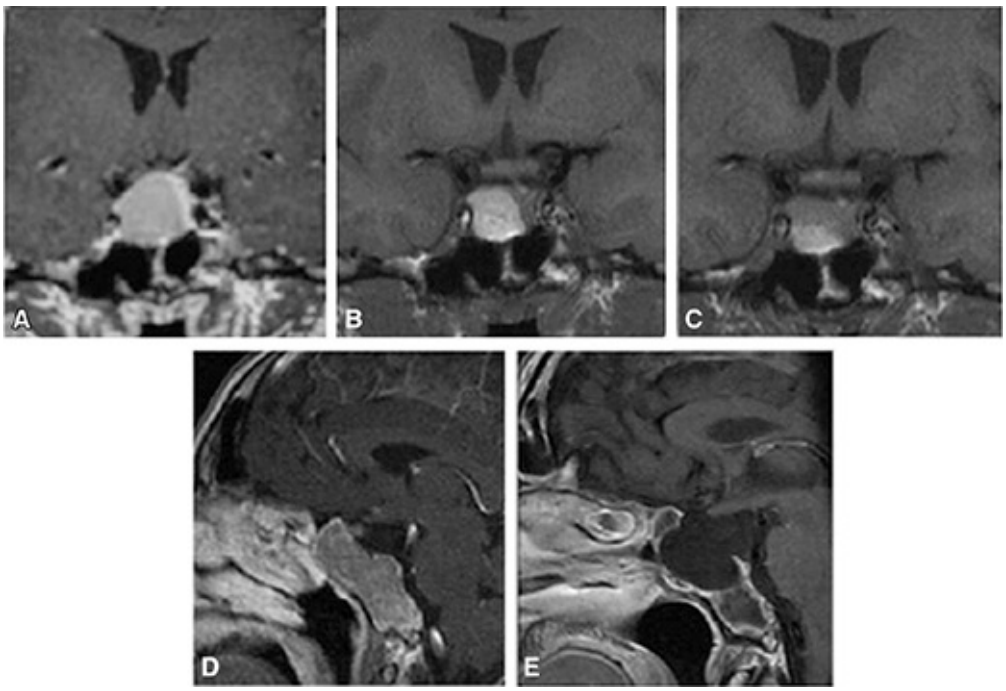

Figure 7-2. Tumor response to cabergoline treatment. Macroprolactinoma with suprasellar extension at baseline **(A)** and after 6 **(B)** and 12 **(C)** months of treatment, reduction of tumor size and signal changes suggesting tumor necrosis. Giant macroprolactinoma with clivus invasion at baseline **(D)** and tumor shrinkage after 18 months of treatment with cabergoline **(E)**.

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A. Gonadal function

Hyperprolactinemia produces hypogonadotropic hypogonadism by inhibition of gonadotropin-releasing hormone pulsatility and luteinizing hormone/follicle-stimulating hormone secretion and by a direct suppression of gonadal steroidogenesis.

In premenopausal women, slight hyperprolactinemia (20 to 50 ng/mL) may produce progesterone insufficiency and a short luteal phase in the menstrual cycle associated with infertility even without menstrual cycle irregularities. As Prl levels increase, the clinical expression becomes more evident with oligomenorrhea, amenorrhea, or even overt hypogonadism, with hypoestrogenism (without breast atrophy), amenorrhea, hot flashes, and vaginal dryness.

Men with hyperprolactinemia usually have decreased libido and erectile dysfunction with low testosterone levels and changes in sperm analysis with infertility. Local compressive symptoms derived from pituitary adenoma are, however, the most common reason for medical consultation.

As a consequence of hypogonadism, bone density is reduced in approximately 25% of patients with hyperprolactinemia.

B. Galactorrea

Galactorrea is a discharge of milk from the breast at any time other than the peripartum or postpartum period. Galactorrea is a nonspecific sign that occurs in approximately 70% of hyperprolactinemic premenopausal women and is unusual (~30%) in men and postmenopausal women.

C. Pituitary function and compressive symptoms

Lactotroph adenomas can produce hypopituitarism by pituitary stalk compression or by destruction of normal pituitary tissue. Depending on size and extensions of the pituitary adenoma, classic compressive symptoms (headache, visual defects, hydrocephalus, liquorrhea [loss of cerebrospinal fluid through the nose], ophthalmoplegia, etc.) may be present. Occasionally, pituitary apoplexy may develop.

VII. EVALUATION AND DIAGNOSIS

A. The evaluation of serum Prl level is required in all men and women with infertility, symptoms of hypogonadism (including irregular menses in women), galactorrea, and in children with delayed puberty. Obviously, serum Prl levels must be measured in all patients with sellar or parasellar masses.

B. In **asymptomatic patients with mild hyperprolactinemia**, medical history and physical examination and biochemical studies (Prl, thyroid, and renal function tests) can easily identify most causes, including physiologic causes, venipuncture stress, Prl pulsatility, macroprolactin, medications, chronic renal failure, or hypothyroidism (Fig. 7-1).

C. In **symptomatic patients with suspected drug-induced hyperprolactinemia,** a new serum Prl measurement after 3 days without the involved drug (temporary drug discontinuation or change of treatment if this change is not contraindicated) should be done to confirm the drug causality.

D. If drug causality cannot be clarified (use of antipsychotic drug that cannot be discontinued or when the onset of the hyperprolactinemia does not coincide with therapy initiation), it is advisable to perform an MRI study to rule out the presence of hypothalamic-pituitary disease. This is specially recommended if Prl levels are greater than 100 ng/mL for most medications and greater

than 200 ng/mL for patients treated with risperidone, phenothiazines, or sulpiride.

E. In all cases with **nonphysiologic "any degree" hyperprolactinemia without an apparent cause,** a pituitary MRI should be performed.

1. The existence of visual field defects in medical examination or a Prl level above **200 ng/mL measured by current enzymatic assays** suggests **prolactinomas**/macroprolactinoma. In general, Prl secretion is proportional to the size of the pituitary adenoma. However, small microprolactinomas and cystic or undifferentiated macroprolactinomas may be associated with Prl values less than 200 ng/mL. Moreover, the "**hook effect**" can occur (an artifact in the immunoradiometric assay for Prl), which can produce a falsely low Prl value in patients with macroprolactinoma and very high Prl levels. When suspected, this artifact can be avoided by **repeating the assay using a 1:100 dilution of serum**.

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2. MRIs can identify **sellar and parasellar masses** (nonfunctioning pituitary adenomas, craniopharyngiomas, lymphocytic, or granulomatous diseases) causing mild hyperprolactinemia (in general, lower than 100 ng/mL), by diminishing the dopaminergic tone. Although these findings suggest a tumor different from a lactotroph adenoma (and therefore a candidate for surgical treatment), we must keep in mind the "hook effect" and the possibility of an undifferentiated or a cystic lactotroph adenoma.

F. In all patients with hypothalamic-pituitary masses, a complete evaluation of **pituitary function** (hypopituitarism and growth hormone cosecretion) and an **ophthalmologic study** is warranted.

G. When an MRI shows a normal hypothalamic-pituitary region and there are no other obvious causes of hyperprolactinemia, the diagnosis of **idiopathic hyperprolactinemia** is made. Most of these cases may be related with small (MRI nonvisible) microadenomas that will become visible during the follow-up, annually, in fewer than 10%. By contrast, spontaneous normalization of Prl levels may occur in **approximately 30%** of cases with idiopathic hyperprolactinemia.

VIII. TREATMENT

A. General concepts

1. The optimal treatment of hyperprolactinemia involves **correcting its cause** when possible. This can be easy in some cases (hypothyroidism or hyperprolactinemia induced by some drugs) but may be impossible in situations, such as in chronic renal failure or antipsychotic treatments.
2. **Dopamine agonists** are the first-line treatment for patients with lactotroph microadenomas or macroadenomas. Medical treatment can normalize Prl levels, restore gonadal and sexual function, and control or reduce tumor size.
3. Dopamine agonists may reduce hyperprolactinemia caused by decreased dopaminergic tone secondary to sellar and parasellar masses, such as craniopharyngiomas or nonfunctioning pituitary adenomas. Because dopamine agonists are not effective treatments for these tumors, surgery must be indicated as first-line therapy.

B. Medical treatment

Dopamine agonists act like native dopamine, interacting with specific dopamine receptors on lactotroph cells–inhibiting Prl synthesis and release and reducing lactotroph cell proliferation. Several medications are available:

1. **Bromocriptine** was the first dopamine agonist available. The usual initial daily dose is 0.625 to 1.25 mg (with a snack) at bedtime, increasing 1.25 mg every 2 to 3 days until reaching a final dose between 5 and 15 mg daily divided in 2 to 3 doses. Bromocriptine normalizes Prl levels in approximately **75% of cases** and reduces tumor size in at least 65% of patients. Poor tolerance, nausea, vomiting, nasal stuffiness, and orthostatic hypotension are the more frequent adverse events. Recently, bromocriptine use has been associated with subclinical **heart valvular fibrosis**. Bromocriptine can be safely used in the unusual cases of tumor growth during pregnancy.
2. **Cabergoline** is currently the **first choice drug** for hyperprolactinemia. Cabergoline has a long biologic half-life allowing a more convenient administration (2 to 3 doses every week), has better tolerability and compliance record, and has greater efficacy than bromocriptine. The initial dose is 0.25 mg **once or twice per week**, followed by increasing the dose on a weekly basis. The final usual doses are between 0.25 and 3 mg per week. Cabergoline normalizes Prl levels in approximately 90% of

cases and reduces tumor size in 90% of patients. Adverse events are similar to those described for bromocriptine, but less severe. Cabergoline may be used in patients intolerant or resistant to bromocriptine. Cabergoline is an agonist of the serotonin receptor 5HT2B and at doses used for Parkinson disease (3 mg/day) can promote tricuspid and pulmonary valve insufficiencies. However, the association between cabergoline at lower dose (such doses used for endocrine diseases) and valvular heart disease has not been observed in several studies. A basal echocardiography at baseline is not mandatory. Echocardiography p. 81p. 82may be necessary to assess for valvular abnormalities during follow-up in those patients who require very high cabergoline doses for prolonged periods.

3. **Other dopamine agonist:** Quinagolide, pergolide, and lisuride are less commonly used dopamine agonists and do not seem to offer any advantage.

C. Goals and follow-up of medical treatment

1. The **main goals of medical treatment** are to normalize Prl levels and reduce tumor size. Although not proven, there is a common impression that the dose of dopamine agonist required to achieve reduction in tumor size may be higher than the dose necessary to normalize serum Prl. In this case, once tumor shrinkage has been achieved, the dopamine agonist dose may be decreased to a minimum needed to maintain serum Prl in the normal range.
2. Follow-up **Prl measurements** must be obtained frequently and according to biochemical response. In patients with macroprolactinoma, it is recommended that **an MRI study** be performed at 3 to 4 months of treatment and regularly thereafter, depending on the clinical and biochemical response. Pituitary functions, visual field, and bone mineral density must be checked regularly.
3. **Discontinuation of dopamine agonist.** In some patients, dopamine agonist treatment can be discontinued. This may be considered in patients (a) treated at least 2 years; (b) who have reduced the minimum dose of dopamine agonist maintaining normal serum Prl; (c) without visible tumor in the MRI or with a great reduction in tumor size; (d) with noninvasive remnant tumor;

and (e) with the upper limit of the pituitary adenoma located more than 5 mm from the optic chiasm. In these cases, the recurrence rate ranges from 26% to 69%, thus requiring a close monitoring which includes serum Prl measurement every 3 months for the first year and annually thereafter and an MRI if Prl levels increased again.

D. Surgery

1. Transsphenoidal surgery is indicated in patients with lactotroph adenomas and pituitary apoplexy or in the presence of severe and acute compressive neurologic symptoms. Surgery is also indicated in patients intolerant or resistant to a dopamine agonist, or those with symptomatic hyperprolactinemia or with visual field defects not responding to medical treatment. Surgery may also be considered in women with giant prolactinomas who wish to become pregnant in the near future.
2. Surgical treatment could also be offered to patients with small microprolactinomas. The success rate is about 75% from the most experienced neurosurgeons. Recurrence of hyperprolactinemia after initial normalization occurs in about 20% of patients. The success rate in macroprolactinomas is much lower.

E. Radiotherapy

External radiation is associated with significant adverse effects (hypopituitarism, visual damage, neuropsychological dysfunction, and increased risks of stroke and secondary tumors). Radiotherapy is reserved for patients resistant to dopamine agonist treatment and not cured by surgery, or for those very rare cases of aggressive malignant prolactinomas.

IX. TREATMENT IN SPECIFIC SITUATIONS

A. Drug-induced hyperprolactinemia

Asymptomatic patients do not require treatment. In symptomatic cases, the causative drug should be suspended or replaced when possible, always with the approval of the physician/psychiatrist responsible for the patient. Aripiprazole is an antipsychotic drug with dopamine agonist and antagonist properties and dampens hyperprolactinemia when added to other antipsychotic treatments. When these options are not possible, dopamine agonists may be considered. However, its efficacy in this clinical setting is more limited, and their use in psychiatric patients has been associated with worsening of psychosis

by counteracting the dopamine antagonist effect of antipsychotics drugs. Therefore, in some cases, the best treatment option is the use of gonadal steroids to correct symptoms related with long-term hypogonadism.

B. Idiopathic hyperprolactinemia and microprolactinoma

Asymptomatic patients do not require specific treatment. Patients with isolated menstrual cycle abnormalities may be treated with oral contraceptives or dopamine p. 82p. 83agonists. More symptomatic patients must be treated with dopamine agonists. After at least 2 years of treatment, dopamine agonist discontinuation may be considered in some cases. In selected cases and centers, surgical treatment may be offered to symptomatic microprolactinoma patients.

C. Macroprolactinoma

All cases must be medically treated to reduce Prl levels, resolve galactorrea, restore fertility, and gonadal and sexual function as well as decrease tumor size and compressive symptoms. Macroprolactinoma patients with visual field defects must not be considered as a neurosurgical emergency, because **dopamine agonists restore visual field defects** to an extent similar to that is produced by surgical decompression. Patients with acute or progressive compressive neurologic symptoms or pituitary apoplexy will require surgical treatment.

D. Prolactinoma resistant to dopamine agonist

A small group of patients diagnosed with prolactinoma (10%) are resistant to dopamine agonist treatment: they do not achieve a normal Prl level, and they fail to achieve a 50% reduction in tumor size. When this occurs, the dopamine agonist dose must be increased to a maximally tolerated dose or the dopamine agonist may be switched (especially bromocriptine to cabergoline). In most dopamine agonist-resistant cases, surgery is indicated. When surgery is unsuccessful or when tumor size is increasing, radiotherapy may be indicated.

E. Malignant prolactinomas

Prolactinomas can be malignant with metastatic extension within or outside the central nervous system. In these cases, the prognosis is poor in spite of multiple treatments, including dopamine agonists, decompressive surgeries, radiotherapy, and chemotherapy. Recently, the use of an alkylating agent, **temozolomide**, has shown some efficacy to reduce Prl levels and control tumor growth in some cases.

F. Prolactinomas and pregnancy

1. In hyperprolactinemic women, dopamine agonists restore fertility even before their first normal menstruation. There is no evidence of any teratogenic effect of bromocriptine or cabergoline. However, given the greater experience with its use, bromocriptine is recommended for women who are attempting to conceive (when dopamine agonist therapy is necessary during pregnancy).
2. For women with macroprolactinomas with optic chiasm compression and are resistant or intolerant to dopamine agonist therapy, surgical resection before attempting pregnancy must be advised.
3. Dopamine agonists should be discontinued as soon as pregnancy is confirmed for most women with prolactinoma. However, in selected women with macroadenomas who become pregnant on dopaminergic therapy and who have not had prior surgical or radiation therapy (especially if the tumor is invasive or is abutting the optic chiasm), it may be prudent to continue dopaminergic therapy throughout the pregnancy.
4. The risk of symptomatic tumor growth during pregnancy is very low for patients with microprolactinoma (2.6%) and for those with macroprolactinomas previously treated with surgery or with pituitary irradiation (2.8%). The risk of symptomatic pituitary tumor enlargement in patients with macroadenoma who did not undergo surgery or irradiation before pregnancy is about 30%.
5. In normal pregnancy, serum Prl levels increase by 10-fold, and pituitary gland volume increases more than twofold; therefore, routine measurements of serum Prl and MRI studies are not recommended during pregnancy because results may be uninterruptable. These patients in which dopamine agonists have been discontinued must be followed by clinical evaluation when necessary and at least every 3 months with special attention to the presence of compressive symptoms or signs. If they develop a new onset or worsening of a previous headache, visual field testing and a pituitary MRI without the use of gadolinium must be done. If tumor growth progression is confirmed, bromocriptine therapy is recommended but only during pregnancy.
6. Surgical treatment should be reserved as a last option for those patients with poor response after the reintroduction of medical treatment.

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8 Nipple Discharge/Galactorrhea

Bhavika Kantilal Patel

I. GENERAL PRINCIPLES

Nipple discharge is the chief complaint in 2% to 5% of women who visit health care providers. Because it can be a presenting symptom of breast cancer, nipple discharge causes considerable anxiety in both patients and their providers and the workup and management of nipple discharge can be confusing. Despite the associated anxiety, nipple discharge is usually physiologic or the result of a benign etiology and is actually a relatively uncommon presenting symptom for those diagnosed with breast cancer (5% to 12% of patients). The primary goal in the evaluation and management of patients with nipple discharge is to distinguish between pathologic and physiologic causes and then diagnose potential cancers in the pathologic group.

In this chapter, we will review the etiologies of nipple discharge, provide a framework for the evaluation and management of nipple discharge, and discuss imaging strategies that optimally distinguish between benign and malignant causal factors.

II. ETIOLOGY OF NIPPLE DISCHARGE

A. Nonpathologic causes

1. Physiologic nipple discharge

Physiologic discharge is usually bilateral, involves multiple ducts, tests negative for blood regardless of color, and can be associated with nipple stimulation or breast compression. It is defined as nonpathologic and unrelated to pregnancy or breastfeeding. Although physiologic discharge is most commonly white or clear, it may also present as straw colored, gray, yellow, green, or brown. Approximately 50% to 80% of women in their reproductive years may express some type of fluid from the breast.

2. Lactation

During the normal hormonal stimulation caused by pregnancy and

breastfeeding, the mammary glands often produce physiologic discharge of milk and colostrum. **This discharge can be observed for up to 1-year postpartum after the cessation of breastfeeding**. Galactorrhea is a bilateral, milky white discharge that is physiologic in a woman who is breastfeeding or pregnant. Evaluation of galactorrhea should include a human chorionic gonadotropin pregnancy test to rule out pregnancy.

3. **Medication-related causes/hyperprolactinemia**

In other clinical settings, galactorrhea is most commonly caused by hyperprolactinemia. Prolactin and thyroid-stimulating hormone levels should also be obtained to determine the presence of an endocrinopathy. Some medications such as those that inhibit dopamine or cause lactograph stimulation, may also result in galactorrhea (Table 8-1). Neurogenic stimulation from chest wall injury or chronic breast stimulation represses the secretion of hypothalamic prolactin-inhibitory factor and can also, result in hyperprolactinemia and galactorrhea. In addition, any disease in or near the hypothalamus or pituitary that interferes with type 1 secretion of dopamine or its delivery to the hypothalamus can cause hyperprolactinemia.

B. Pathologic causes

Nipple discharge is classified as pathologic if it is spontaneous, unilateral, bloody, serous, clear, or associated with a mass. Common causes of pathologic discharge are intraductal papilloma, duct ectasia, carcinoma, and infection.

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TABLE 8-1 Drugs That Cause Hyperprolactinemia

Medication Class	Mechanism
Antipsychotics, first generation	
Chlorpromazine, Fluphenazine, Haloperidol, Loxapine, Perphenazine, Pimozide, Thiothixene, Trifluoperazine	Dopamine D receptor blockade within hypothalamic tuberoinfundibular system
Antipsychotics, second generation	
Aripiprazole, Asenapine, Clozapine, Iloperidone, Lurasidone, Olanzapine, Paliperidone, Quetiapine, Risperidone, Ziprasidone	Dopamine D_2 receptor blockade

Antidepressants, cyclic	
Amitriptyline, Desipramine, Clomipramine, Nortriptyline	Not well understood. Possibly by GABA stimulation and indirect modulation of prolactin release by serotonin
Antidepressants, SSRI	
Citalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline	Same as for cyclic antidepressants
Antidepressants, other	
Bupropion, Venlafaxine, Mirtazapine, Nefazodone, Trazodone	Not applicable
Antiemetic and gastrointestinal	
Metoclopramide, Domperidone (not available in United States), Prochlorperazine	Dopamine D_2 receptor blockade
Antihypertensives	
Verapamil, Methyldopa, most other antihypertensives (including other calcium channel blockers)	Not well understood
Opioid analgesics	
Methadone, Morphine, others	Potentially an indirect effect of mu opiate receptor activation

GABA, *y*-aminobutyric acid; SSRI, selective serotonin reuptake inhibitor.

Adapted from UptoDate medications that cause hyperprolactinemia 2015. Data from Coker F, Taylor D. Antidepressant induced hyperprolactinemia. *CNS Drugs* 2010;24:563; Molitch ME. Drugs and prolactin. *Pituitary* 2008;11:209; Molitch ME. Medication induced hyperprolactinemia. *Mayo Clin Proc* 2005;80:1050; Drugs for psychiatric disorders. *Treat Guidel Med Lett* 2013;11:53.

1. **Intraductal papilloma**
   The most common is a benign papilloma and occurs in, up to 57% of cases involving pathologic nipple discharge. A papilloma is a benign epithelial neoplasm that can cause clear or bloody discharge. Papilloma can be classified as a spectrum of lesions that may be associated with atypical cells and low-grade carcinomas. The management of benign papilloma remains controversial.
2. **Duct ectasia**
   Duct ectasia is another common cause of pathologic discharge and occurs, in approximately 33% of cases.
3. **Carcinoma**
   Malignancies are found in only **5% to 15% of cases** of

pathologic nipple discharge, and the most common malignancy is ductal carcinoma in situ.

4. **Infection**

   Purulent nipple discharge may be observed in association with periductal mastitis.

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C. Clinical evaluation

1. **History**

   The standard of care for women who present with nonlactational nipple discharge should include a thorough physical examination and an understanding of their detailed medical history. The medical workup should include a detailed history about the discharge, including details about the color and, frequency of discharge, whether the discharge is spontaneous or evoked by manipulation of the breast, whether the discharge is bloody, and whether the discharge emanates from multiple ducts or a single duct. Cancers generally present with spontaneous, unilateral, uniductal, and bloody discharge. Bilateral nipple discharge is typically the result of endocrinopathy or a physiologic process. A patient's complete medication history and any history of recent trauma should also be determined. Recent onset of amenorrhea, hot flashes, or vaginal dryness should prompt consideration of hyperprolactinemia.

D. Physical examination

Physical examinations should include a complete breast exam to assess the symmetry and contour of the breasts, any skin abnormalities, edema or erythema, and position of the nipples. An attempt should be made to elicit the discharge and identify the involved duct or ducts. Gentle firm pressure around the areola in a systematic manner can help identify the specific duct producing the discharge. If no discharge is elicited, a warm compress may aid in expression of secretions. Cytology is not routinely recommended or performed because of a reported low sensitivity for detection of cancer (~27%—this is a fairly low sensitivity for a diagnostic examination. Prefer to see 70% or above). However, discharge obtained may be tested for blood with a hemoccult test. Health care providers should also perform a complete physical examination to detect enlarged axillary or supraclavicular nodes and palpable breast masses.

Physical examination should also include checking for signs of

hypothyroidism, hypogonadism, and bitemporal field loss (also known as Chiasmal syndrome) which may be observed with pituitary lesions.

If a patient's medical history and physical examination suggests physiologic discharge and that patient is current on their screening mammography, no additional radiologic investigation is required. Mammography and sonography, however should be performed on all women with pathologic nipple discharge (Fig. 8-1).

E. Diagnostic evaluation

1. Imaging

a. Mammography

Mammography is recommended for any patient that presents with abnormal nipple discharge. Some studies have reported that mammography has a low positive predictive value of just 16.7% and a sensitivity of only 59% when used to diagnose of malignant duct pathology associated with nipple discharge. Despite this, mammography is still recommended as a starting point for evaluating women over 30 years of age who present with nonlactational, spontaneous nipple discharge. The imaging findings associated with pathologic nipple discharge will vary depending on the underlying etiology and imaging modality. On mammography, findings can range from no abnormality to distended retroareolar ducts, a developing asymmetry, architectural distortion, periductal microcalcifications, and/or nipple retraction.

Duct ectasia may be observed on mammography and appears as a general increase in retroareolar density while, focally dilated ducts can be identified as a tubular and branching structure, widest in caliber at the nipple and tapering as it proceeds distally into the parenchyma (Fig. 8-2). When a single dilated retroareolar duct is the only mammographic finding, one should consider that the cause of the dilation is an underlying intraductal carcinoma. If duct dilation is discovered, subsequent management includes targeted breast ultrasound, followed by magnetic resonance imaging (MRI) or galactography. If no ultrasound or MRI correlate is found, then duct excision is usually recommended.

New onset of nipple discharge may also be associated with a developing asymmetry, defined as a new, growing or more conspicuous asymmetry on mammography. Any newly

observed area of mammographic density in the p. 87p. 88setting of nipple discharge should be considered suspicious for breast cancer, and biopsy is usually indicated.

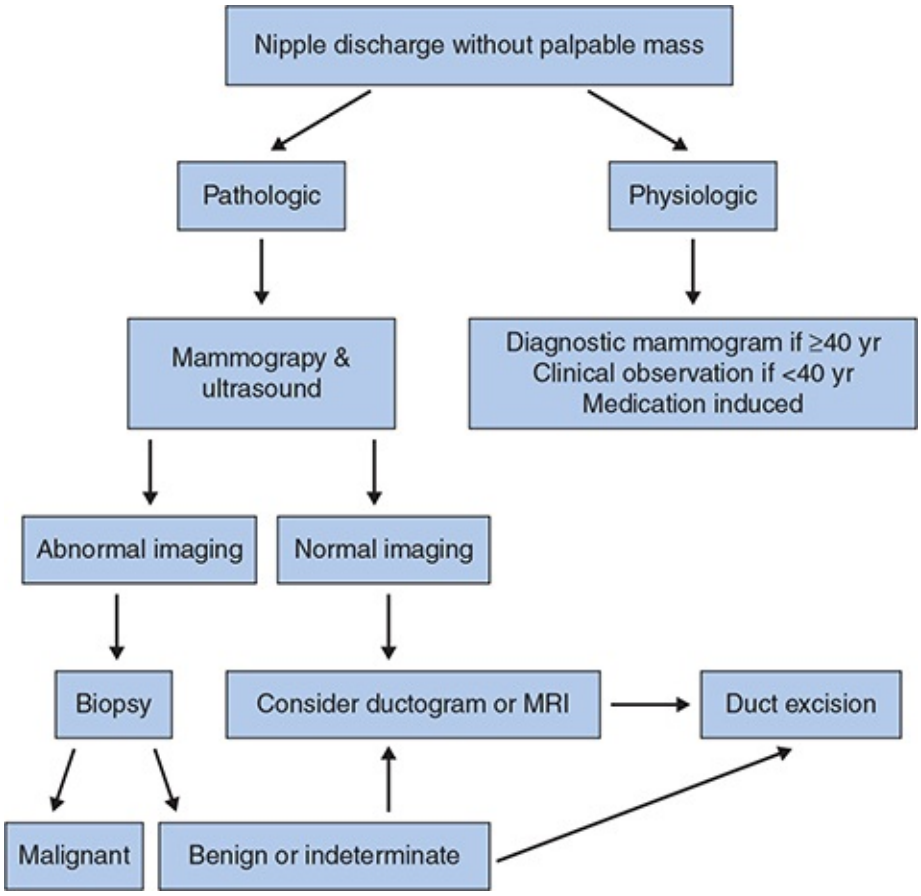

Figure 8-1. Algorithm for evaluation and management of nipple discharge. MRI, magnetic resonance imaging.

Mammography in patients with nipple discharge may also demonstrate an area of architectural distortion.

Microcalcifications on mammography are also observed in the setting of nipple discharge. These calcifications are smaller than 0.5 mm and must be evaluated through magnification mammography, which provides increased spatial resolution. Morphologic features suggestive of malignancy include thin linear, curvilinear, and branching shapes. However, because 20% to 25% of calcifications associated with new pathologic

nipple discharge are associated with breast cancer, biopsy is often performed even if the morphology suggests that microcalcifications are likely benign.

b. Ultrasound

Breast ultrasound is complementary to mammography and is noninvasive, free of ionizing radiation, and is extremely useful in the evaluation of patients with nipple discharge. Ultrasound is used primarily to detect masses and determine whether a palpable or mammographically identified mass is cystic, solid, or within a duct. It can also be used to delineate the relationship of a mass within the involved ductal system and the number of ducts involved. It has been reported that a benign physical examination and a negative subareolar ultrasound practically excludes the possibility of malignancy in patients with pathologic nipple discharge. In patients with pathologic discharge, ultrasound has a reported sensitivity of 97%, specificity of 60%, and positive predictive values of 95%.

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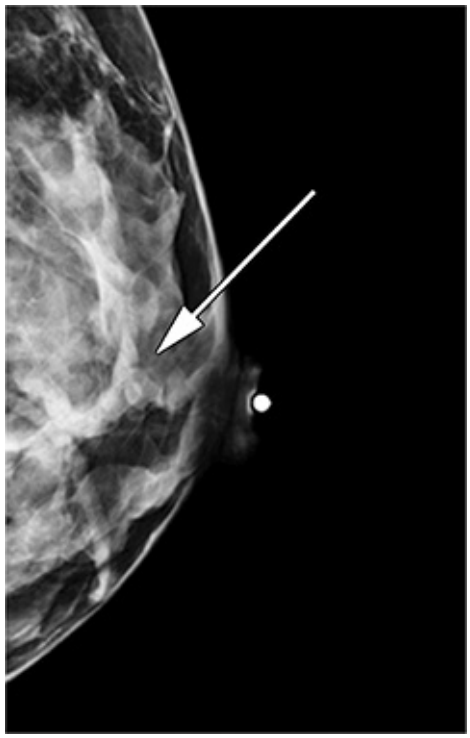

Figure 8-2. Standard CC view of the breast demonstrating a dilated retroareolar duct (*arrow*) seen as a tubular and branching structure in a 43-year-old female with spontaneous unilateral

bloody nipple discharge from a single duct. Ultrasound-guided biopsy of a retroareolar mass revealed invasive ductal carcinoma.

The two most common causes of pathologic nipple discharge are intraductal papilloma and ductal ectasia, both of which can be observed via ultrasound. Duct ectasia is often asymptomatic and discovered incidentally at screening, but may present with bilateral or multiductal nipple discharge. It may develop secondary to ductal inflammation or obstruction and is not associated with an increased risk of carcinoma. Sonographically, this has the appearance of dilated retroareolar ducts that contain anechoic fluid or hypoechoic debris (Fig. 8-3A). Careful evaluation with Doppler and compression is recommended to exclude concomitant neoplastic intraductal masses (Fig. 8-3B).

c. Ductography

Ductography (or galactography) has traditionally been indicated when neither mammography nor ultrasound are able to detect a causative lesion in the setting of pathologic nipple discharge. Ductography localizes intraductal lesions by obtaining mammographic images after the injection of iodine-containing contrast medium into the duct (Fig. 8-4A). Ductograms can be technically challenging and are only possible if the duct demonstrates discharge at the time of the study. The incomplete or failed ductography rate has been reported to be as high as 15%. Because the sensitivity and specificity of subareolar ultrasound is equal or superior to that of ductography routine diagnostic ductography is not recommended because it is invasive, and has a high-technical failure and high false-negative rate.

A successful, positive ductogram identifies an intraductal lesion as a partially or completely obstructed duct or as duct irregularity (Fig. 8-4B). By identifying the involved duct, a ductogram aids in focused surgical excisions. Ductography itself is nonspecific and cannot differentiate benign from malignant lesions. In fact, a filling defect more frequently indicates a benign lesion, such as papilloma.

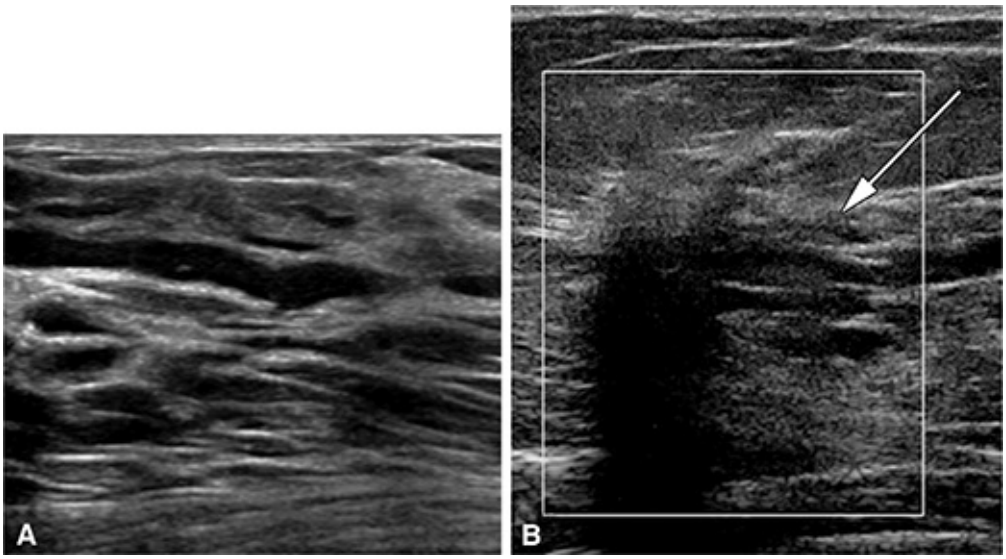

Figure 8-3. **A.** Grayscale ultrasound showing dilated retroareolar ducts containing anechoic fluid and minimal hypoechoic debris in a 44-year-old female with bilateral nonbloody spontaneous nipple discharge. History of prolactinoma. No intraductal mass identified at the time of scanning. **B.** Hypoechoic intraductal mass with adjacent ductal dilation *(arrow)* in a 53-year-old female with bloody nipple discharge. Ultrasound-guided needle biopsy revealed invasive ductal carcinoma.

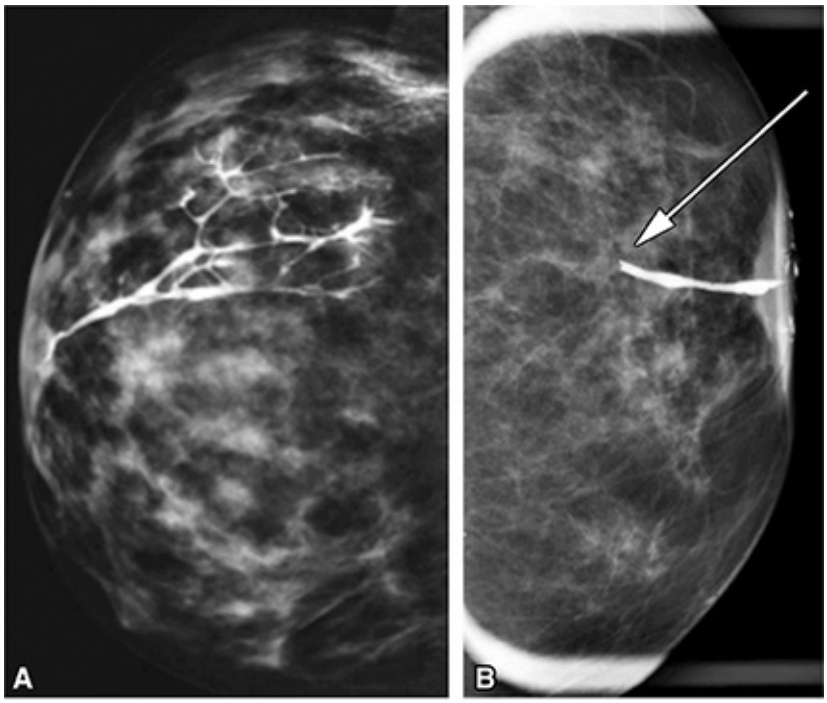

Figure 8-4. **A.** Standard CC view of the right breast demonstrating a normal ductogram with smooth, tapering ducts in a 25-year-old female with history of right nipple discharge. Surgical excision revealed mild duct hyperplasia without evidence for malignancy. **B.** Spot magnification CC view of the left breast demonstrating a dilated duct with abrupt cutoff in a 69-year-old female with left bloody nipple discharge. Surgical excision revealed benign papilloma.

d. Contrast-enhanced MRI

MRI is emerging as a preferred, less invasive alternative to ductography in the evaluation of nipple discharge. MRI yields a high sensitivity (94% to 100%) for the detection of breast cancer but requires the intravenous injection of a gadolinium-based contrast agent. As opposed to ductography, MRI is able to characterize lesions and provide a means for histologic diagnosis via percutaneous MRI–guided core biopsy (Fig. 8-5). MRI had a statistically significant higher overall sensitivity (94.7%) compared with mammography alone or ultrasound alone (26.3% and 63.2%, respectively). However, MRI has a variable specificity (37% to 97%) and high false-positive rate, as reflected by the detection of additional incidental lesions, which require follow-up imaging or biopsy.

2. Laboratory examination

If a physical examination is normal, imaging is negative, and discharge is multiductal and guaiac negative, the patient will require laboratory tests, medical evaluation, and galactorrhea workup. Multiductal discharge should be evaluated with a pregnancy test, prolactin levels, renal and thyroid function tests, and appropriate endocrinologic follow-up if there are abnormal findings. Further endocrinologic evaluation is also indicated if there are other systemic abnormalities, such as menstrual irregularity, infertility, headaches, visual disturbances, or symptoms of hypothyroidism.

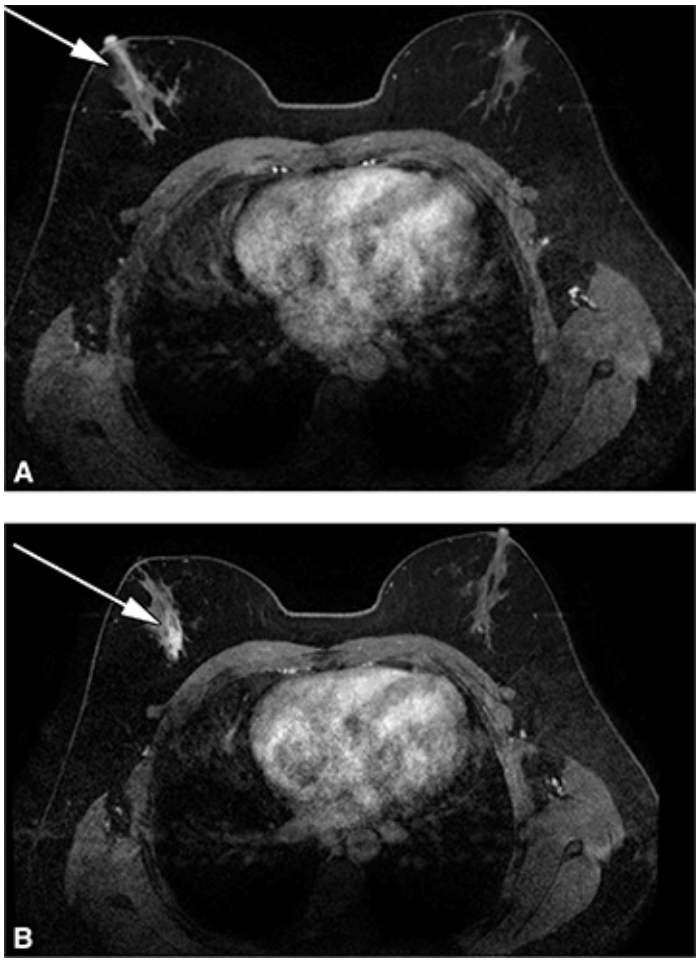

Figure 8-5. Axial T1-weighted fat-saturated postcontrast images demonstrating right ductal dilation extending from the nipple posteriorly (*arrow*) **(A)** to an area of nonmass enhancement (*arrow*) **(B)** in a 19-year-old female with history of bloody nipple discharge. MRI–guided biopsy revealed intraductal carcinoma, which was confirmed on final surgical pathology and also included ductal carcinoma in situ. MRI, magnetic resonance imaging.

F. Hyperprolactinemia

Hyperprolactinemia is a potential cause of oligomenorrhea, amenorrhea, and less commonly galactorrhea. The serum prolactin concentration is often normal in women who present with galactorrhea. In the largest series of patients presenting with galactorrhea, prolactin was normal in 46% of patients. A diagnosis of hyperprolactinemia is made when serum prolactin concentration is well above the normal range (>20 ng/mL [20 µg/L]). Most patients with hyperprolactinemia have a lactotroph adenoma so the evaluation is aimed at (a) exclusion of pharmacologic or extrapituitary causes of hyperprolactinemia and (b) neuroradiologic evaluation of the hypothalamic-pituitary region.

1. **Causes**
    a. **Nonpathologic hyperprolactinemia:** The physician should determine a patient's pregnancy history and check β human chorionic gonadotropin levels.
    b. **Medication-induced hyperprolactinemia:** Common drugs include estrogen, neuroleptic drugs such as risperidone, metoclopramide, antidepressant drugs, cimetidine, methyldopa, reserpine, and verapamil.
    c. **Pituitary adenoma:** The physician should inquire about headache, visual symptoms, symptoms of hypothyroidism, and a history of renal disease. Eventually, an MRI of the head should be performed in patients with any degree of hyperprolactinemia to look for a mass lesion in the hypothalamic-pituitary region, unless the patient is taking a medication known to cause hyperprolactinemia or is pregnant. If a mass lesion is found in the region of the sella turcica, secretion of other pituitary hormones should also be evaluated. If the MRI shows a normal hypothalamic-pituitary region and there are no obvious causes of hyperprolactinemia, a diagnosis of idiopathic hyperprolactinemia is indicated. This syndrome may, in some patients, be due to microadenomas that are too small to be seen on imaging.

G. Treatment

The evaluation of nipple discharge requires a thorough medical history, a careful physical examination, and a stepwise approach to linking the type of discharge with the most suitable diagnostic modality. Primary care providers, working with their radiologists and surgeons, are well positioned to design appropriate diagnostic and management protocols to assess and treat nipple discharge. Bloody nipple discharge, an abnormal mammogram or breast ultrasound, or the presence of a breast mass on physical examination requires evaluation by a surgeon and/or a breast biopsy. Uniductal unilateral discharge is more likely to represent underlying pathology, such as papilloma or intraductal breast carcinoma. Bilateral or unilateral multiductal secretion that tests negative for blood on the guaiac card is usually normal regardless of color (e.g., milky, brown, green, yellow, blue, gray, or clear). Medical evaluation and endocrine workup may be required, but surgical intervention is usually not indicated. Galactorrhea in the absence of hyperprolactinemia usually does not

need to be treated because it is not associated with ongoing disease and it is usually not bothersome. For the unusual patient whose galactorrhea occurs spontaneously and to a degree that causes staining of the clothes, treatment with a low dose of dopamine agonist will reduce the prolactin concentration to below normal and reduce or eliminate the galactorrhea. Ultimately, a thoughtful and methodical approach to nipple discharge can alleviate patient anxiety and aid in the detection of physiologic, benign, and malignant etiologies.

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9 Acromegaly/Gigantism

Merav Fraenkel and Laurence Katznelson

I. GENERAL PRINCIPLES/INTRODUCTION

Acromegaly is a multisystem disorder resulting from chronic growth hormone (GH) hypersecretion. Normally, GH is secreted in a circadian rhythm in pulses by the somatotroph cells of the pituitary gland, under **stimulatory control of growth hormone–releasing hormone** (GHRH) and **inhibitory control by somatostatin**: both GHRH and somatostatin are secreted by the hypothalamus and travel to the pituitary gland via the hypophyseal circulation of the pituitary stalk. Circulating GH stimulates production of insulin-like growth factor 1 (IGF-1) by the liver and local tissues. A serum IGF-1 level serves as an integrated marker of recent GH circulation, and can hence be used as a screening tool for GH excess or deficiency. Acromegaly is due to excessive GH and IGF-1 secretion.

II. EPIDEMIOLOGY

Considered a rare disease, the annual incidence rates of acromegaly range from 2.5 to 4.5 per million population, and the prevalence may be as high as 79 per million. Diagnosis is often made early in the fifth decade of life, and there is no gender difference in the incidence of the disease. Because acromegaly is a chronic and insidious disease, there is often a delay up to 10 years for diagnosis.

III. PATHOGENESIS

Over 90% of cases are caused by a benign tumor of the pituitary somatotroph GH-producing cells. Rarely, acromegaly is caused by GHRH production by a neuroendocrine tumor (such as carcinoid or pancreatic neuroendocrine tumors). Even more rarely, neoplasms may produce GH ectopically. Most cases of acromegaly are sporadic, but familial cases have been identified, including multiple endocrine neoplasia type 1 **(MEN-1), aryl hydrocarbon receptor-interacting protein** mutations associated with **familial acromegaly, and Carney complex**.

IV. CLINICAL FEATURES

Clinical manifestations of acromegaly are a consequence of either local mass effects of the pituitary tumor or of peripheral actions of elevated GH and IGF-1 levels (see Table 9-1 for detailed associated features).

V. ASSOCIATION WITH OTHER MALIGNANCY

There have been conflicting reports of an increased prevalence of malignancy in the setting of acromegaly, particularly of the gastrointestinal tract. Although this association has not been confirmed in all studies, an enhanced cancer-related mortality has been indicated in the presence of acromegaly.

VI. MORBIDITY AND MORTALITY

Comorbidities, including painful arthropathy, carpal tunnel syndrome, headache, hyperglycemia/type 2 diabetes mellitus, hyperlipidemia, hypertension, sleep apnea syndrome, and diaphoresis, are associated with acromegaly. A hypertrophic cardiomyopathy is common at diagnosis, and a dilated congestive cardiomyopathy is seen with advanced disease. Sleep apnea syndrome is common and is a contributor to headache and fatigue. An electrocardiogram and echocardiography should be considered based

p. 94p. 95on clinical evaluation for cardiac disease. In the recent Endocrine Society Guideline, a thyroid ultrasound was recommended to screen for thyroid nodules if thyroid nodularity is noted on palpation. Colonoscopy screening should be performed given the increased prevalence of colon polyps.

All-cause mortality is increased in patients with active acromegaly; by reducing the GH and IGF-1 values to normal, this risk is reduced to that of the general population.

TABLE 9-1 Clinical Features of Acromegaly

General	Dermatology	Endocrine and metabolic effects
Weakness	Oily skin	Hypogonadism
Fatigue	Multiple skin tags	Decreased libido and impotence
	Hyperhidrosis	Menstrual irregularities
Local symptoms due to tumor mass effect	**Cardiovascular**	Impaired glucose tolerance
Diplopia (cranial nerve involvement in the cavernous sinus)	Hypertension	Insulin resistance
	Arrhythmia and	

Visual-field defects (bi-temporal quadrant or hemianopsia)
Headache

Somatic enlargement
Thickening of hands and feet
Increase in shoe, ring, or hat size is common
Frontal bossing
Proganthism
Increased spacing of teeth
Coarse facial features
Carpal tunnel syndrome
Painful arthropathy

conduction disorders
Left ventricular hypertrophy
Congestive heart failure

Colon
Polyps

Pulmonary
Obstructive and central sleep apnea

Visceral enlargement
Thyroid goiter
Heart
Macroglossia
Prostate hypertrophy

Diabetes mellitus type 2
Hypertriglyceridemia

Minerals and electrolytes
Hyperphosphatemia
Hypercalciuria

VII. DIAGNOSIS

In a patient with suggestive clinical manifestations, biochemical testing should be performed to assess for GH and IGF-1 hypersecretion.

A. Biochemical diagnosis: basal and dynamic tests

1. A random **IGF-1** serves as an integrated marker of GH secretion and should be the initial screening test.
2. A random **GH** value is **not useful** for the diagnosis, because there is no clear cutoff value. GH secretion is pulsatile and with a circadian rhythm, has a short half-life, and is affected by different stimuli, such as exercise, fasting, stress, and sleep. The GH response to glucose suppression (normal less than 1 μg/L), utilizing a 75-g **oral glucose-tolerance load** with measurement of GH levels every 30 minutes over 2 hours is useful to complete the diagnosis, particularly in a patient with a borderline IGF-1 value.

B. Imaging. Following the biochemical diagnosis of acromegaly, imaging should be performed in order to localize the tumor and assess tumor size and extent of parasellar p. 95p. 96extension/invasiveness. A magnetic resonance imaging (MRI) scan is superior to a computed tomography scan for anatomical evaluation. If the tumor is found to abut the optic chiasm on imaging, then formal visual-field testing is recommended to evaluate for visual-

field deficits.

C. Other biochemical testing at diagnosis

Serum prolactin level (to rule out cosecretion with GH) and clinical and biochemical assessment of pituitary function (including screening of adrenal, gonadal, and thyroid reserve) should be performed at diagnosis.

VIII. TREATMENT (see Fig. 9-1)

A. Goals of treatment: The major goal is to achieve biochemical control, as defined by a normal random IGF-1 level (age and gender normalized). A random serum GH <1 μg/L corroborates the definition of biochemical control. Because of the variability of the random GH values, a random GH value greater than 1 μg/L is insufficient to confirm persistent disease, and a **GH response to a glucose load** (with control defined by a nadir **GH value <1 μg/L**) is **recommended to validate the finding**. Additional goals include reducing the signs and symptoms, reducing the mortality risk (achieved with biochemical control), maintaining normal pituitary function, and decompressing local structures from tumor mass effects.

B. Surgical treatment

1. Surgery is the recommended primary treatment for most patients with acromegaly. Surgical remission is achieved in over 85% of microadenomas and in approximately 50% of macroadenomas, with most cases of residual tumor p. 96p. 97located in the cavernous sinus. Tumor size and location (e.g., parasellar spread) as well as the experience of the pituitary surgeon are the most important factors for surgical success.

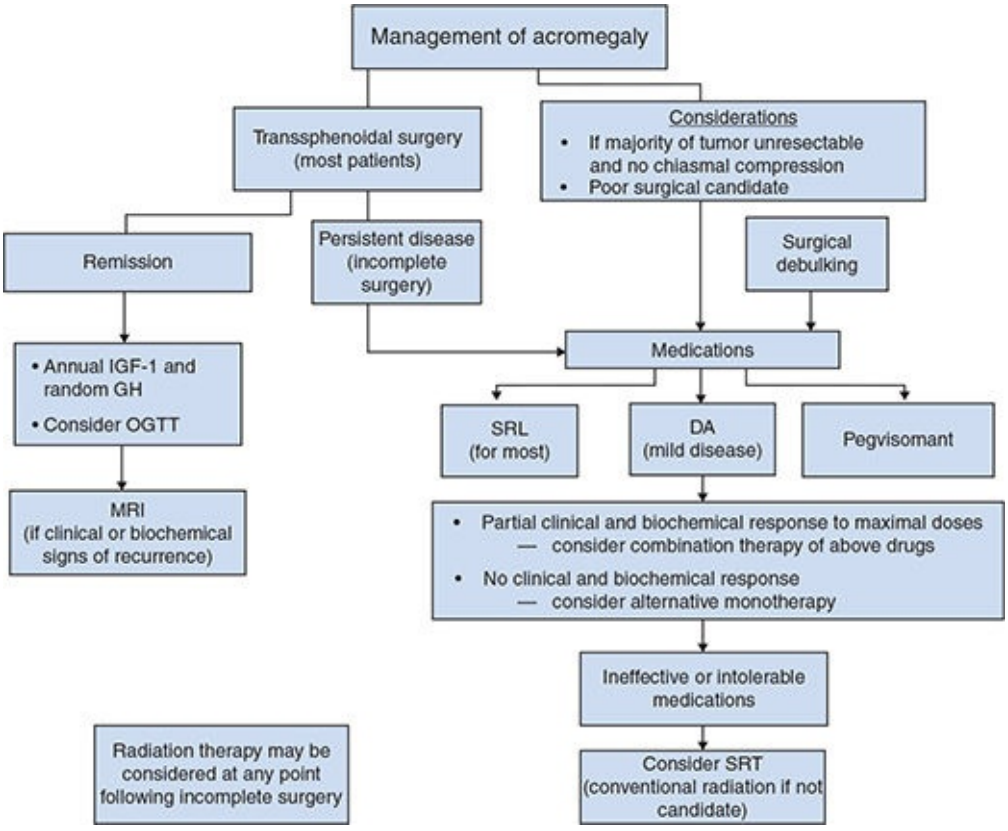

Figure 9-1. Treatment considerations in the approach to a patient with acromegaly due to a pituitary adenoma. DA, dopamine agonist; GH, growth hormone; IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging; OGTT, oral glucose-tolerance test; SRL, somatostatin receptor ligand; SRT, stereotactic radiotherapy. (From Katznelson L, Laws ER Jr, Melmed S, et al. Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014;99:3933–3951. Used with permission of the Endocrine Society.)

2. **Complications of surgery,** for example, bleeding, spinal fluid leak, and meningitis occur in approximately 2% of cases. Permanent diabetes insipidus occurs in <5% of cases. Carotid artery damage is rare (in <1% of cases). Mortality is <1% as well. Permanent hypopituitarism is a function of tumor size, and can be detected in up to 20% of patients.
3. **Postoperative testing:** Serum IGF-1 and a random GH should be measured 12 weeks after surgery. If the random GH is >1 μg/L, GH suppression following a glucose load should be performed. After 12 weeks, repeat imaging may be performed to assess completeness of surgery. In patients with preoperative visual-field defects, repeat testing should be done to assess visual function. Repeat pituitary function testing of adrenal, thyroid, and gonadal function should be performed after 6 weeks in order to assess

residual pituitary function.

4. **Is there a role for preoperative medical therapy with a somatostatin receptor ligands (SRLs)?** There are insufficient data to suggest a role for preoperative SRL therapy to improve surgical biochemical outcomes. However, an SRL can be used preoperatively for 3 to 6 months in patients with severe sleep apnea syndrome because of pharyngeal thickening and/or those with significant cardiovascular disease in order to improve surgical risk.
5. **Role of surgical debulking.** Even if there is significant tumor extension into the parasellar regions, such as the cavernous sinus, surgery has been recommended to debulk the intrasellar tumor component in order to improve subsequent response to medical therapy. Tumor debulking may improve subsequent radiotherapy (RT) response as well.

C. Radiation. Radiation therapy is used mostly in the adjuvant setting to treat residual disease following surgery, especially in patients resistant to or intolerant of medical therapy. Successful RT may lead to lifelong control of the disease, possibly eliminating the need for continued medical therapy. Two main types of RT are used in patients with acromegaly: conventional fractionated RT and stereotactic radiotherapy (SRT), with a Gamma Knife being the most widely used. Control rates of up to 70% are seen with either technique. SRT may achieve biochemical control quicker and is recommended unless the proximity of the tumor to the optic chiasm would result in chiasmal exposure of greater than 8 Gy given the risk of visual loss because of chiasmal damage. Medical therapy is necessary for biochemical control while awaiting effects of radiation on GH and IGF-1 control. In such cases, biochemical remission should be assessed at least annually while medications are withheld. There is an approximately 40% risk of hypopituitarism (including adrenocorticotropic hormone, thyroid-stimulating hormone, and luteinizing hormone/follicle-stimulating hormone) following radiation therapy, and pituitary function should be monitored annually.

D. Medical treatment

Medical therapy is recommended as an adjuvant treatment in patients with persistent disease following surgery. In those patients with a primarily extrasellar mass (e.g., cavernous sinus), or are poor surgical candidates, or by patient preference, primary medical therapy with an

SRL may be offered in lieu of surgery. With medical therapy, biochemical control is assessed through measurement of a serum IGF-1 level. Because medical therapy is only effective during administration, a repeat IGF-1 level should be performed to assess biochemical activity if medical therapy is discontinued.

1. **Somatostatin analogs** (referred to as somatostatin receptor ligands or **SRLs**) are the mainstay of medical therapy. The most commonly used SRLs are **octreotide** and **lanreotide.** Octreotide is available as a rapid-acting subcutaneous (SC) version up to three to four times daily, as well as a monthly intramuscular (IM) **octreotide long-acting release (LAR)**. The starting dose of octreotide LAR is 20 mg monthly, with doses of 10 and 30 mg available for dose titrations. Lanreotide is available as a monthly deep SC **lanreotide depot/autogel (ATG)**. The starting dose for lanreotide ATG is 90 mg monthly, with doses of 60 and 120 mg available for dose titration. Lanreotide ATG has been approved for regimen with less frequent injections as well. Lanreotide ATG and octreotide LAR have p. 97p. 98equivalent biochemical and symptomatic control, as well as side effect profiles. IGF-1 measurements should be performed after 12 weeks of therapy to assess efficacy, prior to the next injection. Short-acting octreotide is occasionally used if there are cost limitations (short acting may be less expensive) or there is a delay in obtaining the long-acting preparations.
    a. **Efficacy:** Early data suggested biochemical control in up to 60% of patients. However, more recent studies suggest biochemical control in approximately 25% to 40% of patients when used as primary or adjuvant therapy. Reasons for lower efficacy rates in more recent studies include lack of preselected patients for response, a more heterogeneous subject population, and studies involving community management with less regimented protocols. Tumor shrinkage of greater than 50% is seen in 60% of patients treated with an SRL.
    b. **Side effects:** Common side effects include abdominal pain, flatulence, and diarrhea, but these usually improve with continued therapy. Cholelithiasis or gallbladder sludge occurs in 25% to 40% of patients, but this is usually asymptomatic, and therefore, routine monitoring with gallbladder ultrasound is not

necessary.

c. **Pasireotide** is a new multireceptor SRL that was approved for use in the United States in 2014. **Pasireotide LAR** is administered as a 20 or 40 mg IM injection every 28 days. In a comparison study of pasireotide LAR and octreotide LAR in patients naïve to SRL therapy, pasireotide administration resulted in higher biochemical controls rates (31% vs. 9%, respectively). Pasireotide has also been shown to attain biochemical control in at least 20% of subjects who are resistant to octreotide or lanreotide management.
    i. **Side effects.** Like octreotide and lanreotide, pasireotide may cause abdominal pain, diarrhea, and cholelithiasis. A significant side effect of pasireotide is de novo type 2 diabetes mellitus in up to 26% of patients and to hyperglycemia in up to 31%. Therefore, glucose levels need to be monitored closely in patients receiving pasireotide.

2. **Pegvisomant** is a competitive GH receptor antagonist that bypasses the tumor and competes with endogenous GH for the GH receptor and prevents functional dimerization of the GH receptor, resulting in a reduction in IGF-1 production. Pegvisomant is administered SC as 10, 15, or 20 mg daily injections, with a maximal daily dose up to 30 to 40 mg. Alternate-day injections may be effective in some patients and, when combined with SRL, once or twice weekly injections may be used. To monitor response to pegvisomant therapy, IGF-1 measurements should be performed every 4 to 6 weeks during dose adjustments and then twice a year for monitoring. If pegvisomant is discontinued, then there may an increase in IGF-1 levels so biochemical activity should be monitored with serum IGF-1 levels. GH levels should not be monitored when assessing therapeutic response given lack of impact at the tumor level.
    a. **Efficacy:** In the recent observational, surveillance ACROSTUDY, pegvisomant therapy led to IGF-1 control in 65% of subjects. Biochemical control is associated with symptomatic improvement, including improvement in glucose homeostasis.
    b. **Side effects:** Surveillance studies have shown that tumor growth is uncommon and may occur in 3% to 5% of cases. It is recommended that serial MRI scans should be performed after 6

to 12 months of initiating therapy and then annually. Lipohypertrophy at the injection site is reported in up to 2.3% of treated patients. The pegylated component of pegvisomant may cause liver function abnormalities, and 1% to 9% may develop significant elevation of transaminases, with no reports of liver failure. Liver enzymes should be monitored monthly for the first 6 months and then twice a year, and therapy discontinued if levels are greater than three times normal.

3. **Dopamine agonists**
   a. **Cabergoline:** Cabergoline is a D2 receptor agonist that, though not approved by the Food and Drug Administration for use in acromegaly, is occasionally used because of its reduced cost and the fact that it is administered orally.

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   i. **Efficacy:** Cabergoline can lead to biochemical control in approximately 30% to 40% of subjects, though it is most effective in patients with modest disease. The presence of hyperprolactinemia does not seem to influence cabergoline effects on GH.
   ii. **Side effects** include gastrointestinal discomfort, orthostasis, fatigue, and nasal stuffiness.

E. Choice of medical therapy

In the setting of mild disease, a dopamine agonist may be used as the initial medical therapy. In more significant disease, either an SRL or pegvisomant should be used as medical therapy. In such patients, the choice of medical therapy may include regulations (e.g., in a number of countries, pegvisomant may be administered after a trial of an SRL), tumor size (an SRL may be preferred in the setting of a large residual tumor), and diabetes mellitus (pegvisomant may be superior).

F. Combination therapy

In those patients completely resistant to or intolerant of an SRL, the patient should be switched to pegvisomant, or considered for a trial of pasireotide. In a patient with partial response despite maximal dosing of an SRL, combination therapy can be considered. The addition of pegvisomant (20 to 80 mg weekly or twice weekly) to a patient with partial SRL response has been shown to achieve biochemical control in up to 95% of patients. The addition of cabergoline to an SRL may also lead to biochemical control in a subset of patients with relative

resistance to an SRL.

IX. LONG-TERM FOLLOW-UP

In patients in surgical remission, annual monitoring with a serum IGF-1 is sufficient for assessment of disease control. Long-term recurrence may be seen in up to 6% of subjects, and patients with dural or bony involvement at surgery may be the most at risk. Serial colonoscopy, to rule out colorectal cancer, should be performed based on standard of care guidelines for the general population: guidelines suggest more frequent colonoscopy if polyps are found at the initial screen. Corrective orthopedic (joint replacement) or plastic surgery (such as mandibular reconstruction) should be withheld until normalization of serum GH and IGF-1 is achieved. If symptoms of sleep apnea syndrome persist, a follow-up sleep study should be performed, because sleep apnea often persists despite biochemical remission.

X. GIGANTISM

Gigantism, a rare condition, relates to excessive growth resulting from the impact of GH hypersecretion on epiphyseal growth plates prior to their closure. The diagnosis and treatment is similar to that of acromegaly in adults. In addition to the standard goals of therapy as described in Section VIII.A, it is critical to achieve biochemical control in order to limit the accelerated linear growth. Because of the age of the patients and the complications associated with it (see Section VIII.C), RT is often not recommended in children with gigantism.

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10 Clinical Disorders of Vasopressin

Brandon Barthel, Cameron Herr, Sanaa Deshmukh, and James R. Sowers

Normal homeostasis requires a stable internal extracellular and cellular environment, including a nearly constant tonicity. A great deal of the stability of this environment depends on the adequacy and adaptability of water metabolism. In spite of the large variation in the intake of water and/or solutes, a remarkably narrow range of plasma osmolality (282 to 298 mOsm/kg) is maintained. This accomplishment is contingent on multiple factors, including the function of osmoreceptors; the magnicellular neurons in the paraventricular area that are capable of producing both functional arginine vasopressin (AVP; also known as antidiuretic hormone [ADH]) and neurophysins; the presence of functional AVP receptors in the kidney; the function of renal tubular cells, which are capable of producing an intact and functional aquaporin; and the maintenance of urinary osmolality. AVP is involved not only in conservation of water by the kidney when needed but it is also an important component of the body's thirst mechanism and is a potent pressor substance. One additional minor, though essential, constituent of water metabolism and homeostasis is the effect of the thyroid and adrenal glands on maintenance of osmolality.

I. ROLE OF VASOPRESSIN IN THIRST

The mechanism of thirst deserves some contemplation. Thirst can be stimulated as a response to increased extracellular fluid osmolality through the activation of osmoreceptors located in the hypothalamus, or as a response to depressed plasma volume through the activation of high- and low-pressure baroreceptors. Despite the existence of these other potential stimulants, the effect of the stimulation of the osmoreceptors seems to be the principal stimulant of thirst in humans.

II. REGULATION OF VASOPRESSIN SECRETION

A. AVP is a nonapeptide synthesized by specialized magnocellular neurons in the supraoptic and paraventricular nuclei of the

hypothalamus. Different stimuli for AVP secretion primarily affect gene transcription and secondarily affect posttranscriptional regulation in these neurons. AVP is transported from the bodies of the paraventricular and supraoptic nuclei to the posterior pituitary along with neurophysins. Neurophysins are synthesized as part of the AVP precursor molecule via genetic transcription in the short arm of chromosome 20 (20p13). Upon stimulation of the magnocellular neurons, an action potential travels through the neuronal axon toward the posterior pituitary where it causes calcium influx and endopeptidase activation with release of the contents of the neurosecretory granules into the perivascular space; and thus, into the capillary system of the pituitary stalk and posterior pituitary.

In addition to their role in hormonal transport, disruption of the structure of neurophysins can have two main effects on AVP action and metabolism. First, there may be a decline in the binding site and activity of the endopeptidase responsible for the cleavage of AVP. Second, there may also be a change in the pattern of polymerization of neurophysin and its binding of AVP, which in turn may result in a specific enzymatic degradation of the hormone. Both of these effects can theoretically lead to deficiency in the amount of available AVP.

B. Stimuli of AVP secretion

1. **Plasma osmolality.** Plasma osmolality is normally the most important determinant of AVP secretion. A change in plasma osmolality of as little as 1% can be p. 101p. 102detected by specialized magnocellular neurons in the circumventricular organs and transmitted to the supraoptic and paraventricular nuclei where AVP is synthesized. Axons from these nerve cells terminate in the distal hypophysial stalk and in the posterior pituitary where they release AVP into the circulation. The secretion of AVP is linear with respect to changes in plasma osmolality. A 1-mOsm/kg H_2O increase in plasma osmolality causes an increase in plasma AVP level from 0.4 to 0.8 pg/mL once a certain osmotic threshold is reached (284.3 mOsm/kg for a young adult). A maximal antidiuretic effect is obtained with increases in plasma osmolality of 5 to 10 mOsm/kg once the maximal urine concentration has been attained. During regular daily

circumstances, spontaneous fluid intake and AVP release are the main factors responsible for the maintenance of osmolality.

2. **Arterial underfilling.** Arterial underfilling is another stimulant of AVP secretion and includes clinical scenarios, such as bleeding, venous pulling, decreased systemic vascular resistance, and “third spacing.” High-pressure mechanoreceptors located in the aortic arch and carotid sinuses, as well as low-pressure receptors located in the atria and in the pulmonary venous system, serve as sensors of volume/pressure status to the hypothalamic magnocellular neurons via afferent branches of the vagal and glossopharyngeal nerves. This system is less sensitive than the osmoreceptor system and requires a 5% to 10% reduction in intrathoracic blood volume before it is activated. In spite of this decreased sensitivity, this system may override osmolar regulation and cause hyponatremia when it is provoked. Moreover, these two systems do not function completely independently from each other. A decrease in arterial filling will decrease the osmotic threshold of AVP secretion. Conversely, an increase in left atrial pressure will raise the osmotic threshold for AVP secretion.
3. **Other nonosmotic stimuli.** Multiple nonosmotic stimuli also exist for the secretion of AVP. **Nausea** is a very potent stimulus, which even in the absence of vomiting or a volume-depleted state, can increase AVP up to 100 to 1 000 times the basal levels. Although the physiologic relevance of this elevation in AVP is unknown, its presence may account for the vasoconstriction and facial pallor seen during episodes of nausea and vomiting. The elevation in AVP related to nausea may also be partially responsible for the increase in release that has been described with certain medications, or in situations in which an emetic response is elicited (e.g., ketoacidosis, motion sickness, acute hypoxia, and vasovagal reactions). p. 102p. 103The secretion of AVP is also influenced by several drugs (Table 10-1). The ability of central angiotensin-2 and various cytokines, especially **interleukin 6** (IL-6), to cause release of AVP is of particular significance because this factor may be important in the pathophysiology of the **syndrome of inappropriate antidiuretic hormone secretion (SIADH)**.

TABLE 10-1 Factors That Influence AVP Secretion

Stimulants of AVP secretion	
Acetylcholine	Hypercapnia
Anesthetic agents	Hypoxia
Angiotensin II	Metoclopramide
Barbiturates	Morphine and other narcotics
β-Adrenergic agonists	Nicotine
Carbamazepine or oxcarbazepine	Oxytocin
Clofibrate	Phenothiazines
Clozapine	Prostaglandin E_2
Cyclophosphamide	Serotonin reuptake inhibitors
Ecstasy	Tricyclics
Histamine	Vincristine
Suppressants of AVP secretion	
Alcohol	Atrial natriuretic peptide
α-Adrenergic agonists	Phenytoin

AVP, arginine vasopressin.

III. EFFECT OF AVP ON THE KIDNEY

A. The kidney is of prime importance in the regulation of water balance and metabolism. This is accomplished through AVP inducing increased water permeability and increased urea movement in the renal collecting ducts, as well as by AVP-stimulating NaCl absorption in the thick ascending loop of Henle. In the collecting ducts, AVP binds to its G-protein–coupled receptor in the basolateral membrane (V_2 subtype) with subsequent generation of cyclic adenosine monophosphate (cAMP), which goes on to activate protein kinase A (PKA). The local concentration of cAMP is limited by phosphodiesterases. Once activated, PKA in turn phosphorylates aquaporin-2 (AQP2) in serine residue 256, making possible its transport to the luminal membrane of the collecting duct cell where it fuses into the membrane. The insertion of the AQP2 channel causes H_2O reabsorption from the urine along an osmotic gradient into the cell. Once in the cell, the H_2O is then transported to the basolateral membrane by aquaporin-3 and aquaporin-4, thereby allowing intracellular water to be absorbed into the vasa recta. This transfer results in transcellular water transport.

Once the stimulus for H_2O conservation ends, AQP2 is recycled by endocytosis (Fig. 10-1).

B. Effect on the permeability of water. The effect of AVP on water permeability is accomplished in both short-acting and long-acting modes.

1. **Short-term effect.** The short-term regulation of water transport occurs through the fusion of AQP2-containing intracytoplasmic vesicles with the apical membranes, thereby increasing the permeability of the collecting duct to water. This effect is rapid in onset (within a few minutes) and rapidly reversible.
2. **Long-term effect.** The long-term regulation of water transport involves gene transcription and protein expression. This effect is mediated by the phosphorylation of a cAMP response element in the 5′ flanking region of the AQP2 gene with consequent increased gene transcription. This effect is not rapidly reversible.

C. Effect of AVP on the concentrating mechanism. AVP increases permeability to urea in the inner medullary collecting duct, thereby enhancing the concentration of urea in the renal medulla. This concentration, in turn, maintains a high medullary interstitial osmotic gradient and facilitates its own action on the concentration of water. This effect is also mediated by increased intracellular cAMP. Additionally, AVP increases the rate of absorption of NaCl in the medullary thick ascending limb, thereby promoting the countercurrent multiplication mechanism that affects the concentrating ability of the kidney in long-standing deficiency of AVP of any etiology. This, together with the long-term effect on expression of AVP in the collecting duct cells, should be taken into account when interpreting a patient with polyuria “inadequate” response to AVP or its analog.

IV. DIABETES INSIPIDUS

A. Definition. Diabetes insipidus (DI) is a disorder where the hallmark is a secretion of a large volume of dilute and hypotonic urine (“diabetes”). More specifically, it can be defined as >30 mL/kg/24 hours, with urine osmolality <300 mOsm/kg and specific gravity <1.010. This contrasts to the hypertonic polyuria caused by the osmotic diuresis in diabetes mellitus. DI can result from a relative or absolute deficit of AVP (central DI), inability of the kidney to respond appropriately to AVP (nephrogenic DI), or physiologic suppression of AVP release as a result of water overload (primary polydipsia).

B. Types of DI

1. Central DI (central or neurohypophyseal)

a. Definition. Central DI is a state of hypotonic polyuria resulting from absolute or relatively deficient secretion of AVP in spite of adequate stimuli and with a normal renal responsiveness to AVP.

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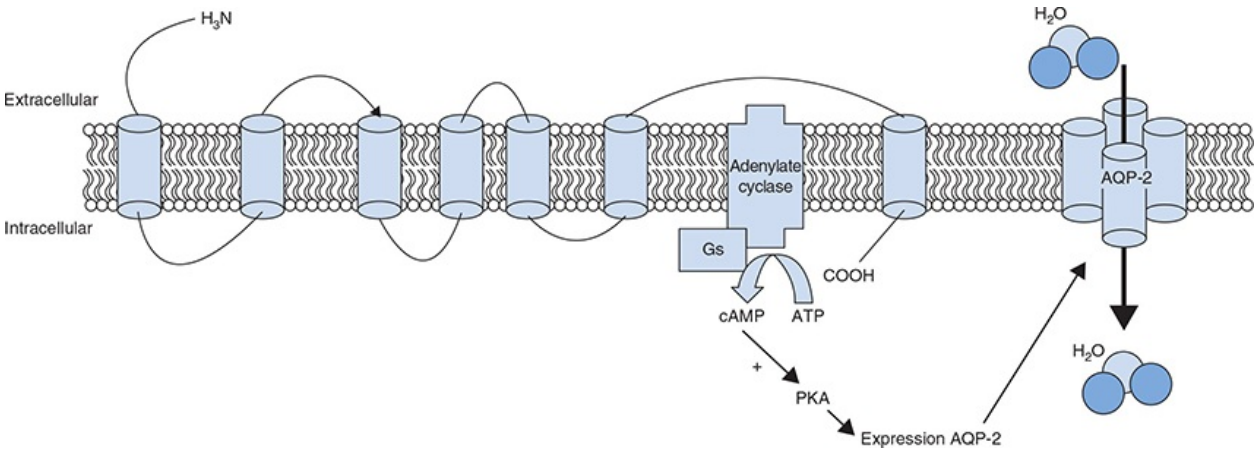

Figure 10-1. Vasopressin binding to its V_2 receptor leads to increased cyclic adenosine monophosphate (cAMP) with subsequent activation of protein kinase A (PKA). PKA activation causes phosphorylation of aquaporin-2 (AQP2) and translocation to the apical plasma membrane. The final effect is water (H_2O) passage through the AQP2 channel.

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b. Classification

i. **Complete central DI** is characterized by total inability to synthesize or release AVP.

ii. **Partial central DI** is characterized by an inability to synthesize and/or release an adequate amount of AVP.

c. Etiology

i. **Familial central DI** is a rare disorder inherited in an autosomal dominant manner with variable expression and usually presenting during childhood. Most of the genetic defects identified involve the neurophysin molecule, with probable altered packaging of the prohormone in the neurosecretory granules.

Acquired central DI can result from numerous conditions
ii. (Table 10-2). Anterior pituitary tumors rarely cause DI.

d. Pathophysiology. Polyuria results because of the inability to secrete enough AVP to maintain normal water homeostasis. However, polyuria does not p. 105p. 106occur until 90% of the vasopressinergic neurons are lost. In the presence of an intact thirst mechanism, the resultant hyperosmolality leads to increase in water intake and normalization of plasma osmolality.

TABLE 10-2 Causes of Central Diabetes Insipidus

Primary causes (not acquired)

Familial (autosomal dominant)
Idiopathic

Secondary causes (acquired)

Traumatic
- Accidental (e.g., head trauma)
- Iatrogenic (e.g., surgery)

Tumors
- Craniopharyngioma
- Primary pituitary tumor
- Metastatic disease (breast cancer, lung cancer)
- Acute leukemia
- Lymphomatoid granulomatosis
- Rathke cleft cyst
- Mixed germ cell tumor (rare)

Granulomatous disease
- Sarcoidosis
- Histiocytosis
- Tuberculosis
- Wegener granulomatosis

Infectious diseases
- Meningitis
- Encephalitis

Vascular
- Aneurysm
- Sheehan syndrome
- Hypoxic encephalopathy

Drugs
- Alcohol

• Diphenylhydantoin Autoimmune • Lymphocytic infindibulohypophysitis (rare; usually affects anterior adenohypophysis) Pregnancy • AVP-resistant DI of pregnancy (accelerated metabolism of AVP)
AVP, arginine vasopressin; DI, diabetes insipidus.

e. **Clinical presentation.** Patients present with polyuria and polydipsia, often during both day and night. Interestingly, there is often a **predilection for cold water**, which quenches osmotically driven thirst. Urine output may vary from a few liters to 20 L/day. Serum osmolality and electrolyte balance is determined by the functional status of the thirst mechanism as well as access to water. Metabolic complications can develop very quickly if the thirst mechanism is impaired (e.g., altered mentation, sedation, and nursing home residents). **Up to 60% of pituitary surgery patients develop transient DI.** When DI is the result of surgical or traumatic injury to the hypothalamic-posterior pituitary area, it may be a classical triphasic response. Phase 1 is transient DI because of axonal shock and inability to propagate action potentials. This is usually seen within 24 hours of the insult and may resolve within 6 days. If seen, phase 2 is an antidiuresis resulting from a SIADH-like surge of AVP secondary to unregulated AVP secretion from axonal degeneration. This typically occurs 5 to 7 days after the primary insult. Phase 3 is often the recurrence of DI around day 12 or 13. Ultimately, the component of DI may or may not resolve over time.

f. **Diagnosis.** The diagnosis of central DI involves ruling out other causes of polyuria. Responsiveness to AVP does not constitute a diagnosis of central DI, because patients with primary polydipsia may also respond to AVP with decreases in urine output. **Primary polydipsia** is a condition characterized by a powerful desire to ingest liquid. It may be from a structural hypothalamic lesion, but is most commonly associated with psychiatric disease. If enough fluid is ingested, it can result in polyuria and reduced plasma osmolality.

The classical picture of **central DI** includes hypotonic polyuria

with normal to slightly elevated plasma osmolality and an inappropriately low AVP concentration. This is in contrast to primary polydipsia, in which the serum osmolality is not high and may even be low.

Neuroimaging with magnetic resonance imaging (MRI) of the neurohypophysis may be useful as an adjunctive diagnostic tool. The pituitary stalk can also be evaluated by MRI. Enlargement is present above 2 to 3 mm and may be caused by infiltrative diseases, infection, or metastasis. The **absence of a bright spot in T1-weighted images of the sella** is a characteristic finding in central DI. However, this does not always hold true because, in early cases of familial hypothalamic DI, the bright spot may still be present.

2. **Nephrogenic DI**
   a. **Definition.** Nephrogenic DI is a hypotonic polyuric state resulting from **renal insensitivity to AVP**. It is characterized by persistent hypotonic polyuria despite the presence of adequate levels of AVP and failure of exogenous AVP to significantly decrease urine volume or increase urine osmolality.
   b. **Etiology.** Like central DI, this condition can also be familial or acquired, and can be complete or partial (Table 10-3).
      i. **Congenital nephrogenic DI.** Mutations in two different areas have been identified. Ninety percent of the implicated mutations cause abnormal folding, and resultant nonfunctioning AVP V_2 receptor proteins present in the collecting duct. The mode of inheritance is X-linked recessive, and heterozygous female carriers may have mild water metabolism impairment with nocturia and subnormal urine-concentrating ability. Ten percent of families with DI have mutations in the *AQP2* gene, located in chromosome 12, region q13. Inheritance of this mutation may be in an X-linked manner (90%), autosomal recessive (9%), or autosomal dominant (1%).
      ii. **Acquired nephrogenic DI.** Hypokalemia and hypercalcemia have long been described as potential causes of DI. In both scenarios, there is downregulation of AQP2 expression in the inner medulla and, in addition,

hypercalcemia and decreased Na-K-2Cl cotransporter concentration in the outer medulla. **Lithium** is known to cause DI in 20% of patients taking this medication, p. 106p. 107 secondary to downregulation of AQP2 channels. Acute kidney injury and urinary tract obstruction are also important causes of nephrogenic DI.

TABLE 10-3 Causes of Nephrogenic Diabetes Insipidus

Familial
Familial X-linked recessive (mutation in V_2 receptor)
Autosomal recessive (mutation in aquaporin gene)
Autosomal dominant (mutation in aquaporin gene)
Acquired
Drugs: lithium therapy (resultant decreases in AQP2 levels), demeclocycline, methoxyflurane
Metabolic: hypokalemia (decreased sensitivity of adenylcyclase to AVP, affects long-term regulation of AQP2), hypercalcemic-hypercalciuria (altered AVP-induced AQP2 regulation via apical calcium sensor receptor)
Bilateral urinary tract obstruction, BPH, neurogenic bladder (impaired long-term AQP2 regulation)
Vascular: sickle cell disease or trait
Infiltrative: amyloidosis
Low-protein diet

AQP2, aquaporin-2; AVP, arginine vasopressin; BPH, benign prostatic hypertrophy.

c. Classification

i. Complete: Characterized by a total inability to respond to AVP even in pharmacologic doses.

ii. Partial: Characterized by responsiveness to AVP in pharmacologic doses.

d. Pathophysiology. The basic abnormality in nephrogenic DI is an inability of the collecting ducts to increase their permeability to water in response to AVP. Hence, there is resultant impairment in water conservation and subsequent increase in plasma osmolality and hypernatremia.

e. Clinical presentation. Familial nephrogenic **DI presents in**

infancy with vomiting, fever, failure to thrive, hypotonic polyuria, and electrolyte imbalances. There may be a family history of other affected males. Recognition of this disease is critical to the survival of the patient. The time of presentation depends on the underlying acquired type and disease process or exposure to medication. **Acquired nephrogenic DI** often presents with moderate polyuria (3 to 4 L/day), and if the thirst mechanism is intact, hypernatremia does not ensue.

3. **Primary polydipsia**
   a. **Dipsogenic DI.** Individuals with dipsogenic DI have a normal osmotic threshold for AVP release, but an unusually lower osmotic threshold for thirst than that for AVP release. This abnormality leads to constant hypotonic polyuria because the serum osmolality is maintained at a level below the threshold for AVP release. Organic causes such as hypothalamic lesions and infiltrative disorders (i.e., sarcoidosis, hemochromatosis, and metastases) have been described as causative factors.
   b. **Psychogenic polydipsia.** This is a condition of compulsive water drinking seen in individuals with underlying psychological or psychiatric disorders. Unlike patients with dipsogenic polydipsia, these individuals do not have a change in thirst threshold, rather their polydipsia stems from cognitive impairment resulting from underlying psychopathology.
4. **DI in pregnancy.** Transient gestational DI has been reported and is considered to be secondary to increased AVP degradation by the placental enzyme vasopressinase.

C. Diagnostic tests for polyuric states. Diagnosis of the etiology of polyuric states may be very difficult. Osmotic causes of polyuria, notably hyperglycemia, can be readily identified by clinical history and basic laboratory workup. A history of psychiatric disease in the presence of hypotonic polyuria is highly suggestive of primary polydipsia (i.e., psychogenic polydipsia). Similarly, hypotonic polyuria

in p. 107p. 108the setting of increased plasma osmolality and serum sodium excludes the diagnosis of primary polydipsia. In the same way, the sudden development of polyuria after surgical or nonsurgical trauma to the pituitary/hypothalamic area is very suggestive of central DI. In the presence of an intact thirst mechanism and access to water, there is typically normal serum sodium. In this

scenario, provocative testing is required to establish a diagnosis. A water deprivation test followed by AVP administration is the most commonly used provocative test because it is based on the premise that dehydration stimulates AVP release and urine concentration.

1. **Water deprivation test**
   a. **Method.** During the water deprivation test, all fluids are withheld in order to cause dehydration and provide a potent stimulus for maximal AVP secretion (i.e., plasma osmolality >295 mOsm/kg). The duration of fluid deprivation depends on the clinical presentation and may vary from 4 to 18 hours. The test should be done in a room without access to a water source. Patients are asked to urinate before the test is started and initial body weight recorded. Thereafter, body weight is monitored every hour, and urine volume recorded with urine osmolality determined hourly. The test should be discontinued if body weight decreases by 3%, urine osmolality remains stable (three consecutive urine osmolalities with variability <30 mOsm/kg), or hypernatremia develops (>145 mmol/L). Once the urine osmolality has stabilized or the patient has lost >2% of body weight, measurements of plasma sodium, osmolality, and AVP are taken. Then, the patient is given AVP (5 U) or the synthetic AVP analog, desmopressin (DDAVP; 1 mg) subcutaneously, with subsequent measurements of urine osmolality and urinary volume at 30, 60, and 120 minutes after injection. The highest value is used to evaluate the patient's response to AVP. For completeness, plasma osmolality should be measured at the beginning of the test, again before the administration of DDAVP, and after the administration of the drug. In individuals with severe polyuria (urine output >10 L/day), water deprivation should be started early in the morning under careful supervision. In patients with less severe polyuria, water deprivation may be started the night before because 12 to 18 hours of fluid deprivation may be required.
   b. **Precautions.** Drugs that influence AVP secretion or action should be discontinued if possible. Caffeine-containing beverages should be avoided on the day of the test, and alcohol and tobacco should be avoided for at least 24 hours before the test. During testing, individuals should be monitored for conditions that may provide nonosmotic stimuli for AVP

secretion (e.g., nausea, hypotension, or vasovagal reactions).

c. **Interpretation**

i. **Healthy subjects.** In healthy subjects, the water deprivation will provide stimulus for maximal AVP secretion and maximal urine concentration. Hence, administration of additional AVP or its analogs will not lead to >10% increase in the osmolality of the already maximally concentrated urine.

ii. **Primary polydipsia.** The absence of an increase of urine osmolality above that of plasma osmolality virtually excludes primary polydipsia, provided surreptitious drinking is excluded. In this last circumstance, neither the serum nor the urine osmolality will increase adequately during the water deprivation test. Another clue to surreptitious water drinking during a water deprivation test is an incongruent degree of weight loss in comparison with what would be expected on the basis of urine output during the test.

iii. **Complete DI.** In both central and nephrogenic complete DI, the urine osmolality does not increase above that of the plasma. The two forms can be further differentiated by the individual's response to the administration of AVP or DDAVP. Although there may be some increase in the urine osmolality in nephrogenic DI, this is usually <10% of the level achieved after dehydration. Patients with central DI usually respond to AVP administration with a >50% increase in urine osmolality.

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iv. **Partial DI.** Individuals with partial DI (both central and nephrogenic) may have urine osmolalities that are higher than their plasma osmolalities after water deprivation. In central DI, however, the measured AVP will be lower than expected for the plasma osmolality, whereas in nephrogenic partial DI, it will be appropriate. Adequate plasma AVP can be estimated based on the serum osmolality; that is, AVP = 0.38 × (plasma osmolality − 280) ng/L.

2. **Hypertonic saline infusion.** This method helps to differentiate partial DI from primary polydipsia.

a. **Method and interpretation.** During this provocative testing, 3% NaCl is infused at 0.1 mL/kg/minute for 1 to 2 hours; subsequently, plasma AVP is measured once the serum osmolality and sodium are >295 mOsm/kg and 145 mEq/L, respectively. Precautions must be taken with individuals who might not be able to handle the increase in volume properly (e.g., patients with congestive heart failure or cirrhosis). When plotted on a nomogram, patients with partial central DI can be distinguished from those with partial nephrogenic DI or primary polydipsia. In patients with nephrogenic DI or primary polydipsia, AVP release in response to hypertonicity is normal, whereas patients with central DI exhibit no or subnormal increases in AVP secretion.

3. **Therapeutic trial of DDAVP.** This procedure is another method by which partial central DI can be separated from partial nephrogenic DI.

   a. **Method and interpretation.** In this approach, a therapeutic trial of DDAVP (10 to 25 μg intranasally or 1 to 2 μg subcutaneously) is given for 2 to 3 days. This will improve central DI while not affecting the patient with nephrogenic DI. Caution must be exercised to avoid water intoxication. Although this is most likely to occur in primary polydipsia, occasionally, patients with central DI may also continue to drink large amounts of water out of habit.

D. Treatment. Management of DI includes maintaining proper fluid metabolism and balance. Identification and, if possible, correction of underlying acquired pathology should always be considered in individuals with DI.

1. **Maintaining fluid metabolism.** Fortunately, most patients with DI have an intact thirst mechanism and can monitor their own water needs. However, for a select few that do not, there should be continuous monitoring of fluid intake and careful balancing of water intake and antidiuretic intervention(s).
2. **Water.** Water intake is the prime target for the management of DI. In any given patient, an adequate amount of water will correct and prevent any of the metabolic derangements that can potentially be caused by DI. This is often overlooked in hospitalized patients. Simply having water at the bedside can prevent consequences of dehydration. The pharmacologic treatment modalities should be

seen as measures that will make the water intake more tolerable by preventing nocturia and subsequent sleep deprivation.

3. **AVP agonists.** AVP agonists should be titrated to minimize sleep disruption caused by nocturia and to minimize breakthrough symptoms throughout the day.
   a. **AVP.** This is the naturally occurring ADH form in humans. Usually administered subcutaneously, it has an onset of action within 1 to 2 hours and a duration of action between 4 and 8 hours. Because of its potential pressor effect, intravenous administration should be avoided.
4. **DDAVP [1-(3-mercaptopropionic acid)-8-D-arginine vasopressin].** This synthetic analog of AVP has modifications of the molecule that result in a prolonged half-life with reduced pressor activity and relative resistance to degradation by vasopressinase. This makes it the treatment of choice during pregnancy. The agent is about 2 000 times more specific for antidiuresis than the naturally occurring substance. It is available for clinical use in oral, parenteral, and nasal spray forms.
   a. **Intranasal application.** The onset of action of the nasally applied drug is rapid (45 minutes), with a peak effect evident within 1 to 5 hours and a duration of action of 6 to 24 hours.
      i. **Nasal spray** is available in a concentration of 0.1 mg/mL and delivers 0.1 mL (10 μg) fixed dose per spray. One dose has an antidiuretic activity p. 109p. 110of 40 IU. The usual dose is 1 to 4 sprays/day in a single dose or in two to three divided doses. It is advisable to give the medication at bedtime to prevent sleep disruption due to nocturia.
      ii. **Rhinal tube** multidose vial comes in a concentration of 0.1 mg/mL and can deliver 5 to 20 μg into a rhinal catheter, from which the drug is blown into the nose.
      iii. **Stimate nasal spray** is available in a concentration of 0.15 mg/mL and delivers 0.1 mL (150 μg). One dose has an antidiuretic activity of 600 IU.
   b. **Parenteral administration.** Parenteral administration is 5 to 20 times more potent than intranasal application. Available in a 4 μg/mL solution, the usual dosage is 1 to 2 μg (0.25 to 0.50 mL) given subcutaneously or intravenously twice daily.

c. **Oral administration.** Oral forms are available in 0.1 and 0.2 mg tablets. The onset of action is 30 to 60 minutes. This form has the advantage of **not requiring refrigeration**. Dosage can be started at 0.1 mg at bedtime or divided into two doses per day. The dosage is titrated based on symptoms up to a maximum of 1.2 mg total daily dose.

5. **Other agents**
   a. **Chlorpropamide.** Chlorpropamide enhances the activity of AVP and possibly its release, reducing polyuria by 25% to 75% in patients with central DI. It is useful for partial central DI with residual capacity to secrete AVP. The usual dose is 100 to 500 mg orally daily. Maximal antidiuretic activity will be noticed after 4 days. The risk of hypoglycemia seems to be low.
   b. **Carbamazepine.** Carbamazepine causes the release of AVP. It can be used in partial central DI in doses ranging from 200 to 600 mg/day.
   c. **Thiazide diuretics.** By causing mild volume contraction, thiazide diuretics reduce the amount of glomerular ultrafiltrate and increase the proximal resorption of salt and water. These agents can be used in the management of nephrogenic DI. The usual effective dose is between 50 and 100 mg/day, which can be enhanced by a low-salt diet. It is good practice to check potassium levels to monitor for hypokalemia, and use potassium supplements if needed.
   d. **Indomethacin.** Indomethacin decreases renal medullary prostaglandin E, thereby enhancing cAMP generation secondary to AVP binding to its V_2 receptor. Prostaglandin synthase inhibitors may be effective even in patients with nephrogenic DI.
6. **Management of nephrogenic DI.** The most effective treatment is thiazide diuretics and mild salt depletion, though prostaglandin synthase inhibitors may also be considered.
7. **Management of primary polydipsia.** The primary treatment is geared toward behavior modification. Drug treatment with AVP, its analogs, or other agents that increase its secretion or action are not indicated.
8. **Treatment during pregnancy.** DDAVP is the drug of choice during pregnancy, because the half-life of AVP is reduced as a

result of increased vasopressinase activity in the placenta.

9. **Treatment of the patient with altered thirst mechanism.** This situation warrants careful and frequent assessment. Fixed fluid intake and antidiuretic medication to maintain balanced water metabolism are the mainstays.
10. **Treatment in the postoperative period**
    - **a.** Careful assessment of water balance postoperatively is of extreme importance because polyuria may represent diuresis of fluid administered during surgery, which might not be obvious if attention is given only to the current fluid balance.
    - **b.** Osmotic diuresis secondary to glycosuria may be a contributing factor to polyuria because the patients are frequently treated with steroid replacement therapy.
    - **c.** True DI resulting from **neurosurgical intervention** often has a **triphasic pattern** as described previously. Caution should be used when administering AVP or DDAVP because of possible water intoxication. Usually, a dose of 1 to 2 μg subcutaneous, intramuscular, or intravenous DDAVP is given while closely monitoring plasma sodium, urinary volume, and urine osmolality. One approach is use DDAVP when polyuria reappears.

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11. **Treatment of the hypernatremic patient.** On occasion, patients with DI may present with hypernatremia because of concomitant illness that impairs water intake. Under these conditions, the initial treatment of choice is correction of the fluid deficit with isotonic normal saline. Once euvolemic, the free-water deficit should be calculated and corrected.
12. **Avoidance of potentially dangerous situations.** Serious complications can developed for patients with intact thirst mechanism that become unable to manage fluid intake. For this reason, a medical card or bracelet indicating the disease may prove to be lifesaving.

V. SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

A. Definition. SIADH is a condition of euvolemic hyponatremia secondary to increased AVP secretion, which causes urinary

concentration and water retention.

B. Pathophysiology

1. Hyponatremia develops in response to AVP (or ADH-like substances) release in spite of low serum osmolality. AVP secretion can occur secondary to ectopic production or pituitary secretion (the latter being responsible for 90% of SIADH cases). **Three patterns of AVP secretion** in the context of SIADH have been described: (a) random hypersecretion, most commonly seen with ectopic tumors; (b) inappropriately elevated and nonsuppressible basal AVP production; and (c) reset osmostat, with AVP secretion triggered by a lower-than-normal osmolality.
2. Increased urinary sodium is a contributor to hyponatremia. Water retention–induced pressure natriuresis and **increased secretion of atrial natriuretic peptide** with secondary natriuresis are possible explanations for this phenomenon.
3. Another common finding of SIADH is **decreased serum uric acid** secondary to V_1 receptor–stimulated uric acid clearance.
4. **IL-6** is a proposed causative factor for SIADH release during sickness, inflammation, and stress, because it can stimulate AVP secretion. (When it is injected into humans, IL-6 stimulates the secretion of AVP.)

C. Etiology (Table 10-4)

1. **Central nervous system disorders.** Almost any central nervous system (CNS) disorder can be associated with SIADH, including vascular events, infections, and metabolic diseases.
2. **Pulmonary conditions.** Many lung pathologies can be associated with SIADH. Whereas in positive-pressure ventilation this is due to the activation of low-pressure cardiopulmonary baroreceptors, the mechanism in other conditions is still not completely understood. As noted earlier, one very plausible candidate is IL-6, because it produces secretion of AVP both in vitro and in vivo.
3. **Neoplasms.** Perhaps the best-understood mechanism of SIADH in neoplastic disease is that seen in small-cell lung cancer, in which cancer cells can produce and secrete AVP and AVP-like substances that possess both immunologic and biologic characteristics of AVP.
4. **Pharmacologic agents.** Several drugs are known to augment AVP secretion, enhance its antidiuretic effect, and stimulate renal

V_2 receptors.

D. Clinical manifestations. Clinical symptoms, when present, are mainly neurologic, but in rare cases, rhabdomyolysis can be present. Neurologic symptoms range from vague headache and nausea to seizures, altered mental status, and focal neurologic deficits. These later manifestations are secondary to cerebral edema resulting from water shift into the brain because of decreased plasma osmolality. Needless to say, a high index of suspicion is required for proper identification. Although not exclusively so, symptoms occur more commonly when serum sodium drops to <125 mEq/L. Symptoms are also related to the rate of decrease in the serum sodium, with symptoms occurring more often with a rapid drop in sodium level.

E. Laboratory findings. Hyposmolar hyponatremia with concomitant submaximal dilute urine is the hallmark of SIADH. Urine sodium levels are elevated, typically above 20 mEq/L. Often, there is a component of **urinary uric acid loss with hypouricemia**. By definition, diseases that impair free-water clearance are absent (e.g., adrenal insufficiency or hypothyroidism). If measured, plasma ADH levels p. 111p. 112will be inappropriately high for the degree of hyposmolarity but may be within the normal range.

TABLE 10-4 Causes of SIADH

CNS disorders
Head injury
Infections: meningitis, encephalitis, abscess
Cerebrovascular accident
Cavernous sinus thrombosis
CNS neoplasm
Guillain–Barré syndrome
Epilepsy
Porphyria
Hydrocephalus
Shy–Drager syndrome
Multiple sclerosis
Psychosis, delirium tremens

Pulmonary disorders

Infectious: pneumonia, tuberculosis, abscess, empyema
Asthma
Pneumothorax
Cavitation
Positive-pressure ventilation
Cystic fibrosis
Neoplasms
Carcinoma: lung (especially small-cell lung cancer), pancreas, duodenum, bladder, uterine, prostate
Lymphoma, leukemia
Ewing sarcoma, mesothelioma
Thymoma (carcinoid)
Pharmacologic agents
Angiotensin-converting enzyme inhibitors
Carbamazepine
Chlorpropamide
Clofibrate
Cyclophosphamide
Selective serotonin reuptake inhibitors (especially in the elderly)
Haloperidol
Monoamine oxidase inhibitors
Nicotine
Oxytocin
Phenothiazine
Thiazide diuretics
Tricyclic antidepressants

CNS, central nervous system; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

F. Diagnosis. Following are the SIADH diagnostic criteria established by Bartter and Schwartz:

1. Decreased effective osmolality of the extracellular fluid
2. Inappropriate urinary concentration in the presence of hypo-osmolality
3. Clinical signs of euvolemia: absence of signs of hypovolemia (tachycardia and orthostatic changes) and hypervolemia (edema and ascites)

4. Elevated urinary sodium excretion with normal salt and water intake
5. Absence of other causes of euvolemic hypo-osmolality (hypoadrenalism or hypothyroidism)

Additional testing is usually not necessary if the above criteria are met, but occasionally, a water load test may confirm the diagnosis. In cases of SIADH, <80% of a water load of 20 mL/kg will be excreted. This challenge should not be done in patients with Na <125 mmol/L or plasma osmolality <275 mOsm/kg because of the risk of worsening the hyponatremia/hypo-osmolality.

Distinguishing the euvolemic from the hypovolemic patient with concomitant renal salt wasting may be a challenge, because urinary sodium concentration and fractional excretion of sodium are identical in these two conditions (Table 10-5). One way to make the distinction is to administer 1 L of 0.9% NaCl intravenously over 24 hours for 2 days. If this improves the hyponatremia by >5 mEq/L, the patient is most likely hypovolemic. In patients with SIADH, this maneuver does not increase the serum sodium. On the other hand, fluid restriction of 600 to 800 mL/day for 2 to 3 days improves hyponatremia in SIADH but not the hyponatremia in renal salt wasting.

G. Treatment. The treatment for SIADH includes correction of the underlying pathology that gave rise to the metabolic aberration (if possible), and management of the hyponatremia. If a medication is identified as a causative factor, it should be discontinued. The therapeutic approach to the hyponatremic patient depends on the following factors: evidence of symptoms, acuteness of onset of hyponatremia, and the presence of risk factors for complications resulting from correction of the hyponatremia. Symptomatic disease is most likely to be found with an acute decrease in serum sodium (i.e., a decrease of at least 0.5 mEq/L/hour) and is more commonly seen when serum sodium falls to <125 mEq/L. The duration of hyponatremia should also be taken into account. Whereas chronic hyponatremia (>48 hours) is associated with a higher chance of cerebral demyelinization if it is corrected too rapidly, acute hyponatremia is more likely to lead to the development of cerebral edema if it is not corrected quickly

1. **Acute or symptomatic hyponatremia.** The goal of therapy should be to raise serum sodium at a rate no greater than 0.5 mEq/L/hour up to 125 mEq/L, then fluid restriction is applied.

However, in young women with severe symptomatic hyponatremia, a higher rate of correction is often used (1 to 2 mEq/L/hour until sodium reaches 125 mEq/L). The total correction should be <15 mEq/day. Hypertonic saline (3% NaCl) at the rate of 1 to 2 mL/kg/hour is recommended. Addition of a loop diuretic may be used to enhance the correction of the hyponatremia by increasing free-water excretion. Such patients require close neurologic and electrolyte monitoring and should be managed in an intensive care unit.

2. **Chronic or asymptomatic hyponatremia.** The simplest available option for the treatment of SIADH, besides correction of the primary cause, is fluid restriction. The nonfood fluid intake is usually restricted to 500 to 1 000 mL/day. The p. 113p. 114drawback of this method is the high likelihood of the patient's failure to adhere to the regimen. Additional therapeutic strategies involving interference with the AVP renal effect are very appealing, but there are pitfalls identified especially with old nonspecific medications. Demeclocycline (1 200 mg/day initially, followed by 300 to 900 mg/day) or lithium (900 to 1 200 mg/day) has been used. Both of these agents have disadvantages, including a narrow therapeutic window and toxicity for lithium, and photosensitivity and toxicity for demeclocycline—this last especially in the presence of hepatic dysfunction. Furthermore, demeclocycline requires 3 to 6 days before its onset of action can be noted. Another way to increase free-water clearance is by administration of a loop diuretic supplemented with 2 to 3 g/day of NaCl and monitoring for hypokalemia. There also exists the option of inducing osmotic diuresis by administering urea (30 to 60 g/day). However, this last option has the disadvantage of being unpalatable and causing gastrointestinal symptoms. It is also not commonly used in clinical practice.

TABLE 10-5 Comparison of Various Hyponatremic States

Diagnosis	Volume status	Urinary sodium conc. (mEq/L)	Fractional excretion of sodium (%)
SIADH	Euvolemic	>20	>1

Renal	Hypovolemic	>20	>1
Extrarenal	Hypovolemic	<10	<1
Dilutional hyponatremia	Hypervolemic	<10	<1

SIADH, syndrome of inappropriate antidiuretic hormone secretion.

The **newest treatment option for hyponatremia** due to SIADH is the **aquaretics**. These compounds act by blocking the binding of AVP to its V_2 receptor in the basolateral membrane of the renal collecting duct, promoting free-water clearance without Na^+ or K^+ loss. This new class of medications is known as the **vaptans** and includes Satavaptan, Tolvatan, and Lixivaptan, the selective V_2-receptor antagonists; and Conivaptan, a V_1/V_2-receptor antagonist. Tolvaptan and Lixivaptan taken orally have been shown to be effective in raising the serum sodium in patients with mild-to-moderate hyponatremia, but only Tolvaptan is the Food and Drug Administration (FDA) approved. Both drugs were evaluated in trials of patients with euvolemic hyponatremia, with sodium in the range of 127 to 132 mmol. Conivaptan is approved by the FDA for parenteral use and is useful in the inpatient setting. With an onset of action of 1 to 2 hours, Conivaptan can raise the sodium more rapidly than fluid restriction alone. Care must be taken to ensure that the sodium level is not raised too quickly, especially in critically ill patients. The vaptans have the advantage over diuretics of not causing neurohormonal activation, but long-term outcomes data and safety profiles have not been established at this point.

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Preoperative, Intraoperative, and Postoperative Management Following Pituitary Surgery

11

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I. INTRODUCTION

The most common sellar and parasellar pathologies requiring surgery are pituitary adenomas, Rathke cleft cysts (RCC) and craniopharyngiomas. Surgery is considered first-line therapy for the great majority of symptomatic pituitary adenomas, with the exception of prolactinomas, which are typically treated first with dopamine agonist therapy. Surgery is also considered first-line therapy for symptomatic RCC and craniopharyngiomas. In this chapter, we describe the (a) preoperative preparation, indications for, and goals of transsphenoidal surgery, (b) intraoperative management, including the key operative steps and technical nuances of surgical management of pituitary tumors and related lesions as well as important anesthesia considerations, and (c) the postoperative management of patients undergoing transsphenoidal surgery for these three common sellar and parasellar pathologies. This chapter also emphasizes the need for a team approach and “center of excellence” model to optimize the care of patients with pituitary pathology.

II. PREOPERATIVE MANAGEMENT

Patients diagnosed with a symptomatic pituitary adenoma, RCC, or craniopharyngioma should undergo (a) complete pituitary hormonal testing, including an assessment of all anterior and posterior hormonal axes, (b) sellar magnetic resonance imaging (MRI) with gadolinium (or computed tomography [CT] sellar imaging if MRI is not available or the

patient has an MRI–incompatible implant, such as a pacemaker), and (c) medical clearance and routine preoperative testing and bloodwork, which, in some instances, may also include additional assessment such as an ophthalmology evaluation preferably with a neuroophthalmologist with visual-field testing for any patient whose tumor comes in contact with the optic chiasm or nerves. Cardiac or pulmonary function testing may also be indicated depending upon a given patient's comorbidities.

A. Hormonal testing

1. All patients undergoing pituitary-related surgery warrant full anterior and posterior hormonal assessment, including morning plasma adrenocorticotropic hormone (ACTH) and serum cortisol, thyroid-stimulating hormone (TSH), total T_4 or free T_4, luteinizing hormone, follicle-stimulating hormone, testosterone or estrogens depending on the patient's gender, prolactin, growth hormone (GH) (in the setting of acromegaly), and insulin-like growth factor 1 (IGF-1). Arginine vasopressin measurement is useful if there are signs and symptoms of diabetes insipidus. Posterior pituitary function is assessed based upon urine-specific gravity, serum sodium, and urine output.
2. Typically, in the immediate preoperative period, the most important hormonal deficiencies that warrant treatment are adrenal insufficiency and diabetes insipidus which are treated with hydrocortisone and desmopressin (DDAVP), respectively. An appropriate daily dose of hydrocortisone is determined largely by the presence or absence of adrenal insufficiency symptoms, and additional hydrocortisone must be administered during times of increased physiologic stress, including during surgical resection of a pituitary adenoma.
3. For patients with functional adenomas, including those with Cushing disease, acromegaly, prolactinomas, and TSH-secreting adenomas, additional hormonal testing or therapies may be needed to confirm the diagnosis, determine appropriate management, or prepare the patient for surgery.

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B. Cushing disease

1. For patients with suspected Cushing disease, diurnal fluctuations in serum cortisol levels can make it difficult to accurately assess

hypercortisolemia, necessitating measurement of not only serum levels of ACTH and cortisol but also levels of 24-hour urinary-free cortisol and midnight salivary cortisol. Patients with normal or elevated ACTH in the setting of Cushing syndrome have ACTH dependence most commonly caused by a pituitary adenoma or an ectopic source of ACTH production, such as a bronchial, thymic, or pancreatic islet cell tumor. Patients with low ACTH in the setting of Cushing syndrome have ACTH-independent Cushing syndrome most commonly as a result of a cortisol-secreting adrenal adenoma. Low- and high-dose dexamethasone suppression testing can be performed to distinguish among these three entities.

2. In a subset of patients without a well-defined adenoma seen on pituitary MRI and with established ACTH-dependent Cushing syndrome or with a clinical presentation suggestive of an ectopic ACTH source, inferior petrosal sinus sampling (IPSS) with corticotropin-releasing hormone (CRH) stimulation may be indicated. IPSS with CRH-stimulation testing determines whether the source of ACTH is from the pituitary gland or from a peripheral focus. When IPSS identifies a pituitary source of ACTH production in a patient with ACTH-dependent Cushing syndrome, surgical exploration of a radiographically normal pituitary gland is indicated. In all, 20% to 30% of MRIs in patients with confirmed Cushing disease are normal. Microadenomas are often found and confirmed histopathologically in these patients, many of whom reach remission. IPSS also has some, albeit limited, utility in localizing a pituitary source of ACTH to the right or left side of the sella, guiding surgical exploration of the gland.

C. Acromegaly

1. Because of its pulsatile pattern of release from the pituitary gland, serum **GH level is not a reliable indicator** of the presence of acromegaly. Patients with clinical findings consistent with acromegaly can be **reliably diagnosed by elevated levels of IGF-1**. In patients where acromegaly is strongly suspected but IGF-1 levels are normal or minimally elevated or confounded by puberty or pregnancy, an **oral glucose-tolerance test** can confirm the diagnosis of acromegaly. In patients with clinical and biochemical evidence of acromegaly but no significant MRI findings, an ectopic source of GH-releasing hormone may be the cause. Imaging with octreotide single-photon emission computed

tomography (SPECT) scanning can be useful in this situation.

D. Prolactinoma

1. In patients with pituitary adenomas, elevated serum prolactin can result from mass effect on the pituitary stalk or from a prolactinoma. Additionally, hyperprolactinemia can result from several classes of medications, primary hypothyroidism, chronic renal failure, cirrhosis, and nearly any pathology of the hypothalamus or pituitary gland. Once these other causes are ruled out, it is important to distinguish between stalk effect and a prolactinoma as the etiology of hyperprolactinemia, given the differing treatments options.
2. Generally, serum prolactin levels of >200 μg/L are the result of a prolactinoma. More modest elevations of prolactin may be attributed to a microprolactinoma or to stalk effect and should be interpreted in conjunction with imaging findings. For example, a prolactin level of 100 μg/L is likely to be stalk effect in the setting of a large macroadenoma. However, this same value is more likely to represent a prolactinoma if imaging reveals a 7-mm microadenoma.
3. One important consideration in diagnosing a prolactinoma is **the Hook effect**. When prolactin is exceedingly high, a sampling error common to immunoassays can result in a falsely low reading. Serial dilutions of the sample can identify the Hook effect and give an accurate prolactin value.

E. Thyrotropinoma

1. Patients with a suspected thyrotroph adenoma will have clinical and biochemical evidence of secondary hyperthyroidism, including elevated or normal TSH in the setting of elevated T_4 and T_3. Such patients must be treated with methimazole p. 117p. 118and/or propylthiouracil until euthyroid, as indicated by a normal total T_3 level, prior to undergoing general anesthesia. Failure to do so puts the patient at risk for thyroid storm intraoperatively or in the immediate postoperative period.

F. Imaging

1. All patients require MRI of the pituitary gland with and without gadolinium with thin-cut neuronavigation protocol. Typically, a

pituitary adenoma is best seen on T1 postgadolinium sequences and appears as a mass within or adjacent to the pituitary gland with less intense enhancement than the normal gland.

2. In patients with suspected Cushing disease, a dynamic pituitary study repeats the T1 sequence at different time intervals after gadolinium administration, increasing the visibility of microadenomas which absorb the contrast more slowly than the normal pituitary.
3. Patients with MRI-incompatible implants should undergo dedicated sellar CT imaging with contrast-enhanced sequences and thin-cut coronal and sagittal reconstructions.

G. Indications and goals of surgery

1. The endonasal endoscopic surgical approach (Fig. 11-1) is indicated for patients with (a) pituitary macroadenomas, RCC, and craniopharyngiomas causing symptoms of mass effect (visual loss, hypopituitarism, and/or intractable headaches), (b) endocrine-active adenomas causing Cushing disease, acromegaly, TSH hypersecretion, and medication refractory prolactinomas, (c) pituitary apoplexy: relatively sudden expansion of a sellar mass usually due to intralesional infarction, hemorrhage, or necrosis (Table 11-1).
2. Although most patients with prolactinomas are successfully treated medically using the dopamine agonists cabergoline or bromocriptine, a minority (10% to 15%) may require surgical removal or debulking because of medication ineffectiveness or side effects. Additionally, in rare instances, a medically treated invasive macroprolactinoma may decrease in size, potentially resulting in cerebrospinal fluid (CSF) leakage through the parasellar skull base eroded by the tumor. This situation markedly increases the risk of meningitis and tension pneumocephalus.
3. Regardless of the adenoma subtype, **the goals of surgery** (Table 11-2) are (a) selective removal of the adenoma with resolution of mass effect and/or hypersecretion syndrome, (b) preservation or restoration of pituitary gland function, (c) effective skull base closure, and (d) complication avoidance.
4. **For symptomatic RCC, surgical goals** are (a) fenestration and biopsy of the cyst wall, (b) removal of cyst contents with resolution of mass effect, and (c) preservation or restoration of pituitary gland function.

a. For **craniopharyngiomas**, the goals of surgery also depend upon several preoperative factors, including whether the patient has intact or deficient hormonal status, visual function, tumor anatomy relative to the optic apparatus and pituitary gland, and whether the patient has undergone prior surgery or radiotherapy.

TABLE 11-1 Indications for Pituitary Surgery

- Symptoms and signs of mass effect:
  - Visual loss
  - Hypopituitarism
  - Intractable headache
- Hypersecreting endocrinopathy:
  - Acromegaly (GH)
  - Cushing disease (ACTH)
  - Prolactinoma (PRL)
  - TSH-secreting adenoma
- Pituitary tumor apoplexy

ACTH, adrenocorticotropic hormone; GH, growth hormone; TSH, thyroid-stimulating hormone.

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TABLE 11-2 Goals of Pituitary Tumor Surgery

- Reduction of mass effect (with resolution of visual deficits, hypopituitarism, and headache)
- Resolution of hormonal hypersecretion (for ACTH, GH, PRL, and TSH–secreting tumors)
- Preservation or restoration of pituitary gland function
- Complication avoidance

ACTH, adrenocorticotropic hormone; GH, growth hormone; PRL, prolactin; TSH, thyroid-stimulating hormone.

b. In general, for first-time operations in patients with craniopharyngiomas and intact or relatively intact hormonal function, a gland and stalk preserving surgery is the objective (Fig. 11-3). In patients with multiple preoperative hormonal deficiencies (including diabetes insipidus), it is reasonable to try to achieve a gross total tumor removal, including stalk resection.

c. The major limitation and risk in craniopharyngioma surgery are

tumor adhesions to critical neurovascular structures, including the optic apparatus, Circle of Willis vessels, and hypothalamus. Aggressive attempts at total removal of these lesions can result in serious complications.

d. Given that many craniopharyngiomas are radiosensitive, aggressive subtotal removal with follow-up stereotactic radiotherapy if and when needed, is the most reasonable approach. Because a majority of craniopharyngiomas arise in the suprasellar and retrochiasmal space, an endonasal endoscopic route is appropriate for most patients, although, in some instances, a craniotomy may be needed.

III. INTRAOPERATIVE MANAGEMENT

Pituitary surgery necessitates many of the same practices common to most other operations, including preoperative antibiotics, attentive perioperative management of comorbid conditions, and close intraoperative monitoring of important physiologic parameters.

A. Anesthesia considerations

1. Three endocrinopathies warranting special attention from the anesthesiologist are adrenal insufficiency, hyperthyroidism, and acromegaly. Close monitoring and immediate recognition and treatment of hypothermia, hypotension, and bradycardia associated with adrenal insufficiency are essential for preventing intraoperative cardiovascular collapse. This problem can be avoided by administering stress dose hydrocortisone or other glucocorticoid immediately before the operation and redosing every 8 hours for at least 24 hours postoperatively. Patients with Cushing disease or normal adrenal axis function generally do not need to be given perioperative steroids. Perhaps more importantly, such administration of glucocorticoids interferes with postoperative assessment of this hormone axis, making it difficult to determine whether remission is achieved in patients with Cushing disease or if true postoperative adrenal insufficiency is present.

2. The stress of surgery can provoke decompensated thyrotoxicosis or “thyroid storm” in patients with hyperthyroidism. This is typically prevented by preoperative normalization of thyroid hormone levels, but in the event it occurs, the anesthesiologist must recognize and treat the hyperthermia, tachycardia, and

hypertension characteristic of this pathology.

3. As many as 10% to 30% of acromegalics may be classified as having a “difficult airway” because of the effects of excess GH, such as macroglossia, prognathism, and generalized hypertrophy of the laryngeal, pharyngeal, and vocal fold tissues. The possibility of difficult intubation should be considered and accounted for by the anesthesiologist prior to induction.

B. Surgical technique

1. The **endonasal transsphenoidal approach** with endoscopic visualization (Fig. 11-1) is the route of choice for the great majority of pituitary adenomas, and RCCs and for most craniopharyngiomas, although the transsphenoidal microscopic route p. 119p. 120is still used by some practitioners. Craniotomy is rarely indicated for pituitary adenomas and RCCs although a significant minority of craniopharyngiomas may warrant a transcranial approach.

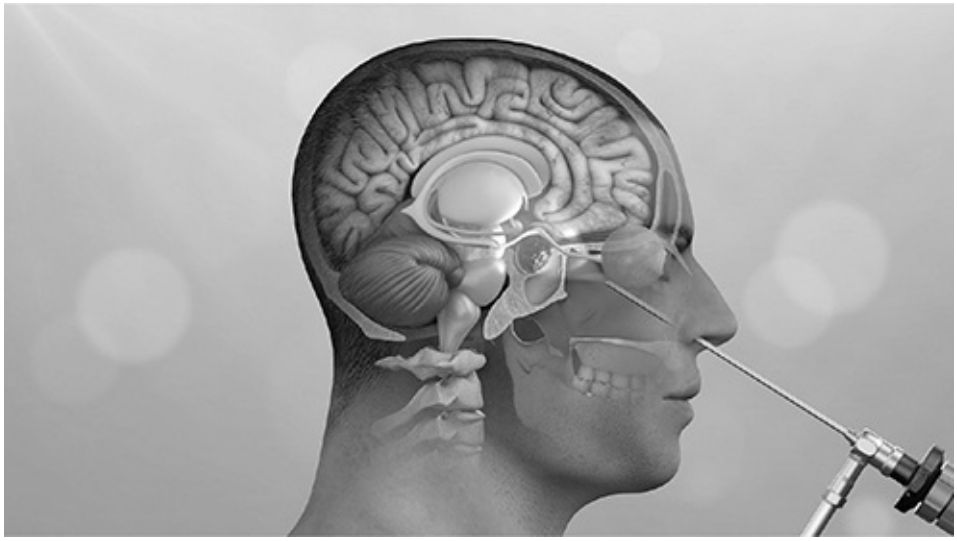

Figure 11-1. Artist’s rendering of endonasal endoscopic approach to pituitary adenoma using a rigid endoscope with high-definition visualization.

2. Since first introduced over a century ago, the safety and efficacy of transsphenoidal pituitary surgery has increased significantly. The operating microscope was introduced in the 1960s, providing superior illumination and magnification, and the concept of selective adenomectomy with pituitary gland preservation was

realized. The endoscopic era of transsphenoidal pituitary surgery began in the late 1990s when a wider viewing angle, improved image quality, and smaller scope diameter were achieved. Over the past two decades, improved instrumentation, computerized image guidance, the Doppler probe for carotid artery localization, and enhanced neuroanatomical knowledge have enhanced the safety and efficacy of the procedure. More reliable skull base closure techniques have further improved outcomes, and expanded the reach of transsphenoidal pituitary and skull base surgery.

3. Increasingly, pituitary adenomectomy and removal of other midline skull base lesions, such as RCC and craniopharyngioma, are performed using a **fully endoscopic technique using a binostril two-surgeon approach** with two neurosurgeons or a neurosurgeon and otolaryngologist working together throughout the majority of the procedure (Fig. 11-2). The operation is typically performed with a 0-degree rigid endoscope with 30- and 45-degree endoscopes available for providing angled visualization. The basic operative steps of transsphenoidal pituitary surgery begin with the approach through the nasal cavity, during which we use a bilateral nasoseptal rescue flap technique (Fig. 11-3) that preserves the posterior nasoseptal arteries bilaterally allowing for elevation of nasoseptal flaps to aid in closure and protects the olfactory epithelium during the operation all while providing unhindered exposure to the anterior face of the sphenoid sinus. This is followed by the sphenoidotomy, sellar bone removal, localization of the carotid arteries with the Doppler probe (Fig. 11-4), sellar dural opening, selective removal of the adenoma, and finally skull base and CSF leak repair. As an example, a large endocrine-inactive adenoma removed via the endonasal endoscopic approach is shown in Figure 11-5.
4. For symptomatic RCC (Fig. 11-6), the approach is identical to that used for pituitary adenomectomy. After opening the sellar dura, a low vertical linear incision is usually made through the anterior pituitary gland (which is typically pushed anteriorly by the cyst itself). The cyst contents are drained, and the cyst lining is carefully explored with angled endoscopes to make certain that all accessible cyst contents are removed. The sellar floor reconstruction is then performed p. 120p. 121with or

without a fat graft and/or septal bone graft depending upon whether a CSF leak is encountered.

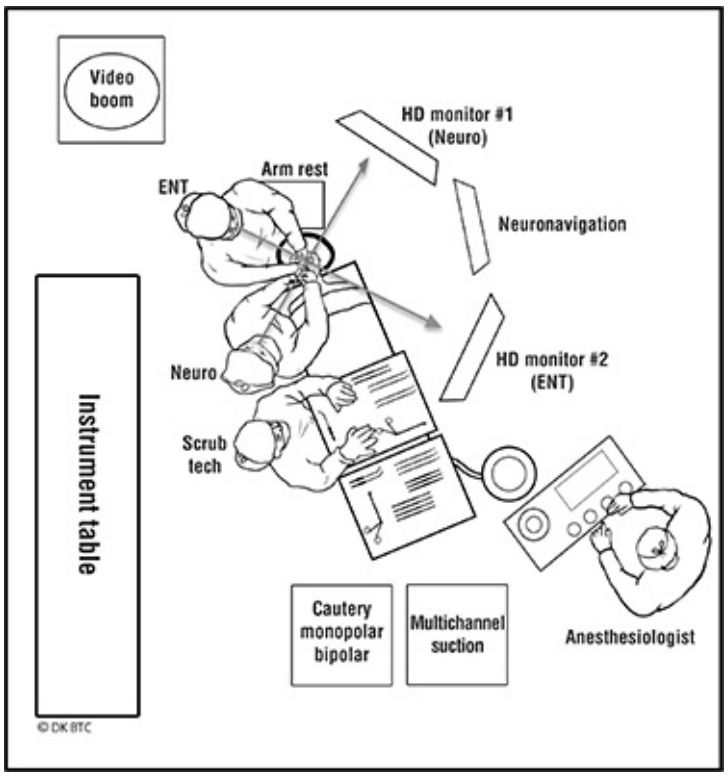

Figure 11-2. Diagram of the operating room set-up for endonasal endoscopic surgery for two surgeons with two high-definition video monitors, neuronavigation monitor and ancillary equipment.

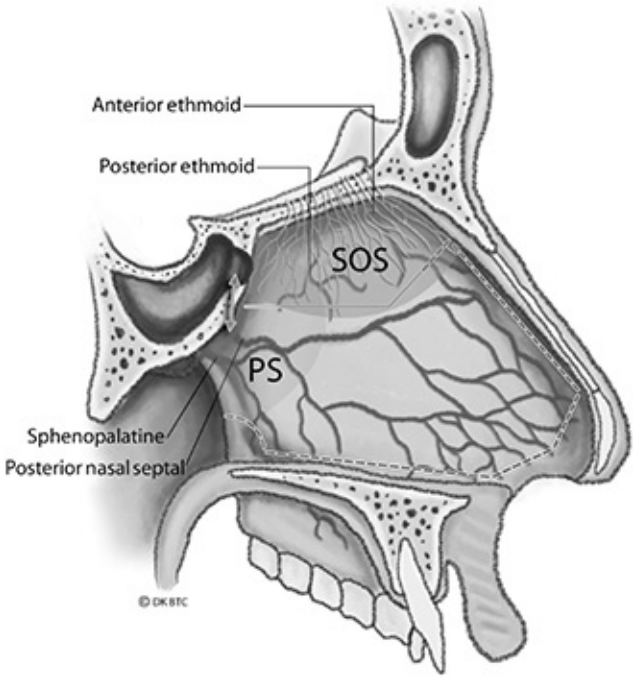

Figure 11-3. Illustration of the nasoseptal rescue flap concept with preservation of sphenopalatine and posterior nasoseptal arteries and septal olfactory strip (SOS). This approach results in a very high (>97%) preservation of olfaction and eliminates risk of sphenopalatine artery postoperative hemorrhage.

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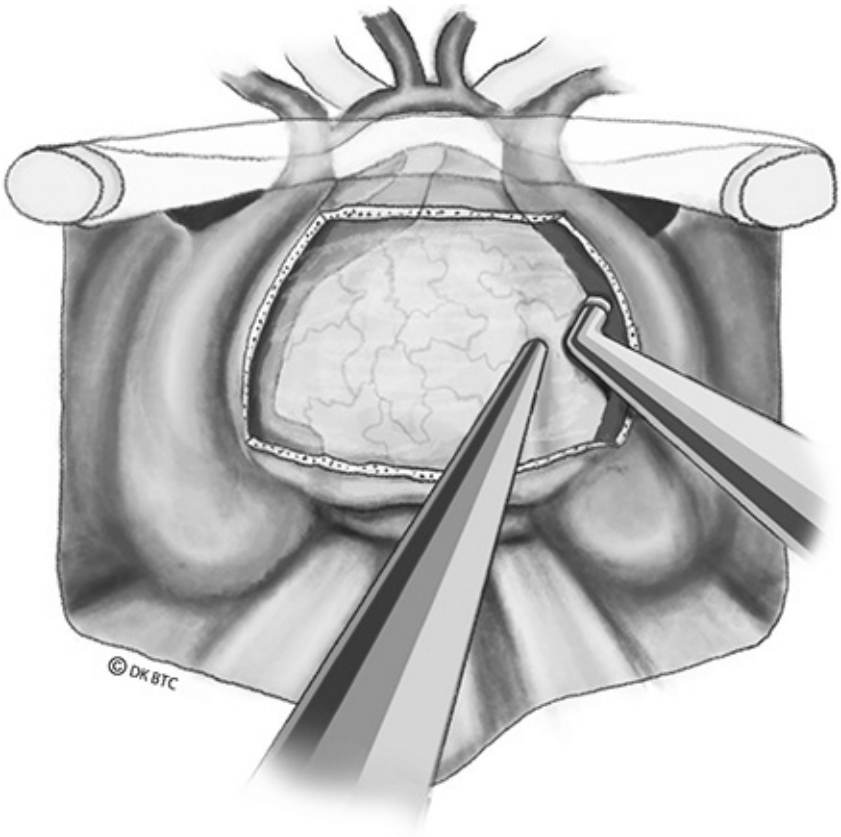

Figure 11-4. Drawing of a Doppler probe for localizing the left cavernous carotid artery with the medial edge of the cavernous sinus exposed.

5. For sellar and suprasellar craniopharyngiomas (Fig. 11-7) which typically extend into the retrochiasmal space, an extended transsellar, transplanum approach is utilized. The initial steps are the same as pituitary adenoma removal. After the sphenoidotomy, more extensive bony removal includes not only the sellar face but also the planum sphenoidale. The dura and arachnoid mater are both opened to expose the anterior aspect of the pituitary gland and the suprasellar cistern. After the tumor is removed or debulked, the skull base is reconstructed typically with a combination of harvested abdominal fat, collagen matrix, septal bone graft, and use of a pedicled, vascularized nasoseptal flap.

IV. POSTOPERATIVE MANAGEMENT

1. After endoscopic endonasal surgery, for most patients with a pituitary adenoma or RCC, patients typically are admitted to a nonintensive care unit (ICU) setting with careful monitoring of neurologic status, fluid and electrolyte balance, and selective

assessment of endocrine function, including monitoring for diabetes insipidus and adequate adrenal (cortisol) function. Most patients with a craniopharyngioma, undergoing endonasal endoscopic transsellar transplanum resection with nasoseptal flap reconstruction, are admitted to the ICU for at least one night and then for one to two nights in the intermediate care unit. Most patients with macroadenomas and larger RCCs as well as all craniopharyngioma undergo an early postoperative CT scan the day of surgery to assess for any possible postoperative complications and to assess the integrity of the skull base closure.

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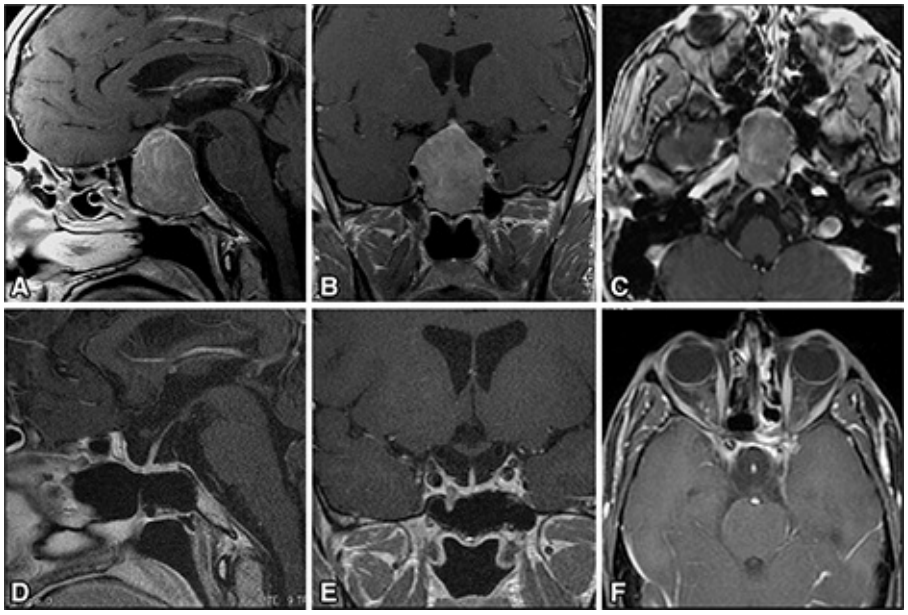

Figure 11-5. A 51-year old man with large endocrine-inactive pituitary macroadenoma. Preoperative **(A–C)** MRI shows severe gland elevation and compression. Four-year postoperative MRI **(D–F)** after endoscopic resection shows gross total removal without recurrence and gland re-expansion. His preoperative hypopituitarism resolved after surgery. MRI, magnetic resonance imaging.

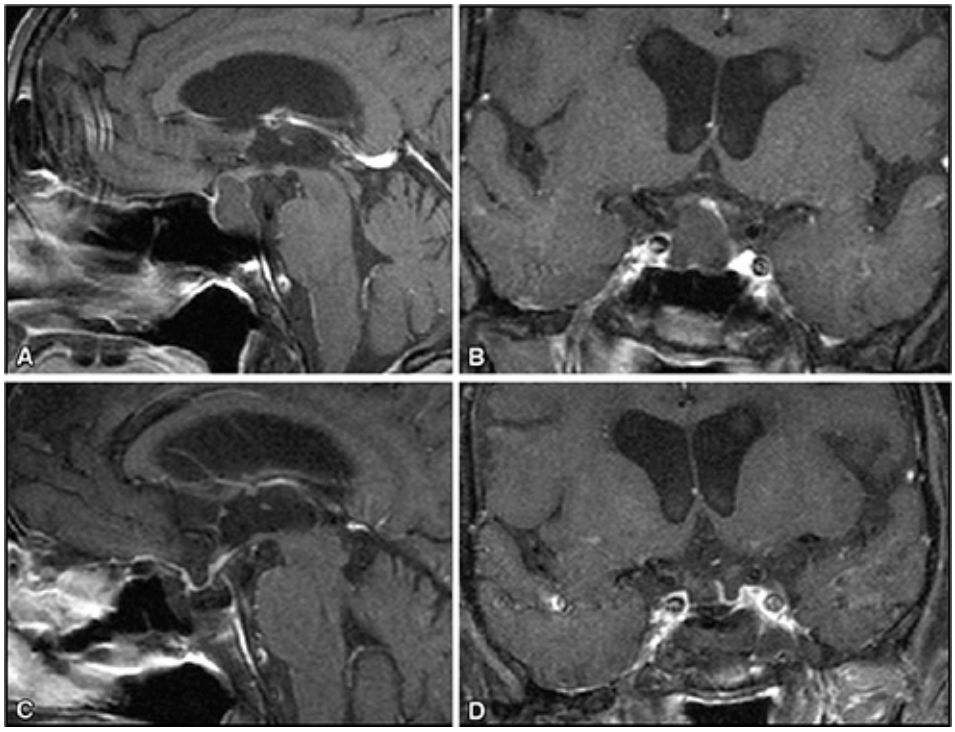

Figure 11-6. An 83-year old woman who presented with recurrent severe bouts of hyponatremia, adrenal insufficiency, low IGF-1, and low gonadotropins. Preoperative **(A** and **B)** MRI shows large sellar and suprasellar nonenhancing mass consistent with Rathke cleft cyst. Day 1 postoperative MRI **(C** and **D)** after endoscopic resection cyst fenestration shows gland re-expansion. At 2 years after surgery, she has had no further hyponatremia and remains on adrenal and thyroid replacement. IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging.

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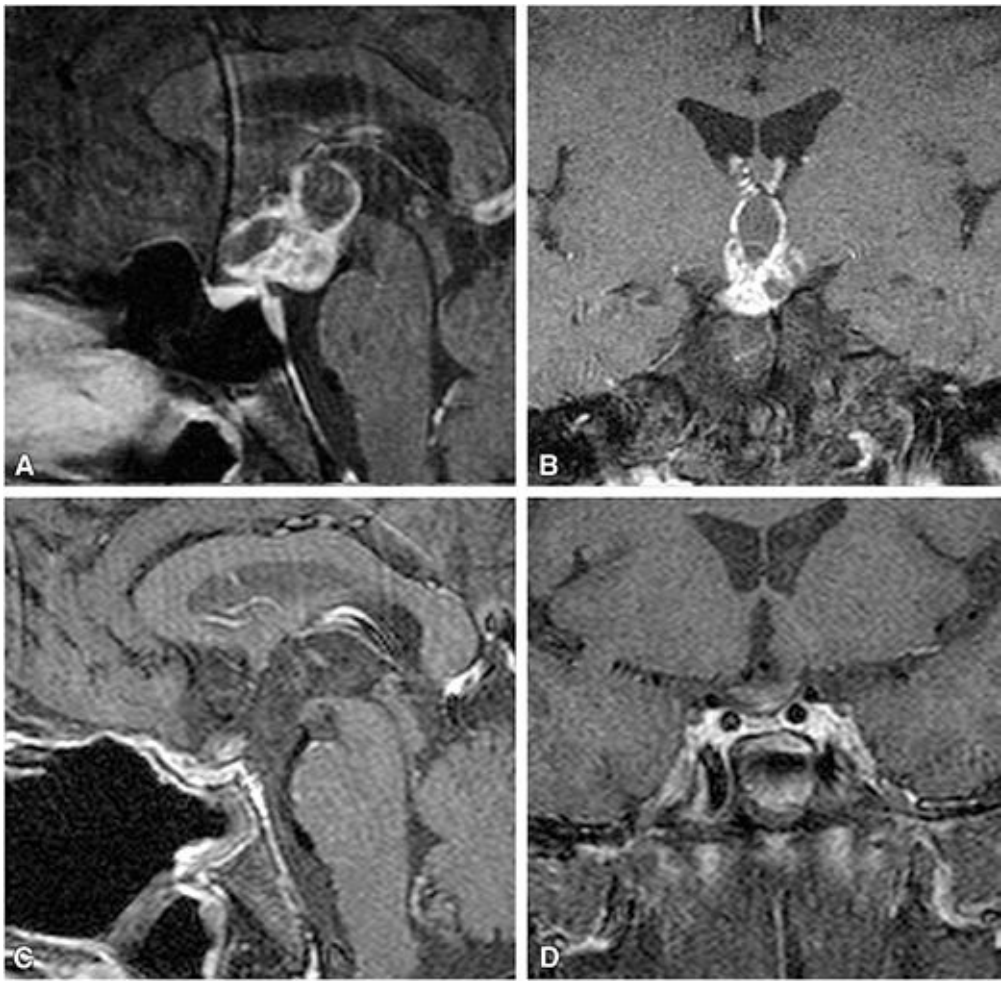

Figure 11-7. A 52-year old man with 2 years of cold intolerance, weight gain, and recent visual loss, with complete anterior and posterior pituitary failure. Preoperative MRI **(A** and **B)** shows suprasellar and retrochiasmal cystic and solid craniopharyngioma. Postoperative MRI **(C** and **D)** 1 year after endonasal endoscopic removal shows no residual or recurrent tumor and intact nasal septal flap skull base reconstruction. The patient has improved vision and remains on full pituitary hormonal replacement, including DDAVP. DDAVP, desmopressin; MRI, magnetic resonance imaging.

2. After surgery for a functional pituitary adenoma, including acromegaly, Cushing disease, and prolactinomas, early postoperative remission can typically be determined by measuring serum GH, cortisol, and prolactin levels, respectively, during the first 48 hours postsurgery. Hospital stay after pituitary surgery is typically two nights, although some patients can be discharged on postoperative day 1. Follow-up in the early postoperative outpatient setting includes assessing serum sodium levels for **delayed hyponatremia, which may occur in up to 10% of patients (typically within 4 to 8 days of surgery)**.

Subsequent surveillance includes clinic visits with the neurosurgeon and endocrinologist, regular follow-up imaging (sellar MRI), and appropriate hormonal testing. The first outpatient postoperative visit is at 10 to 14 days after surgery, and a follow-up visit typically occurs 3 months after surgery, including a complete pituitary hormonal evaluation. An early postoperative MRI or CT scan is typically performed within 2 days of surgery for patients with macroadenomas or other larger tumors. The next follow-up MRI is usually performed at 3 months after surgery.

3. Depending upon the success of surgery and the need for adjuvant therapy, other specialists in addition to endocrinologists and neurosurgeons, that may be needed p. 124p. 125for the long-term care of pituitary adenoma patients, include radiation oncologists, neuroophthalmologists, and neurooncologists (Fig. 11-8).

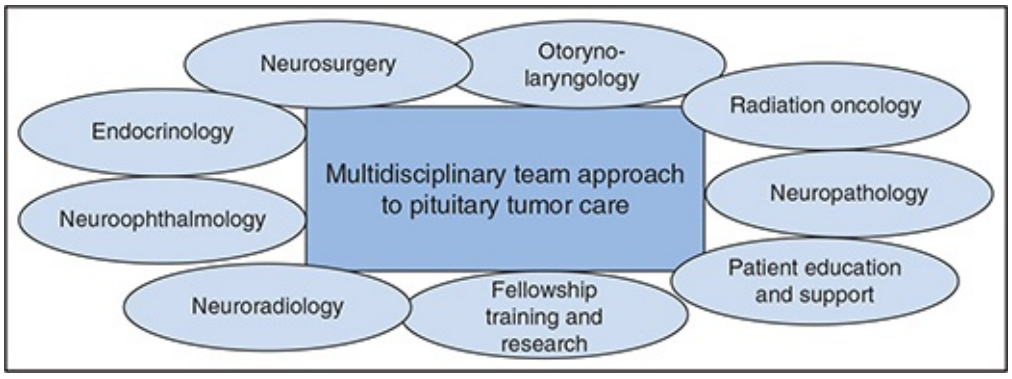

Figure 11-8. Team approach to pituitary tumor care emphasizing a multidisciplinary effort to optimize outcomes. (Reproduced with permission from McLaughlin N, Laws ER, Oyesiku NM, et al. Pituitary Centers of Excellence. *Neurosurgery* 2012;71(5):916–926.)

V. CLINICAL OUTCOMES, REMISSION RATES, AND COMPLICATIONS

A. Pituitary adenoma

1. At high-volume pituitary centers with experienced surgeons, pituitary adenoma surgery generally has a high success rate in terms of endocrine remission rates, preservation of hormonal function, visual recovery, and headache resolution, with low complication rates. As shown in Table 11-3, remission rates are significantly higher for functional microadenomas associated with

acromegaly, Cushing disease, and prolactinomas than for functional macroadenomas. Tumor invasiveness into the surrounding skull base and cavernous sinus often precludes complete microscopic removal in these larger tumors even with the use of endoscopy. For such large macroadenomas or invasive adenomas that cannot be completely removed, adjuvant therapies, including medical therapies and/or radiosurgery or stereotactic radiotherapy, may be needed to achieve remission and to halt tumor progression.

2. Complication rates in several recent large retrospective series of patients with pituitary adenomas, using the endonasal endoscopic approach for pituitary adenomas are shown in Table 11-4. As can be seen, major severe complications in general are quite low ranging from 0% to 2% for carotid artery injury, visual worsening, and meningitis and new hypopituitarism typically being under 10%. It is also notable, however, that for giant adenomas (4 cm or greater in size), that complication and remission rates are lower. Although there is some evidence suggesting that endoscopic visualization may help maximize tumor removal and improve outcomes, the impact on long-term remission rates, pituitary gland dysfunction, and surgical complications remains under investigation.

TABLE 11-3 **Remission Rates (%) for Endocrine-Active and Inactive Pituitary Adenomas**

Type of tumor	% surgical remission	
	Microadenoma	Macroadenoma
GH—Acromegaly	80–90	50–60
PRL—Prolactinoma	80–90	40–60
ACTH—Cushing disease	85–95	55–70
Endocrine-inactive macroadenoma		50–80

GH, growth hormone; PRL, prolactin; ACTH, adrenocorticotropic hormone.

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TABLE 11-4 **Complication Rates (%) after Endonasal Endoscopic Pituitary Adenoma**

Surgery (in Recent Large Surgical Series)

Author series	*n*	Anterior hypopituitarism	Perm DI	CSF leak	Meningitis	Epistaxis	Carotid injury	Sellar/SS hematoma	Visual decline	Death
Dehdashti, 2008	200	3.0	1.0	3.5	1.0	1	0	0.5	0	0
Gondim, 2011	301	11.6	6.3	2.6	0.6	1.9	0.9	0.6	0.3	1
Berker, 2012	570	2.1	0.5	1.0	0.8	0.6	0.2	0	0	0
Halvorsen, 2014	238	N/A	N/A	4.7	2	N/A	0.4	1.3	2	1.3
Paluzzi, 2014	555	3.1	2.5	5.0	0.9	1	0.3	1.1	0	0.2
Dallapiazza, 2015	80	7.5–10	5.0	2.5	1.3	1.3	1.3	1.3	0	0
Magro, 2016	300	13.7	6.2	2.7	3.3	2.3	0.3	2.0	2.4	0.7
Overall	2 244	2–14	1–6	1–5	1–3	1–2	0–1	0–2	0–2	0–1
Koutourousiou, 2013	54	16.7	9.6	16.7	5.5	0	0	3.7	3.7	5.5
Giant adenoma										
Smith, 2015	68	0	5.9	0	1.5	0	1.5	0	0	0
Cushing disease										

DI, diabetes insipidus; CSF, cerebrospinal fluid; SS, suprasellar.

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B. Rathke cleft cyst

1. Recent series of clinical outcomes after surgical treatment of RCC report excellent rates of improvement of headaches (71% to 100%), visual disturbances (64% to 100%), and hyperprolactinemia (67% to 100%) but less successful rates of recovery of pituitary gland function, both anterior (18% to 70%) and posterior (0% to 50%). A recent meta-analysis found an overall recurrence rate for these lesions of 12.5% with recent series reporting recurrence rates from 0% to 21%. Squamous metaplasia found on histopathologic examination has been shown to increase the rate of recurrence.
2. Gross total removal of the cyst wall does not improve recurrence rates when compared to cyst drainage with fenestration, but does appear to increase the rates of new endocrinopathy. New hypopituitarism has been reported from 0% to 67% in various series, but is typically around 5% to 15% when utilizing the cyst fenestration approach.

C. Craniopharyngioma

1. Given their invasiveness to surrounding structures, subtotal removal of craniopharyngiomas is common, and most will require radiosurgery or stereotactic radiotherapy for treatment of residual or recurrent tumor. Recent endoscopic series report complete removal rates ranging from 37.5% to 75%. Improvement of mass

effect-related visual deficits is high, occurring in 74.7% to 86.4% of patients presenting with this symptom.

2. However, the rate of new or worsened hypopituitarism of the anterior gland is also quite high, ranging from 38% to 47%, and the rate of new diabetes insipidus is reported from 42% to 48%. Other complications of craniopharyngioma surgery include worsened vision (2% to 2.5%), CSF leak (3.8% to 23.4%), and hyperphagia due to hypothalamic injury that occurs 39% to 46% of the time in the adult population.

VI. CONCLUSIONS

Surgery for pituitary adenomas, RCC, and craniopharyngiomas is considered safe and effective therapy for the majority of patients, particularly in experienced hands. Given the complexity of these patients, who may have acute and long-term pituitary hormonal dysfunction, related comorbidities, visual and other neurologic deficits, as well as potential need for adjuvant therapies, a multidisciplinary "center of excellence" approach is strongly encouraged to optimize clinical outcomes.

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12 Growth Hormone in Adults

Norman Lavin

I. INTRODUCTION

A. Growth hormone deficiency (GHD) in adults may lead to cardiovascular risk and increased mortality from cardiac and cerebrovascular disease. Treatment with growth hormone (GH) can enhance and normalize vascular and muscle cell proliferation. In animals, it reduces infarct volume and improves neurologic function after ischemia, promotes survival and myelinization of neuronal cells, and stimulates brain angiogenesis in response to hypoxic stimuli.

B. The adult growth hormone deficiency syndrome (AGHDS) is a well-defined clinical entity characterized by decreased lean body mass and bone mineral density (BMD), increased visceral adiposity, abnormal lipid profile, decreased muscle strength and exercise endurance, and diminished quality of life. Recent studies have emphasized the increased morbidity/mortality of hypopituitary patients, and there are now data implicating GHD as a cause of this increase. GH replacement therapy has been shown to reverse many of these abnormalities and to be well tolerated. Many in the community of endocrine caregivers remain skeptical of GH treatment. Therefore, a large fraction of patients with AGHDS are not treated. The accumulation of long-term treatment data will be required to provide reassurance that GH treatment is a safe and necessary form of hormone replacement therapy for patients with AGHDS.

II. GH PHYSIOLOGY

A. GH is a protein consisting of 191 amino acids that is synthesized and secreted by cells called somatotrophs, located in the anterior pituitary gland. This hormone controls several complex physiologic processes, including growth metabolism. It is currently used in children as well as in adults. GH also helps maintain blood glucose within a normal range because it is a counterregulatory hormone to insulin.

Effects are mediated primarily by insulin-like growth factor 1 (IGF-1), a hormone that is secreted from the liver, as well as other

tissues, in response to stimulation from GH. The GH-promoting effects are primarily the result of IGF-1 acting on its target cells. GH stimulates the liver to secrete IGF-1, which stimulates proliferation of chondrocytes (or cartilage cells) that results in bone growth in the child. IGF-1 also appears to be a key player in muscle growth. It stimulates both the differentiation and proliferation of myoblasts and stimulates amino acid uptake and protein synthesis in muscle and other tissue.

B. The GH molecule is synthesized, stored, and secreted by pituitary cells comprising approximately 45% of all anterior pituitary cells. Thus, the normal adult pituitary gland contains up to 15 mg of GH. Additional hormones peripherally that regulate GH production include glucocorticoids, estrogen, and thyroid hormone. Approximately 65% of total daily GH production occurs at night, triggered by the onset of slow-wave sleep. Random measurement of GH levels is typically futile because normal values are not usually detected at any specific time of the day or night because they are pulsatile in production. GH is produced continuously, but declines with aging. During adulthood, daily GH output is approximately 20 to 600 µg/day, with women exhibiting higher secretion rates. GH release is influenced by many biochemical and physiologic signals, and they are further influenced by nutritional factors, especially obesity, that leads to blunting of GH secretion.

III. CONTROL OF GH SECRETION

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Two hypothalamic hormones and one hormone produced in the stomach control GH release and secretion (Table 12-1).

A. Growth hormone–releasing hormone (GHRH) from the hypothalamus stimulates the synthesis and secretion of GH from the pituitary gland.

B. Somatostatin is a peptide produced by several tissues in the hypothalamus and elsewhere, which inhibits the release of GH.

C. Ghrelin is a peptide hormone secreted from the stomach that binds to receptors on somatotrophs in the pituitary gland and stimulates secretion of GH.

D. GH secretion is part of a negative feedback system: High levels of IGF-1 lead to suppression of GH by directly suppressing the

somatotroph and also stimulating release of somatostatin from the hypothalamus. GH also inhibits GHRH secretion.

IV. ADULT GROWTH HORMONE DEFICIENCY SYNDROME

AGHDS is a clinical entity characterized by decreased lean body mass and decrease in BMD as well as increased visceral adiposity and an abnormal lipid profile. There is also decreased muscle strength, exercise endurance, and a diminished quality of life. Some data indicate increased morbidity and mortality associated with GHD secondary to cerebral or cardiovascular disease as well as bone fractures. GH replacement has been shown to reverse many of these abnormalities.

V. EVALUATION

A. IGF-1.

Because GH is secreted in an episodic manner, random sampling has little validity in the diagnosis of GHD. A random IGF-1 level, however, can be obtained at any time of the day and is a strong surrogate marker for the level of GH in the absence of catabolic conditions and/or liver disease. Contrariwise, a normal IGF-1 level does not exclude a diagnosis of GHD. Therefore, if it is clinically indicated, GH-stimulation tests should be performed. Additionally, the presence of low levels of three or more pituitary hormones other than GH strongly suggests the presence of GHD, and therefore, stimulation testing may not be required in this situation.

B. Stimulation tests

1. Current diagnostic testing involves provocation of GH secretion, including the insulin-tolerance test, which is considered to be the "gold standard." This test is p. 130p. 131fairly risky, particularly in patients with known seizure disorders or cardiovascular disease, and in the elderly. It may result in hypoglycemic seizures and, possibly, even death. The combination of GHRH and arginine is safe and provides a strong stimulus to GH secretion. Other tests include arginine alone, clonidine, glucagon, levodopa, or the combination of arginine plus levodopa.

TABLE 12-1 Control of Growth Hormone Secretion

Stimulators	Inhibitors
1. GHRH	**1.** Somatostatin

2. Stage III and stage IV sleep	**2.** Elevated IGF-1 levels
3. Stressors	**3.** Hyperglycemia
4. α-Adrenergic stimuli	**4.** Elevated free fatty acid levels
5. Fasting	**5.** Serotonin antagonists
6. Melatonin	**6.** Corticotropin-releasing factor
7. Estrogens	**7.** β-Adrenergic stimuli
8. Dopaminergic stimuli	**8.** Progesterone
9. Exercise	**9.** ACTH deficiency
10. Serotonin	**10.** Hyperthyroidism
11. Hypoglycemia	**11.** Hypothyroidism
12. Interleukin 1, 2, and 6	**12.** Obesity
13. Levodopa	**13.** Depression
14. Clonidine	**14.** Corticosteroids
15. Bromocriptine	**15.** Amitriptyline
16. Arginine/lysine	**16.** Substance P
17. Ghrelin	

ACTH, adrenocorticotropic hormone; GHRH, growth hormone–releasing hormone; IGF-1, insulin-like growth factor 1.

2. Because GHRH stimulates the pituitary directly, it can give a false-normal GH response in patients with GHD of hypothalamic origin. In this situation, arginine alone may be used, without concomitant GHRH, using a lower cutoff level. It is still not clear what the lower cutoff level should be, because different centers use different values. Many endocrinologists consider a level of <5.1 μg/L as low on the insulin-tolerance test, and <4.1 μg/L as low on the GHRH/arginine-stimulation tests; others consider <8.0. Some use 10.0 as a cutoff value.
3. Obesity or acute overfeeding can markedly blunt the GH response from the insulin-tolerance test.
4. The sequential arginine and GHRH infusion requires 0.5 g/kg of arginine with a maximum dose of 30 g infused in saline over 30 minutes, followed by a single bolus injection of 1 μg/kg of GHRH with a maximum of 100 μg.

C. Imaging studies. Neurologic imaging (such as magnetic resonance imaging) determines the presence of intracranial disease associated with GHD. A dual-energy X-ray absorptiometry (DEXA) scan may be needed to document the presence of osteoporosis.

VI. PSEUDO-GHD STATES

A. **Reversible and/or apparent GHD** may occur in a cold environment during exercise, postpartum, in obesity, hyperthyroidism, hypercortisolism, Addison disease, congestive heart failure, and protracted critical illness.

B. **A low IGF-1 level** in the presence of *increased GH secretion*, as demonstrated by stimulation tests, may reflect a peripheral resistance to GH.

VII. ETIOLOGY

Adults with GHD can be grouped into three categories:

A. Previous childhood-onset GHD (transition)

1. The history of childhood GHD is less predictive of adult GHD because from 26% to 81% of such patients "normalize" GH release in adulthood—that is, even though as children they had abnormal stimulation tests, repeat tests are now normal (the reasons are not clear, but may include inadequate GH investigation as a child). Idiopathic causes account for most GHDs in childhood, but there is not total consensus that this entity occurs in adults (see Endocrine Society Consensus Statement). Children with idiopathic GHD are less likely to have permanent GHD as adults and should be retested.
2. Children who had a congenital anomaly of the pituitary gland or a tumor in the hypothalamic/pituitary region, or previous surgery or radiotherapy in this area, or a proven genetic or molecular defect involving the capacity to secrete GH, probably do not need to be retested.

B. Acquired deficiency secondary to structural lesions or trauma

1. Tumors in the pituitary and hypothalamic area may cause hypopituitarism. The most common cause of GHD in adults is a pituitary adenoma, or following specific treatment of the adenoma with surgery or radiation therapy. Irradiation is a common cause of hypopituitarism and may be progressive over time in as many as 50% of patients after a 10-year follow-up.
2. Other space-occupying lesions, such as craniopharyngiomas, Rathke cleft cysts, arachnoid cysts, meningiomas, dysgerminomas, metastatic tumors, astrocytomas, or gliomas can result in GHD following surgery and/or radiation.
3. GHD is sometimes a result of compression of the portal vessels in

the pituitary stalk secondary to an expanding tumor mass, directly or by raised intracellular pressure.

4. Infiltrative diseases, such as histocytosis, sarcoidosis, and tuberculosis, are additional causes.

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5. Traumatic brain injury has been reported to cause GHD in as many as 25% of all patients where the injury occurred years earlier (Table 12-2) (see Chapter 6). Studies of traumatic brain injury from all causes have found evidence of chronic hypopituitarism, defined by deficient production of one or more pituitary hormones at least 1 year after injury. Hypopituitarism, and in particular adult GHD, is associated with symptoms that resemble those of post-traumatic stress disorder, including fatigue, anxiety, depression, irritability, insomnia, sexual dysfunction, cognitive deficiencies, and decreased quality of life.

C. Empty sella syndrome in adults

1. The empty sella syndrome may be associated with endocrine dysfunction, including isolated GHD, as well as multiple pituitary hormone deficiencies.
2. Empty sella is characterized by the herniation of the subarachnoid space within the sella, which is often associated with some degree of flattening of the pituitary gland. In a study of 34 patients diagnosed radiographically to have empty sella, 12 had endocrine dysfunction. The most common endocrine disorder noted was hyperprolactinemia, which was seen in five patients, and the most common hormonal deficiency was isolated GHD, seen in four patients. The high incidence of endocrine abnormalities in patients with primary empty sella mandates that these patients should routinely undergo an endocrine evaluation to detect these deficiencies early and appropriate replacement instituted where necessary, thus ensuring them of a better quality of life.

VIII. CLINICAL

AGHDS may include the following signs and symptoms (Table 12-3):

A. Weakened heart muscle contraction and heart rate

B. Arterial plaques

C. Elevated blood pressure

D. Decreased cardiac ejection fraction and diminished arterial

distensibility

E. Increased inflammatory markers, such as C-reactive protein (CRP)
F. Elevated lipids or fats in the blood, such as total cholesterol, low-density lipoproteins (LDLs), and triglycerides
G. Decreased exercise capacity, probably secondary to decreased cardiac output
H. Decreased energy
I. Abnormal body composition
    1. Increased abdominal obesity
    2. Decreased bone density
    3. Increased incidence of fractures and osteoporosis
    4. Decreased muscle strength and muscle size
    5. Decreased lean body mass
    6. Increased fat mass

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J. Problems with sleep quality
K. Decreased social contact
L. Decreased libido
M. Weight gain
N. Psychological symptoms
    1. Shyness
    2. Withdrawal from others
    3. Nervousness or anxiety
    4. Sadness or depression
    5. Feelings of helplessness

TABLE 12-2 Etiology of GHD

1. Pituitary disease: pituitary adenoma, metastatic neoplasm, parasellar surgery, craniofacial irradiation, pituitary apoplexy, head trauma, lymphocytic hypophysitis
2. Hypothalamic etiologies: irradiation, infiltrative processes, primary or metastatic neoplasms, ependymoma, third ventricular cyst, trauma
3. Hypophyseal stalk injury: head trauma, metastatic lesions, infiltrative disease
4. Craniopharyngioma, hypothalamopituitary damage, parasellar lesions: meningioma, central nervous system lymphoma, chordomas, arterial-venous malformation, internal carotid aneurysms
5. Idiopathic isolated GHD of childhood: adult patients with prior childhood diagnosis of GHD
6. Systemic factors: hypothyroidism, Addison disease, high-dose glucocorticoids or Cushing syndrome, obesity, advanced age, hypothermia, acute overfeeding, protracted critical

illness
GHD, growth hormone deficiency.

TABLE 12-3 Symptomatology and Physical Stigmata in Growth Hormone–Deficient Adults

Symptoms	Signs
1. Systemic: fatigue, limited exercise capacity **2.** Psychological: impaired mood and social outlook; reduced memory, well-being, and concentration; apathy **3.** Sexual: diminished libido and sexual activity	**1.** Dyslipidemia: elevated LDL and total cholesterol; variably increased TG and reduced HDL **2.** Osteopenia/osteoporosis **3.** Increased (visceral) body fat; mild insulin resistance **4.** Sarcopenia/muscle weakness; thinning skin **5.** Reduced extracellular fluid space; less sweating **6.** Diminished renal blood flow; low cardiac output; diastolic dysfunction **7.** Mild anemia
HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, thyroglobulin.	

IX. PATHOGENESIS

A. Experimental animal infarction models suggest that IGF-1 may promote survival of myocytes exposed to ischemic injury, in part by advancing glucose uptake.

B. IGF-1 has also been identified as a neuroprotective agent. Low-normal levels of IGF-1 may predict increased risk of ischemic heart disease and ischemic stroke which may be associated with pituitary dysfunction, particularly GHD/gonadotropin deficiency. The higher IGF-1 levels observed in patients with better outcomes suggest a possible neuroprotective role of IGF-1. Circulating IGF-1 levels may predict functional performance during rehabilitation and ischemic stroke outcome.

C. The cardiovascular profile in patients with GHD demonstrated increased incidence of plaque formation, increased intima-media thickness, decreased production of nitrous oxide, abnormal lipid profile, inflammatory markers, and development of insulin resistance. Several studies demonstrated an increased stiffness of arteries in

comparison with controls. Böger et al. demonstrated that GH was responsible for endothelial nitric oxide production. Nitric oxide is not only a potent vasodilator but also an inhibitor of LDL oxidation.

1. GHD may result in impaired cardiac performance manifested by a reduction in the left ventricular mass and ejection fraction, but data are inconsistent.
2. Atherosclerosis is an inflammatory process, and inflammation markers such as CRP or interleukin 6 are highly sensitive indicators of atherosclerosis. In patients with GHD, CRP may be increased.
3. Adults with GHD demonstrate alterations in plasma fibrinolytic balance, including elevated levels of plasminogen activator inhibitor 1 with decreased tissue plasminogen activator activity. These changes may contribute to the increased cardiovascular morbidity in AGHDS.
4. Some articles conclude that the beneficial effects of GH on the cardiovascular system are strongly suggestive but not completely proven.

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X. FIBROMYALGIA

A. Fibromyalgia syndrome is an idiopathic condition in which patients experience intense pain in specific tender points, as well as profound fatigue and sleep disturbances.

B. GHD that occurs in a subset of patients with fibromyalgia is of clinical relevance because it is a possibly treatable disorder utilizing GH with demonstrated benefits to patients. Dinser et al. reported that approximately 30% of patients with fibromyalgia had an abnormally low response to insulin-induced hypoglycemia and arginine-stimulation testing.

C. In a study by Cuatrecasas in *BMC Musculoskeletal Disorders*, GH treatment in fibromyalgia patients with low GH levels reduced the number of tender points within a few months. GH also improved fatigue, pain, and mental health without causing negative reactions.

D. The decision to treat patients with fibromyalgia by GH supplementation awaits confirmatory long-term studies of its efficacy and side effects profile.

E. One study suggested that low levels of IGF-1 cannot be explained by

clinical associations, but suggests that low IGF-1 levels in patients with fibromyalgia are a secondary phenomenon because of hypothalamic–pituitary–GH axis dysfunction.

F. At present, there are no definitive conclusions as to the link between hypothalamic–pituitary–adrenal axis dysfunction and GHD in fibromyalgia. Nevertheless, the presence of clinically significant GHD in a subpopulation of patients with fibromyalgia seems well established. Understanding its links with chronic stress may provide some insights into mechanisms, whereby environmental stressors and developmental factors interact with inherited susceptibility to modify gene expression and ultimately generate symptoms.

XI. CARDIOVASCULAR

A. A study from the French Registry of Acute ST-Elevation or Non-ST Elevation Myo Cardial Infarction (FAST-MI) Registry evaluated IGF-1 at hospital admissions for acute myocardial infarction (MI), recurrent MI, and stroke over a 2-year follow-up. They concluded that low IGF-1 scores are associated with an increased risk of all-cause death, recurrent MI, and stroke in MI patients. IGF-1 induces vasodilatation by nitric oxide production, reduces endothelial dysfunction, promotes mRNA expression for specific contractile proteins, improves myocardial contractility, stimulates ischemic preconditioning, and limits ischemia-reperfusion injuries.

B. Low serum levels of IGF-1 have been associated with carotid intima-media thickness, the presence of congestive heart failure, and angiographically documented coronary disease. Low IGF-1 levels have also been associated with an increased risk of ischemic heart disease. Low IGF-1 concentrations were also associated with higher mortality after acute MI.

C. This study is the largest study that reports the relationship between serum levels of age-adjusted IGF-1 and long-term cardiovascular outcomes after an acute MI. The results show that low levels of age-adjusted IGF-1 at time of admission in acute MI patients are associated with an increased 2-year risk of death, recurrent MI, or stroke. Patients with acute MI had reduced serum levels of IGF-1 compared with healthy controls, and among the acute MI patients, those with lower IGF-1 levels hit a higher frequency of 90-day events, such as recurrent ischemia, reinfarction, revascularization, sustained ventricular tachycardia, and, after discharge, even death. These authors' results are

interesting to consider with regard to a potential role for acute administration of IGF-1 at the acute phase of MI.

D. **General benefits of GH.** GH has both direct effects on vascular function and also effects mediated through IGF-1 itself. The cardiovascular risk associated with GHD appears to be related to several factors, including hypertension, inflammation, dyslipidemia, and insulin resistance. After administration of GH, there is an increase in flow-mediated dilatation and reduction of arterial stiffness. There is also a slight decrease in blood pressure.

E. **Heart and vessel anatomy.** Increased intima-media thickness and abnormal arterial wall dynamics have been documented in GHD. GH treatment has reversed these disorders. Some studies show reduced left ventricular posterior wall, and interventricular p. 134p. 135septal thickness and left ventricular diameter mass. After GH administration, there were increases in the left ventricular mass, left ventricular end diastolic volume, and stroke volume. Changes in these parameters may correlate with reported subjective benefits of increased exercise tolerance and energy.

F. **Results on the impact of IGF-1 in cardiovascular disease**, however, are still controversial.

XII. CHRONIC FATIGUE SYNDROME

Preliminary studies of GH therapy in a subset of patients with chronic fatigue syndrome and GHD have also shown some encouraging results.

XIII. ADIPOSE TISSUE

Adult GH-deficient patients demonstrate increased fat mass, particularly visceral adiposity, and several studies have shown significant decreases in total body fat content in responwse to GH treatment. These decreases occur in both subcutaneous and visceral fat within 6 months after initiation of therapy. GH administration increases lipolysis. Untreated adults have decreased lean body mass and, with treatment, an increase in muscle mass ensues.

XIV. STRENGTH

Some studies have shown increases in isometric or isokinetic strength. In other studies, exercise capacity and physical performance were improved

by treatment and demonstrated by the facts that VO_{2max} and maximum work capacity were increased.

XV. GH TREATMENT IN THE ELDERLY

There are many unanswered questions about the use of GH in the elderly (as well as in adults) with GHD. Currently, research has brought us to an important beginning in deciphering the actions of GH in this age group. Gotherstrom et al. have described a 10-year prospective study of the metabolic effects of GH replacement in adults. There was a sustained reduction of body fat during the study period, sustained improvement in serum lipid profiles, and lowering of hemoglobin A_{1c} by the end of the study.

Their study concludes that a low dose of GH can improve body composition and serum lipid profile without any significant impairment of glucose metabolism. GH replacement should, therefore, be considered in elderly GHD adults.

XVI. GH AND DIABETES MELLITUS

A. In another study by Gotherstrom looking at GH-deficient adults, the conclusion was that GH did not affect the risk of diabetes mellitus in patients who had normal body mass index. After 10 years of GH replacement in adults, there was no increased incidence of diabetes or malignancy. Contrawise, GH-deficient patients had increased serum insulin concentration and evidence of insulin resistance. Glucose-clamp studies have confirmed these observations. Patients with an excess of GH may also demonstrate insulin resistance.

B. In a different study, a low mean dose of GH normalized serum IGF-1 levels and improved body composition in elderly GH-deficient patients without any significant deterioration in glucose homeostasis.

XVII. LIPIDS

A. GH replacement reduces visceral fat, and total cholesterol and LDL levels may decrease in 10% to 20%. In one review, 63 adults with GHD were assessed after 7 years of treatment. Total cholesterol and LDL decreased and high-density lipoprotein increased, whereas triglyceride concentrations remained unchanged.

B. The administration of GH reduces CRP and improves lipoprotein metabolism. Furthermore, GH decreases fat mass and improves insulin sensitivity.

XVIII. BONE DENSITY

A. Low BMD in adults has been demonstrated in patients with GHD. The age of onset appears to determine the severity of the osteopenia, and the severity of GHD p. 135p. 136correlates with the severity of osteopenia. There is an increase in the volume of trabecular bone, increased reabsorption, and increased osteolite thickness, suggesting delayed mineralization. Fracture rates up to two to five times greater than normal have been reported in GH-deficient patients. One study showed that GH induced an increase in BMD. The mean initial dose of GH was 0.98 mg/day, which was gradually lowered, so that at the end of the study the mean dose was 0.47 mg/day. GH replacement induced a sustained increase in total lumbar and femur neck BMD and bone mineral content as measured by DEXA scan. The authors concluded that 10 years of GH replacement in patients with GHD induced a sustained and, in some cases, a progressive increase in bone mass and bone density.

B. GH stimulates both bone formation and reabsorption, but with <12 months of treatment, the BMD by DEXA scanning may not increase, but after 18 to 24 months of treatment, most studies have shown increases in BMD.

C. Ten years after it was administered, GH continued to reduce the risk of fractures and helped maintain bone density in postmenopausal women who had osteoporosis, according to a new study published in the *JCEM*.

D. 15-Year GH replacement in GHD adults induced a sustained increase in total body and lumbar (L2–L4) spine bone mineral concentration and BMD. This meta-analysis suggests a beneficial effect of human growth hormone (HGH) replacement on BMD in adults with GHD. When compared with non-GHD control populations, adults with GHD and hypopituitarism have been shown to have twofold to fivefold higher fracture rates. It is interesting that GH replacement initially decreases the bone density, which is followed by a subsequent increase after at least 1 year of replacement. The results of short-term (12 months or less) randomized controlled trials of GH replacement were indeed mostly negative, revealing a decrease or no change within a short period of time, but long-term usage shows significant improvement in BMD. This biphasic effect of HGH replacement observed in randomized studies has been previously described in the

literature and is consistent with the hypothesis that GH stimulates both bone formation and bone resorption as evidenced by changes in bone markers, which results in increased bone turnover. The Endocrine Society recommends GH for this abnormality using a fixed starting replacement dose of 0.2 to 0.3 mg/day in adults aged 30 to 60. Women require higher replacement GH doses as compared with men because *oral estrogen inhibits GH-induced IGF-1 synthesis*.

XIX. ADOLESCENTS

A. After discontinuation of GH therapy in children 15 to 17 years of age, there may be a reduced acquisition of bone mineral content. An important issue, therefore, is whether therapy should be maintained or reinstituted, at least until the subjects reach peak bone mass.

B. There is some evidence that BMD is greater in those who continue GH therapy for an additional 2 years after cessation of growth.

C. When GH therapy is stopped at a young age, the GH-deficient adult may gain weight and become relatively obese. They may be more predisposed to atherosclerosis, perhaps secondary to high levels of cholesterol and triglycerides.

D. Young adults who were GHD during childhood and not provided with GH during adulthood may have signs and symptoms of impaired psychological well-being, including feelings of depressed mood, emotional instability, social isolation, anxiety, and reduced vitality. One of the striking effects of GH therapy in GHD adults is the improvement in psychological well-being.

XX. QUALITY OF LIFE

Quality of life is assessed by means of a self-administered survey. Energy and vitality are diminished in GH-deficient patients. Many studies showed definite benefit after patients received GH, whereas in others, improvements were more limited or no improvement was seen.

XXI. ARGUMENTS AGAINST GH TREATMENT

A. Safety concerns. Although treatment appears to be safe overall, certain areas require long-term surveillance, such as risks of glucose intolerance and pituitary p. 136p. 137hypothalamic tumor recurrence and cancer. Although there are benefits in diminishing and decreasing cardiovascular risk factors, reductions in cardiovascular

mortality have yet to be confirmed.

B. Adverse effects. The most common side effects are related to fluid retention as well as paresthesias, joint stiffness, peripheral edema, arthralgia, and myalgia. Carpal tunnel syndrome has been described in as many as 2% of patients. Most of these adverse reactions, however, improve with dose reduction. Benign intracranial hypertension has been linked to GH treatment in children, but only one case has been reported in adults. Gynecomastia has been reported in a very few elderly individuals receiving GH in high doses.

C. GH and tumor formation. There is a concern that GH therapy could lead to tumor recurrence or the development of malignancies. However, an increase in recurrence rates of either intracranial or extracranial tumors has not been demonstrated in AGHDS. There are no published data of long-term observational studies in patients with AGHDS treated with GH that showed any increased incidence of cancer.

D. Unmasking of thyroid and cortisol deficiency. Although it is not an adverse effect, GH replacement can cause a lowering of free thyroxine (T_4) levels, perhaps because of increased deiodination of T_4, enhancing the extrathyroidal conversion of T_4 to tri-iodothyronine (T_3). Lowering of T_4 during treatment with GH, therefore, reflects biochemical unmasking of subclinical central hypothyroidism. GH treatment has also been found to cause a lowering of serum cortisol levels, revealing central hypoadrenalism that has been masked, likely because of enhanced conversion of cortisone to cortisol during the GH-deficient state. 11β-Hydroxysteroid dehydrogenase type I isoenzyme acts as a reductase that converts cortisone to cortisol and is increased in GHD and reduced by GH replacement. Therefore, free T_4 levels and cortisol levels should be monitored during treatment.

E. Contraindications. GH treatment is contraindicated in the presence of an active malignancy. GH treatment of patients with diabetes mellitus is not a contraindication, but may require adjustments in antidiabetic medication.

F. Cardiovascular. The relevance of the beneficial effects of GH on the cardiovascular system is strongly suggested, but not fully proved. The results in a large cohort of GH-treated patients (the KIMS or Pharmacia & Upjohn database) demonstrated no difference in cardiovascular risk in comparison with that in a control population

after a mean of 3 years. In one study, after GH treatment in the elderly, there were no significant changes in electrocardiogram parameters or blood pressure. In this study, patients with GHD did not show cardiac structural or functional differences compared with healthy controls, with no significant changes after GH treatment.

G. Acromegaly. GH therapy is the recommended treatment in adult patients with GHD, but one argument against this is in acromegaly, in which there is excess GH, and the main cause of mortality is cardiovascular disease.

H. Low IGF-1—not a risk factor. Among older adults, a decreasing IGF-1 level over time does not predict subsequent all-cause mortality. Studies do not confirm the hypothesis that the declining IGF-1 level is a mortality risk factor. In conclusion, there is no evidence that older adults with decreases in IGF-1 levels over a period of years have diminished likelihood of long-term survival. Of course, there are other studies countering these conclusions.

I. Neoplasms

1. Although a theoretical increased risk of developing new or recurrent neoplasms has been suggested in some studies in adults, this increase has not been found in most studies of treatment in patients with adult-onset GHD.
2. "The long-term risks of high-dose growth hormone use are little studied, but available evidence suggests that long-term high-dose growth hormone may have serious medical consequences, including cardiac, endocrine, or respiratory effects, as well as increased risks for certain cancers," said Brian Brennan at McLean Hospital in Belmont, MA and Harvard Medical School in Boston. Brian Brennan states that his findings suggest that mounting illicit GH abuse may represent a dangerous new form of drug abuse with potentially severe public health consequences. Individuals with prolonged excessive GH from a pituitary tumor have a tendency to develop tumors elsewhere in the body. This raises the concern that

   p. 137p. 138GH treatment might promote the development of growth of tumors, but this has not been observed to be the case with GH therapy.

J. Elderly. Normal age-related GH and serum IGF-1 reductions are associated with age-related changes that are similar to the signs and symptoms seen in GHD adults. Reports of effects of GH on BMD in

non-GHD normal aging are conflicting. Thus, the use of GH to counter some of the effects of normal aging is still controversial.

K. **Diabetes.** Because GH antagonizes the action of insulin, it may tend to raise blood glucose values, although this has not proven to be a significant problem in children. Despite widely demonstrated benefits of GH replacement treatment in adult GHD, an increase in the risk of developing diabetes should be considered.

L. **Ecuadorian dwarves.** GH receptor deficiency (GHRD) in Ecuadorian adults is associated with obesity and enhanced insulin sensitivity. In a group of Ecuadorian dwarves, GHRD is associated with insulin efficiency and obesity. Studies state that these patients did not develop diabetes because they lack the counterregulatory effect of GH, thereby inducing a state of enhanced insulin sensitivity to compare to control relatives without diabetes and despite less insulin secretion. They said that there was a sixfold increase in the development of type II diabetes with GH therapy, which did not resolve when GH therapy was stopped. They suggest that the obesity of GHRD can best be attributed to unopposed insulin action associated with leptin resistance and that the elevated adiponectin concentrations are an accompaniment rather than a cause of their enhanced insulin sensitivity. They conclude, therefore, that the absence of GH is to the benefit of these patients and that GH therapy should not be given, at least to this subgroup of patients.

M. **Athletics:** GH has been touted to achieve faster recovery from injury and enhanced ergogenicity, although there is no evidence that GH or IGF-1 actually improves competitive performance in young, healthy adults.

XXII. ARGUMENTS FOR GH TREATMENT

A. Cardiovascular

1. GH therapy offers significant clinical benefits in body composition, exercise capacity, skeletal integrity, and quality of life. GH reduces visceral fat and increases muscle mass and cardiac performance. Total cholesterol and LDL levels decrease, and CRP declines. CRP is a good indicator of cardiovascular risk because it accelerates vascular inflammation by interacting with endothelial receptors. Most patients with GHD have elevated CRP levels. Most, but not all, studies demonstrate a significant decrease of CRP levels with GH replacement.

2. An improvement in the lipid profile is often seen after GH treatment. A meta-analysis of several studies documented the effects on total cholesterol, with significant changes more prominent in elderly patients than in the young. Apoprotein B-100 is a known independent risk factor for cardiovascular disease that has been shown to decrease after GH therapy. LDL concentrations also decrease.

   Arterial distensibility and plaque formation are improved with GH treatment. GH is also a cytokine, and its receptor belongs to the family of cytokine receptors. Intracellular activation occurs through the signal-transducing activator of transcription protein 4, a well-known pathway for cytokines. One could speculate that by interfering with the action of proinflammatory cytokines, GH reduces or even reverses intima-media thickness and plaque formation.

   There is improved peripheral vasodilatation and production of nitric oxide. Systolic and diastolic blood pressure measurements decrease slightly but significantly in hypertensive patients.

B. Acquired immune deficiency syndrome (AIDS): GH in adults has been approved by the Food and Drug Administration for people whose bodies are under stress or wasting because of the effects of AIDS, burns, or traumatic injuries. In AIDS, the wasting syndrome is characterized by significant unintended weight loss. GH may help with weight gain.

C. Crohn disease: Crohn disease is a chronic inflammatory disorder of the bowel. In one study, researchers evaluated whether the administration of GH would improve p. 138p. 139the symptoms of the disease. At 4 months, the Crohn disease activity index score had decreased significantly in the GH group. This compared with a much smaller decrease in the placebo group. Side effects included some swelling and headache, which usually went away during the first month of therapy. Researchers need to study the effects of GH further with clinical trials to determine its value in treating Crohn disease.

D. Low IGF-1 linked to Alzheimer disease: It is widely accepted that the IGF-1 is involved in the body's aging process. New research suggests that it might also play a role in Alzheimer disease in elderly men. This study showed a significant link between low serum levels of

IGF-1 and insulin-like growth factor binding protein 3 in Alzheimer disease in men but not in women. The investigations, therefore, justify a longitudinal study to evaluate these data.

E. **Cognition:** Decreases in GH secretion with age may contribute to cognitive changes associated with aging. In this study, the data confirmed that cognitive performance in elderly males is associated with GH secretion with respect to target detection and speed of responding in conditions of selective attention, short-term memory, and basic processing speed.

F. **Hearing:** The study evaluated a hearing status of GH in adults with isolated GHD belonging to an extended Brazilian kindred with a homozygous mutation in the GH receptor gene. They concluded that compared with controls in the same area, subjects with untreated congenital lifetime idiopathic GHD report more misophonia and dizziness and have a preponderance of mild high-tone sensorineural hearing loss and have an absence of stapedial reflex and other abnormalities. These were reversed with GH treatment.

G. **Hypopituitary control and complications study:** The data from the study conclude that GH replacement provides sustained improvement in quality of life for up to 10 years.

H. **Prader–Willi syndrome (PWS)** (see Chapter 16): Altered GH secretion has been related to reduced cardiac mass and systolic function compared to controls. They conclude that GH therapy increased the cardiac mass of PWS adults without causing overt abnormalities of systolic and diastolic function. Although the association between lean mass and left ventricular ejection fraction during GH therapy corroborates a favorable systemic outcome of long-term GH treatment in adults with PWS, subtle longitudinal modifications of functional parameters advocate appropriate cardiac monitoring in the long-term use of GH for these patients. Current data suggest that long-term GH administration can favor preservation of cardiac and metabolic parameters in adult PWS patients. GH treatment can be seen as a critical upholder of physiologic homeostasis and could create extended benefits for cardiovascular health in adults with this disorder.

I. **The anaerobic energy system** underpins the initiation of all physical activities, including those of daily living. GH treatment improved sprinting in recreational athletes, a performance measure dependent on the anaerobic energy system. The physiologic and

functional link between GH and the anaerobic energy system is unknown. They conclude that GH regulates anaerobic capacity, which determines quality of life and selective aspects of physical function.

Strength and endurance are measures of muscle function that depend on muscle size, muscle fiber composition, and the availability of energy to support the exercising muscle. This energy is available as adenosine triphosphate (ATP), which is produced by two complimentary energy systems, one anaerobic (oxygen-independent) and the second aerobic (oxygen-dependent). The amount of preformed ATP present in muscle is sufficient to sustain physical activity for the first 5 to 10 seconds. Thereafter, anaerobic glycolysis provides energy for an additional 30 to 40 seconds. The aerobic energy system supports endurance exercise, whereas the anaerobic energy system powers intensive activity of short-term duration. The anaerobic energy system supports activities of daily living, such as rising from a chair, climbing stairs, and rushing for a bus. Thus, it is conceivable that impairment of anaerobic capacity leads to the perception of increased fatigue during the execution of ordinary activities of daily living, a symptom commonly observed in adults with GHD.

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Muscle strength and aerobic capacity are impaired in GHD and restored by GH replacement over a period of a few months. A study of physical performance by Meinhardt observed that GH induced a significant and selective improvement in sprinting, a measure of performance dependent on anaerobic capacity. This study was undertaken in GH-sufficient healthy adults using a superphysiologic dose of GH.

J. **Aerobic capacity:** A recent study confirms previous findings that aerobic capacity is impaired in GH-deficient adults. Adults with GHD have impaired cardiac function, diminished lung capacity, and reduced red cell mass, factors that collectively reduce oxygen delivery to exercising muscles. These defects lead to a decrease in oxygen supply to a reduced muscle mass, explaining impaired aerobic capacity in adults with GHD.

K. **Anaerobic and aerobic capacity:** In summary, anaerobic and aerobic capacities are reduced in adults with GHD. GH status is an independent determinate of anaerobic and aerobic capacities. We conclude that GH regulates the anaerobic energy system, and GH

treatment helps reverse these concerns.

L. Sleep: Low energy and fatigue are frequent complaints in subjects with GHD. Because interrelations between sleep and GH regulation are well documented, these complaints could partly reflect GHD.

GHD is associated with sleep disorders that may cause poor subjective sleep quality and daytime sleepiness. Disturbed sleep is likely to be partly responsible for increased tiredness, a component of quality of life in GHD. GH treatment may reverse these concerns.

M. Traumatic brain injury and GHD (see Chapter 6): Head injuries can cause cognitive impairments and reduce GH levels. Human GH can improve quality of life in traumatic brain injuries.

N. GH reverses nonalcoholic steatohepatitis (NASH) in patients with human GHD: NASH is an emerging progressive hepatic disease and demonstrates steatosis, inflammation, and fibrosis. Insulin resistance is a common feature in the development of NASH.

Six months of GH replacement therapy in a few patients ameliorated NASH and the abnormal lipid profile concomitant with a marked reduction in oxidative stress. These results suggest that GH plays an essential role in the metabolic and redox regulation in the liver.

XXIII. TREATMENT

A. GH dose requirements should be lower in older patients. Higher GH doses are needed to achieve the same IGF-1 levels in women receiving oral estrogen replacement. For ages 30 to 60 years, a starting dose of 300 μg/day is recommended. Daily dosing should be increased from 100 to 200 μg every 1 to 2 months—the goals being an appropriate clinical response, no side effects, and an IGF-1 level in the age-adjusted reference range. Clinical benefits may not become apparent for up to 6 months of treatment. Patients >60 years of age should be started on an even lower dose, such as 100 to 200 μg/day, with slower incremental increases.

B. After maintenance doses have been achieved, monitoring usually occurs at 3- to 6-month intervals. In addition to a normal IGF-1 level for age, monitoring should include a clinical evaluation, assessment of side effects, a lipid profile, a fasting glucose, a free T_4 and thyroid-stimulating hormone, a cortisol level, and, if indicated, a BMD scan. Assessment of quality of life provides another modality for monitoring response to therapy.

C. It is not clear how long one should administer GH therapy. If benefits are being achieved, I would continue the therapy, but begin tapering the dose unless clinical goals decline. On the other hand, if there are no apparent or objective benefits after at least 1 year of treatment, discontinuing GH therapy should be considered.

D. Recommendations:

1. GH dosing regimens should be individualized rather than weight based.
2. GH treatment should start with low doses and be titrated according to clinical response, side effects, and IGF-1 levels.

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3. GH dosing should take age, sex, and estrogen status into consideration.
4. During GH treatment, patients should be monitored at regular intervals, such as every 1 to 2 months during dose titration and every 6 months thereafter with a clinical assessment and an evaluation for adverse effects, IGF-1 levels, and other parameters of GH response.

XXIV. CONCLUSION

A. The treatment of GHD in adults has been reported to improve quality of life and energy levels, reduce pain, improve depression, enhance self-esteem, improve cholesterol and LDL levels, enhance cognitive psychometric performance, improve exercise capacity, and improve muscle strength. GH therapy offers benefits in body composition, skeletal integrity, and quality of life measures. However, reductions in cardiovascular events and mortality have yet to be absolutely demonstrated.

B. Many endocrinologists remain skeptical of using GH as treatment for GH-deficient adults and, therefore, a large fraction of patients who have this deficiency are not treated. It appears that more long-term treatment data will be required to provide reassurance as to whether GH treatment is a safe and necessary form of hormone replacement therapy for adult patients with GHD.

XXV. FUTURE CONSIDERATIONS

In animal models, IGF-1 promotes survival and myelinization of neuronal cells as well as stimulating brain angiogenesis in response to hypoxic

stimuli caused by ischemia or trauma. It is possible that higher serum IGF-1 levels could promote an increased delivery of IGF-1 from the periphery to brain-damaged cells. IGF-1 can cross the blood–brain barrier. Low IGF-1 levels during the acute phase of stroke are associated with a poor outcome or even death. Higher IGF-1 levels, on the other hand, were observed in patients with better outcomes, suggesting a possible neuroprotective role of IGF-1 and its potential use to improve motor and cognitive recovery during rehabilitation after stroke.

The role of GH in normal aging is poorly understood. This is a new area of research, and additional recommendations about risks and benefits will evolve in the near future.

Decreases in GH secretion with age may contribute to cognitive changes associated with aging. Future studies are needed to prove that cognitive performance, short-term memory, and basic processing speed are improved with GH treatment.

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13

Pituitary Disorders and Tall Stature in Children

Phillip D. K. Lee

Pediatric pituitary disorders involve one or more of the six anterior pituitary hormones: growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin (PRL), as well as the posterior pituitary hormone, antidiuretic hormone (ADH). Except for PRL, clinical disorders involving deficient secretion are much more common than excess secretion. Unique aspects of pituitary disorders in children when compared with adults include:

- Etiology: An increased incidence of congenital and genetic conditions.
- Clinical: Adverse effects on bone (height) growth and sexual development.
- Diagnosis: Pediatric-specific test procedures and laboratory reference ranges.
- Treatment: Pediatric formulations and dosing, monitoring procedures.

GH is the most commonly deficient hormone in pediatric **hypopituitarism**, occurring either as an isolated deficiency or in combination with other pituitary hormone deficiencies; the prevalence in the pediatric population has been estimated to be as high as 1 in 3 500. TSH is the second most common pediatric pituitary hormone deficiency, occurring in approximately one third of cases of GH deficiency and rarely as an isolated deficiency. Deficiencies of other anterior pituitary hormones (ACTH, LH, FSH, and PRL) usually occur in association with GH and TSH deficiencies. ADH deficiency, or central diabetes insipidus (CDI), has an estimated overall population prevalence of 1 in 25 000 and may occur as an isolated condition or with anterior hormone deficiencies. **Panhypopituitarism** refers to concurrent deficiencies of two or more pituitary hormones. Excessive pituitary hormone secretion is a rare occurrence, with GH, PRL, and ADH accounting for the majority of pediatric cases.

I. ANTERIOR PITUITARY HORMONE DEFICIENCY

A. Congenital hypopituitarism refers to pituitary hormone deficiency with onset at or before birth. **Neonatal hypopituitarism** occurs

from birth to 1 month old; most cases are congenital. Congenital hypopituitarism is most commonly idiopathic or associated with prematurity, perinatal insult, and/or hypoxia. The most common congenitally deficient pituitary hormone is GH, which can present with severe neonatal hypoglycemia because of the key role of GH as a glucose counterregulatory hormone in infants.

The following descriptive categorization systems have been devised for cases of congenital hypopituitarism.

1. **Isolated GH deficiency (IGHD)** is a clinically defined group of conditions involving congenital GH deficiency, usually not associated with other pituitary hormone deficiencies. Most cases are sporadic and thought to be due to fetal, natal or postnatal pituitary or hypothalamic insult although anatomic defects consistent with this etiology are identified in a minority of cases. Familial short stature and/or GH deficiency has been identified in up to 30% of IGHD cases suggesting a genetic etiology. *GH1* mutations occur in some cases of IGHD types 1a and 1b, and in most cases of IGHD type 2; *GHRHR* mutations in some cases of IGHD type 1b.
   - **a.** IGHD type 1a, the most severe form of IGHD, is characterized by autosomal recessive transmission, variable decreased birth length, neonatal hypoglycemia and cholestatic jaundice, undetectable serum GH, characteristic facies, and frequent development of GH neutralizing antibodies during GH treatment.

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   - **b.** IGHD type 1b is similar to type 1a but with a milder phenotype, low serum GH; and lack of neutralizing antibodies during GH treatment.
   - **c.** IGHD type 2 is autosomal dominant with low serum GH levels.
   - **d.** IGHD type 3 is X-linked, with low serum GH levels and sometimes accompanied by X-linked agammaglobulinemia.
2. **Combined pituitary hormone deficiency (CPHD)** is a descriptive categorization of multihormonal pituitary deficiency without identified acquired etiology. Although each of the six CPHD conditions has been associated with a particular genetic disorder (as specified below), genetic testing has revealed a mutation or deletion of the specified gene in only approximately

12% of patients with clinically identified familial CPHD; the percentage is much lower for sporadic cases.

a. **CPHD1**, *POU1FI*, combined GH, TSH, and PRL deficiencies.
b. **CPHD2**, *PROP1*, all anterior pituitary hormones.
c. **CPHD3**, *LHX3*, all anterior pituitary hormones except ACTH; rigidity of the cervical spine, hearing impairment.
d. **CPHD4**, *LHX4*, GH deficiency ± other anterior pituitary hormone deficiencies, abnormalities of the cerebellum and sella turcica, Arnold–Chiari malformation.
e. **CPHD5**, *HESX1*, GH deficiency, with or without other anterior pituitary hormone deficiencies, some cases of septo-optic dysplasia.
f. **CPHD6**, *OTX2*, GH deficiency, ± other pituitary hormone deficiencies, pituitary hypoplasia, ectopic posterior pituitary, Arnold–Chiari malformation.

B. Gene mutations associated with anterior pituitary hormone deficiency

Anterior pituitary embryogenesis begins with a cascade of genetic events resulting in invagination of the oral ectoderm to form Rathke's pouch, which gives rise to the anterior pituitary gland. Mutations or deletions of genes coding for DNA transcription factors involved in this process can affect multiple anterior pituitary and extrapituitary cells lineages and may be associated with ocular and other craniofacial malformations; phenotypic variability and severity depends on the nature of the gene defect and tissue specificity of gene expression. Many of these genes interact with the Sonic Hedgehog (*SHH*, 7q36.3) system, a key element of vertebrate organogenesis.

Subsequent gene activity leads to differentiation of gonadotrophs (*GATA2*, *FGFR1*), corticotrophs (*TBX19*, *PITX1*), and thyrotrophs, somatotrophs and lactotrophs (*POU1F1*, *PITX2*); defective action of the associated genes results in cell lineage–defined deficiency. Although genetic causes of hypopituitarism are rare, genetic abnormalities are being identified for an increasing percentage of congenital cases.

1. Gene mutations affecting embryogenesis of Rathke's pouch

a. ***BMP4*** (14q22.2) is expressed in the diencephalic floor, optic vessel, and optic cup. Mutations are associated with ocular and midline defects, developmental delay and growth retardation,

but not specifically with hypopituitarism.

b. ***ARNT2*** (15q25.1) homozygous mutation has been associated with combined anterior pituitary hormone and ADH deficiencies, congenital brain and eye malformations, kidney and gastric disorders, spastic cerebral palsy, seizures, and early demise (Webb–Dattani syndrome).

c. ***OTX2*** (14q22.3) heterozygous mutation is associated with GH deficiency, often with other anterior pituitary hormone deficiencies, pituitary hypoplasia, ectopic posterior pituitary, and Arnold–Chiari malformation.

d. ***HESX1*** (3p21.2-p21.1) heterozygous mutations are associated with GH deficiency and variable deficiencies of other anterior pituitary hormones, as well as septo-optic dysplasia, pituitary hypoplasia, congenital panhypopituitarism, and ectopic posterior pituitary.

e. ***GLI2*** (2q14.2) heterozygous mutations have been associated with Culler–Jones syndrome (postaxial polydactyly, pituitary ectopia and GH deficiency, variable occurrence of other pituitary hormone deficiencies; variable penetrance within a pedigree) and Holoprosencephaly 9 (midline brain, craniofacial, and limb abnormalities, panhypopituitarism).

f. ***GLI3*** (7p14.1) heterozygous truncating mutations have been associated with Pallister–Hall syndrome (GH deficiency, hypothalamic hamartoma, polydactyly, p. 144p. 145and hypoplastic anus). Other *GLI3* mutations are associated with Grieg cephalopolysyndactyly syndrome, which does not include GH deficiency.

g. ***SOX2*** (3q26.33) heterozygous mutations have been associated with anophthalmia or microphthalmia, pituitary hypoplasia, hypopituitarism (especially GH and gonadotropin), neurodevelopmental delay, craniofacial and genital abnormalities, hearing impairment, and esophageal atresia.

h. ***SOX3*** (Xq27.1) microduplication of nucleotides 711-743 resulting in an expanded alanine repeat region has been associated with X-linked IGHD with mental retardation. Other duplications have been associated with X-linked pituitary

hypoplasia/ectopia and panhypopituitarism without mental retardation. *SOX3* gain of function has been reported in a female patient with hypopituitarism.

i. ***OTX1*** (14q22.3) heterozygous mutations have been associated with microphthalmia or anophthalmia and hypopituitarism (IGHD, hypogonadotropic hypogonadism, or panhypopituitarism).
j. ***FGF8*** (10q24.32) heterozygous mutations cause hypogonadotropic hypogonadism without anosmia, sometimes with midline cranial and/or limb malformations, and congenital facial palsy (Moebius syndrome). *FGF8* is involved in *LHX3* and *LHX4* expression.
k. ***LHX3*** (9q34.3) heterozygous mutations have been associated with complete deficiency of all anterior pituitary hormones except ACTH, as well as rigidity of the cervical spine and hearing impairment.
l. ***LHX4*** (1q25.2) heterozygous mutations are associated with GH deficiency, alone or with other anterior hormone deficiencies, pituitary hypoplasia, cerebellar defects, abnormalities of the sella turcica, and ectopic posterior pituitary.
m. ***FGFR1*** (8p11.23) is involved in migration of gonadotropin-releasing hormone (GnRH) neurons during embryogenesis. Mutations are associated with Kallmann syndrome 2 (autosomal dominant hypogonadotropic hypogonadism with or without anosmia). *FGFR1* mutations are also associated with several skeletal and craniofacial malformation syndromes with or without pituitary involvement.
n. ***PROP1*** (5q35.3) is involved in differentiation of all six anterior pituitary endocrine cell lineages. Homozygous or compound heterozygous *PROP1* mutations are the most commonly identified cause of familial panhypopituitarism.
o. ***IGSF1*** (Xq26.1) codes for a cell adhesion molecule involved in neural development. Mutations have been associated with central hypothyroidism (probably because of impaired pituitary response to thyrotropin-releasing hormone [TRH]), variable occurrence of GH and PRL deficiencies, as well as macroorchidism and delayed puberty in males.

2. **Genes involved in differentiation and function of anterior pituitary cell lineages**

a. ***POU1F1,*** aka *PIT1* (3p11.2) is involved in differentiation of thyrotrope, somatotrope and lactotrope cell lineages. Heterozygous and homozygous mutations have been associated with combined GH, TSH, and PRL deficiency.
b. ***PITX2*** (4q25) mutations have been associated with Rieger syndrome, an autosomal dominant condition characterized by GH deficiency with or without other hormone deficiencies, eye, tooth, and multiple other anomalies.
c. ***PITX1*** (5q31.1) codes for a protein involved in regulation of PRL secretion. *PITX1* with *TBX19* is involved in proopiomelanocortin (POMC) gene expression. Pituitary disorders involving *PITX1* alone have not been described. *PITX1* is also involved in limb development; defects have been associated with clubfoot, polydactyly, and Liebenberg syndrome (carpal synostosis, elbow dysplasia, and brachydactyly).
d. ***TBX19***, aka *TPIT* (1q23-q24) is involved in the differentiation of POMC neurons and, with *PITX1*, in POMC gene expression. *TBX19* mutations are associated with isolated ACTH deficiency.
e. ***TBL1X***, aka *TBL1* (Xp22.3-p22.2) encodes a subunit of the nuclear corepressor silencing mediator for retinoid and thyroid hormone receptors. Mutations have been associated with X-linked central hypothyroidism, which may be due to decreased *TRH* and/or *TSHB* transcription, and sensorineural hearing loss.

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f. ***NR0B1,*** *aka DAX1* (Xp21.3) mutations are associated with X-linked congenital adrenal hypoplasia and male hypogonadotropic hypogonadism, sometimes occurring as a contiguous gene syndrome including glycerol kinase deficiency *(GKD)*, Duchenne muscular dystrophy *(DMD)*, and nonspecific mental retardation (*IL1RAPL1*). Delayed puberty has been reported in female carriers. *NR0B1* duplication is a cause of 46, XY sex-reversal.
g. ***KAL1*** (Xp22.32) codes for anosmin-1, a protein involved in cell migration and adhesion during embryogenesis of GnRH and olfactory neurons. *KAL1* mutation causes X-linked Kallmann syndrome (hypogonadotropic hypogonadism with or without anosmia).

3. Genes coding for anterior pituitary hormones and

regulatory receptors

a. ***GH1*** (17q24.2) codes for pituitary GH. Deletions and mutations have been identified in IGHD types 1a, 1b, and 2, and in the condition of bio-inactive GH.
b. ***GHRHR*** (7p14) codes for the G-protein coupled pituitary GHRH receptor. Mutations causing GH deficiency have been associated with IGHD type 1b.
c. ***FSHB*** (11p14) and ***LHB*** (19q13.32) code for the β-subunits of FSH and LH, respectively. Mutations are extremely rare and have been associated with varying degrees of hypogonadism and infertility.
d. ***TSHB*** (1p13.2) codes for the β-subunit of TSH. Homozygous mutations have been associated with variable degrees of central hypothyroidism.
e. Homozygous mutations of the hypothalamic genes ***KISS1*** (1q32.1) and ***GPR54*** (19p13), which code for kisspeptin and its receptor, respectively, are associated with partial to complete isolated normosmic hypogonadotropic hypogonadism.
f. ***GNRHR*** (4q21.2) codes for the G-protein coupled pituitary GnRH receptor. Mutations are associated with normosmic hypogonadotropic hypogonadism.
g. Mutations of ***TRHR*** (8q23), which codes for the pituitary TRH-receptor, are associated with isolated TSH deficiency.
h. ***CGA*** (6p14.3) codes for the common α subunit of TSH, LH, and FSH; clinical conditions associated with mutations or deletions have not yet been reported.

C. Other causes of congenital hypopituitarism

1. **Empty sella** is a condition in which the sella turcica is filled with cerebrospinal fluid; the pituitary may be flattened, displaced, or absent. The etiology is unclear although the usually normal or enlarged sella implies prior occupancy by the pituitary.
2. **Septo-optic dysplasia** (*aka* de Morsier syndrome) is a variably defined condition consisting of optic nerve hypoplasia, midline craniofacial/brain defects (e.g., absence of the corpus callosum or septum pellucidum), and pituitary hypoplasia. GH deficiency with or without other anterior pituitary and ADH deficiencies may occur. However, septo-optic dysplasia may occur without ophthalmologic evidence of optic nerve hypoplasia, and the majority of children with optic nerve hypoplasia do not have

hypopituitarism. A minority of cases of septo-optic dysplasia with hypopituitarism have been associated with mutations of *HESX1*, *SOX2*, or *SOX3*. The association of diabetes insipidus, diabetes mellitus, optic nerve atrophy, and deafness (DIDMOAD or Wolfram syndrome) is discussed in Section V.

3. **Other craniospinal and midline craniofacial defects** have been associated with hypopituitarism (particularly GH deficiency) including spina bifida, encephalocele, holoprosencephaly, Arnold–Chiari malformation, and midline craniofacial defects, for example, cleft lip and palate, choanal atresia, single central incisor. A minority of these cases have identified genetic or acquired etiology. Hydrocephalus may cause hypopituitarism because of a direct pressure effect.
4. **Other congenital syndromes.** GH deficiency with or without other pituitary hormone deficiencies has been reported to occur in a number of congenital syndromes with varying degrees of validation for definitive association, for example, Prader-Willi (15q11-13), Russell-Silver (7p11.2), Peters Plus (13q12.3), Robinow (9q22.31), and 18p- syndromes. Bardet–Biedl syndrome has been associated with GH deficiency and/or hypogonadotropic hypogonadism; at least 19 different gene mutations have been identified for this condition, and genotype/phenotype associations for the pituitary dysfunction are incompletely defined. p. 146p. 147Most congenital syndromes that include short stature are not associated with pituitary hormone deficiencies.

D. Acquired anterior hypopituitarism

1. **Autoimmune hypopituitarism**, as evidenced by anti-pituitary antibodies and/or lymphocytic hypophysitis, occurs in autoimmune polyglandular syndrome 1 (APS1, *aka* autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy), caused by mutations in the *AIRE* (autoimmune regulator) gene (21q22.3) and APS2 (*aka* Schmidt syndrome). Antibodies to PIT1, the product of *POU1F1*, have been found in cases of APS2 and, rarely, in adult-onset CPHD. Hypopituitarism has not been consistently reported in APS3 or APS4. Evidence for autoimmune hypopituitarism occurs sporadically in antiphospholipid syndrome and autoimmune

connective tissue disorders.

2. **Iatrogenic.** Radiation therapy for intracranial and head/neck malignancy is often associated with pituitary hypofunction and, rarely, hyperfunction (e.g., precocious puberty), is dose-related, and can be progressive over several months or years. GH and TSH are preferentially affected in children. Surgical treatment of pituitary and other central nervous system (CNS) tumors may also result in pituitary dysfunction.
3. **Brain trauma.** Single (usually GH) or multiple pituitary hormone deficiencies may occur as a result of direct open or closed head injury as well as motion-related trauma; for example, shaken baby syndrome and motor vehicle accidents. Trauma-related pituitary deficiency may be progressive over several years.
4. **Pharmacologic.** Supraphysiologic glucocorticoid therapy is associated with ACTH deficiency. GH and TSH secretions may be suppressed by exogenous GH and thyroid hormone treatments, respectively. Suppression of gonadotropin secretion is a desired effect of continuous treatment with GnRH agonists. Pharmacologic hypopituitarism is usually transient and resolves with discontinuation of the causative medication or lowering of the dose to physiologic levels or lower. However, full recovery may take several weeks to months, especially for ACTH.
5. **Tumors and other mass lesions**
   a. **Craniopharyngiomas,** which account for 5% to 15% of pediatric intracranial tumors, are derived from the embryonic craniopharyngeal duct. Most craniopharyngiomas have both intra- and suprasellar components, and are histologically benign, hormonally nonfunctional, and rarely metastasize, although they are often locally invasive and infiltrative, causing compression of the pituitary gland, septum pellucidum, and ventricular outflow. Decreased growth rate, vision disturbances (including sudden loss of vision), and headaches (due to increased intracranial pressure) are typical clinical findings. Clinical presentation is from birth through adulthood; with peak incidence between 5 and 14 years old.
   b. **Rathke's cleft cyst,** often confused with craniopharyngioma, is an epithelial, intrasellar cystic lesion derived from remnants of Rathke's pouch. Most lesions are small and asymptomatic; however, the cyst(s) may expand causing hypopituitarism,

vision disorders, and neurologic symptoms.

c. **Neurofibromatosis type 1 (NF1)**, a progressive multisystem disease with a population incidence of 1 in 2 000 to 1 in 4 500 results from heterozygous mutations or deletions of *NF1* (17q11.2), which codes for neurofibrillin, a tumor-suppressor. Hypophyseal neurofibromas are common and can lead to GH deficiency, sometimes accompanied by other anterior hormone deficiencies. A clinical diagnosis can be made by meeting two of seven National Institutes of Health (NIH) criteria: ≥5 café au lait spots ≥5 mm (prepubertal) or ≥15 mm (postpubertal), ≥2 neurofibromas or ≥1 plexiform neurofibroma, axillary or inguinal freckling, optic glioma, ≥2 Lisch nodules (iris hamartomas), distinctive osseous disorder (sphenoid dysplasia, tibial pseudoarthrosis, and vertebral dysplasia), and first degree relative with NF1. However, 50% of cases are spontaneous mutations and only 50% of these NF1 cases meet the NIH criteria; therefore, *NF1* analysis may be indicated in a prepubertal children with multiple café au lait spots alone.

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d. **Other CNS lesions** may affect pituitary function by causing a mass effect, invading the sella, and/or disrupting the pituitary blood supply. These include mass lesions (e.g., arachnoid, dermoid, and epidermoid cysts, functioning and nonfunctioning pituitary adenomas and malignancies, vascular malformations), infectious or systemic conditions (tuberculosis, abscess, sarcoidosis, lymphocytic hypophysitis), and extrapituitary intracranial lesions (germinoma, optic glioma, meningioma).

   Because of its encasement in the sella turcica, compensatory hyperplasia of a pituicyte subset due to primary end organ dysfunction could lead to pituitary hypofunction, particularly GH deficiency. In this respect, severe primary hypothyroidism with significant thyrotrope hypertrophy has been associated with GH deficiency which may persist after normalization of TSH levels.

II. DIAGNOSIS OF ANTERIOR PITUITARY HORMONE DEFICIENCY. Test protocols for diagnostic evaluation of hypopituitarism are detailed in Appendix A and are briefly discussed here

in relation to pediatric considerations. There are few universally accepted guidelines or protocols for evaluation of pituitary function in children; clinical acumen and experience are essential elements of the diagnostic process. In some clinical situations (e.g.,postpituitectomy) minimal confirmatory diagnostic testing may be required.

A. Medical history and physical examination. Because GH deficiency occurs in most cases of pediatric anterior pituitary hormone deficiency, special attention should be given to accurate measurements of length (before 2 years old) or height (after 2 years old), and calculation of height velocity. Abrupt decrease in height velocity, significant decrease in height velocity between 3 and 9 years old, and decreased height velocity with excessive weight gain can indicate endocrine abnormalities in children. Delayed sexual maturation (no evidence of gonadal steroid effect by 14 years of age in a male, 13 years of age in a female) can be a presenting sign of gonadotropin deficiency. Other important components of the medical evaluation include medications, family growth and pubertal histories, CNS or vision complaints, body proportions, dysmorphic features, and skin lesions. Formal ophthalmologic examination should be considered for patients with midline craniofacial defects, nystagmus, and abnormal funduscopic examination or vision disturbances.

Most **neonates** with GH deficiency have normal birth size for gestational age because of the independence of fetal growth from pituitary GH. An exception is placental insufficiency, which may separately affect fetal growth, resulting in intrauterine growth retardation and small-for-gestational age, and pituitary development and function. Other risk factors for neonatal hypopituitarism include midline craniofacial defects, prematurity, intracranial pathology, hypoxia, and mechanical ventilation. Severe hypoglycemia is often a presenting sign of hypopituitarism in a neonate. Cryptorchidism, micropenis, and scrotal hypoplasia may occur in a male infant because of fetal gonadotropin deficiency. Linear growth deceleration due to congenital GH deficiency typically has clinical onset after 6 months old; onset may occur earlier in severe cases.

B. Imaging studies

1. **Bone age radiograph:** A hand and wrist radiograph of the opposite hand of use (left hand in a right-handed individual) is compared with the Greulich and Pyle atlas of age-standardized radiographs. A lack of concordance between the patient’s

chronologic and bone ages is not diagnostic of abnormality and is commonly observed in healthy children; however, a significant (>1 year) discordance can be supportive of pathology. A bone age ≥6 to 7 years can be used to calculate the predicted adult height using the Bayley and Pinneau tables included as an Appendix to the Greulich and Pyle atlas; the error margin for this estimate is usually accepted to be ±10 cm. Significant discordance between the predicted adult height and the midparental height may provide evidence for pathology. Caveats for utilization of a bone age radiograph include interobserver variability and the cross-sectional nature of the procedure. In addition, the predicted adult height may be less reliable if the height velocity or rate of pubertal development p. 148p. 149is atypical. Given the usual rates of bone ossification, bone age radiographs are usually not performed more frequently than annually.

2. **Cranial imaging:** Magnetic resonance imaging, with and without contrast is a preferred procedure for pituitary imaging. Radiographs and computerized tomography may be preferred in some cases, particularly if bone imaging is needed.
3. **Other imaging studies:** Skeletal radiographs and radionuclide bone scans may be useful for defining limb, skull, and vertebral abnormalities and in assessment of conditions such as NF1 and McCune–Albright syndrome.

C. Genetic testing: Pediatric hypopituitarism is rarely caused by genetic defects; however, genetic testing should be considered in familial cases or if there are clinical features suggestive of a genetic etiology. A variety of methods are available including chromosome analysis, chromosomal single nucleotide polymorphism chromosomal microarray, whole exome sequencing, and targeted gene sequencing. Consultation with a clinical geneticist may be useful prior to consideration of testing.

D. Hormone testing

1. **GH** secretion is episodic. Therefore, random levels are often very low and have no utility in assessing GH adequacy. By convention, standard GH testing protocols involve low response to two pharmacologic stimuli (e.g., insulin-induced hypoglycemia, glucagon, clonidine, arginine). Synthetic GHRH and ghrelin analogs have been used in adults; there is limited experience with

these agents in children.

Controversies include variable definition of a normal GH response, GH assay variability, and normal GH levels in abnormally short children with low insulin-like growth factor-I (IGF-I) levels. In addition, GH therapy has been efficacious in promoting growth in short children without GH deficiency, raising questions about the clinical utility of GH testing as a determinant of treatment. Nonetheless, documentation of GH deficiency by standard provocative testing has continued relevance in the evaluation of pediatric pituitary function; documentation of GH deficiency may have important implications for the evaluation and treatment of individual patients.

Low levels (corrected for age and sex) of IGF-I, IGF-binding protein-3 (IGFBP-3), or the IGF-related acid-labile subunit may be indicative of GH deficiency; however, normal levels do not rule out GH deficiency.

2. **TSH.** The combination of low serum thyroxine (T_4) and unmeasurably low TSH indicates pituitary TSH deficiency. Low T_4 with normal or slightly elevated TSH may be observed in TRH deficiency (hypothalamic hypothyroidism), euthyroid sick syndrome, and thyroxine-binding globulin (TBG) deficiency. Synthetic TRH (protirelin) stimulation testing may assist in making a diagnosis; however, this test has fallen out of favor because of the lack of normative values, co-occurrence of GH deficiency in most cases of pediatric TSH deficiency (thereby providing a diagnostic clue) and variable availability of protirelin.
3. **ACTH.** Standard testing involves intravenous synthetic cosyntropin, consisting of the N-terminal 24 amino acids of the 39-amino acid ACTH molecule; cortisol levels are measured at baseline, 30 minutes, and 60 minutes. This test relies on the physiologic need for tonic ACTH secretion to allow rapid synthesis and release of cortisol in response to a pulse dose of cosyntropin (i.e., simulating a stress response). An adequate test is often defined as a baseline or stimulated cortisol level ≥20 μg/mL or an increase of ≥10 μg/mL above baseline. Controversies include the predictive value of the cosyntropin test for risk for adrenal crisis and the relative merits of standard (250 μg), low (1.0 μg), or scaled cosyntropin doses. Pretest ACTH and cortisol levels can

distinguish primary adrenal insufficiency and eliminate the need for a cosyntropin test.

Metyrapone blocks adrenal 11 β-hydroxylase and, consequently, cortisol synthesis, resulting in a rise in ACTH secretion. However, the metyrapone test is relatively cumbersome and has been associated with exacerbation of adrenal crisis. ACTH stimulation testing with ovine corticotropin-releasing factor (oCRF) has also been described but is not widely used in pediatrics.

4. **Gonadotropins.** In primary hypogonadism, LH and FSH levels typically rise to abnormally high levels after 8 to 9 years old. In delayed puberty, low basal p. 149p. 150gonadotropin levels with significant increases following intravenous administration of synthetic GnRH may provide biochemical evidence of impending puberty. However, if there is a lack of response to GnRH, it may be difficult to distinguish hypogonadotropic hypogonadism from constitutional delay of puberty.
5. **PRL.** A low PRL level may be observed in genetic conditions that cause hypopituitarism and in cases of hypothalamic injury. A moderately elevated PRL level is often measured in cases of pituitary stalk transection; levels >100 to 200 ng/dL may indicate prolactinoma. TRF (protirelin) stimulates prolactin secretion; however, pediatric ranges and clinical significance have not been established.
6. **Combined anterior pituitary testing.** Standard pediatric pituitary testing often involves sequential administration of two GH secretagogues (e.g., clonidine immediately followed by arginine) after an overnight fast to rule out GH deficiency. Cosyntropin stimulation testing may be performed with the GH test. Other combined testing protocols have been described (e.g., TRF, GnRH, and CRF administrations with GH testing) but are not commonly used in pediatrics.
7. **Neonatal hypopituitarism.** The clinical presentation and evaluation of congenital and neonatal hypopituitarism is unique in several important respects:
   a. **Critical blood sample during hypoglycemia:** A special diagnostic situation is the neonate with severe unexplained

hypoglycemia, often heralded by a seizure. A blood sample for GH, cortisol, insulin, and β-hydroxybutyrate levels, obtained during hypoglycemia, can be useful in distinguishing and diagnosing hypopituitarism (low GH, cortisol), adrenal insufficiency (low cortisol), hyperinsulinism (high insulin, low β-hydroxybutyrate), or an inborn error of metabolism (elevated β-hydroxybutyrate).

b. GH: A random GH level >10 ng/mL in a neonate argues against a diagnosis of hypopituitarism. In a full-term infant, random GH levels are typically >10 ng/mL in cord blood and during the first week of life.

c. Gonadotropin: Although most cases are idiopathic, incomplete fetal genital maturation (e.g., cryptorchidism, micropenis, hypospadias) in a full-term male infant can be indicative of hypopituitarism because late-gestation fetal gonadotropin production is required for testosterone production and virilization. In male infants with intact gonadal–hypophyseal axis, a random testosterone level is usually >50 ng/dL in the first 48 postnatal hours and at 30 to 60 days of life (during the physiologic "minipuberty"). A low anti-Mullerian hormone level at these timepoints may also indicate decreased testicular function.

d. TSH: Depending on the newborn screening methodology, a low T_4 level with normal or low TSH levels may be reportable in routine newborn screening programs. Upon further evaluation, most such cases are not clinically relevant and/or may be due to TBG deficiency, a usually benign X-linked condition. However, such results may also be seen in hypopituitarism; therefore, complete evaluation is advisable if there is clinical reason to suspect hypopituitarism.

III. TREATMENT OF PITUITARY HORMONE DEFICIENCY

A. General principles: The primary treatment goal for pediatric hypopituitarism (and pediatric disease in general) is to optimize growth, neurodevelopment, and sexual maturation. All clinically relevant pituitary hormones can be replaced using pharmaceutical agents.

B. GH: Biosynthetic human GH (somatropin, biosimilars) has been commercially available for treatment of childhood GH deficiency

since the mid-1980s, with numerous studies demonstrating efficacy for normalization of growth if treatment begins before onset of puberty. Published data have not shown a relationship of GH therapy to primary, recurrent, or secondary malignancies or progression or growth of neurofibromas in NF1. Patients with *GH1* mutation frequently develop neutralizing antibodies to exogenous GH; synthetic IGF-I (mecasermin) treatment may be an alternative treatment in this situation.

C. TSH: Thyroid hormone replacement therapy with once-daily levothyroxine (LT_4, 2 to 6 mcg/kg/day) is usually adequate for maintenance of normal circulating thyroid hormone levels; coadministration of triiodothyronine (LT_3, liothyronine) is unnecessary, p. 150p. 151and the use of desiccated thyroid is discouraged. Monitoring of serum T_4 and/or free T_4 should guide therapy. TSH levels will be low in TSH deficiency and usually normal in hypothalamic hypothyroidism; TSH monitoring during treatment is unnecessary.

D. ACTH: Glucocorticoid, rather than ACTH, replacement therapy is standard. Cortisol (hydrocortisone) doses are usually calculated based on body surface area, 6 to 12 mg/m^2/day, corrected for oral bioavailability (e.g., calculated dose × 1.5), and timed according to the half-life of the medication (e.g., q8 to 12h). More potent, longer-acting preparations (e.g., prednisone/prednisolone, dexamethasone) are typically used for older children and adolescents. Monitoring is based on clinical symptomatology and examination; there are no suitable biochemical markers to guide therapy. Significant physical stress, such as febrile illness or trauma, can be treated with doubling or tripling of the oral glucocorticoid dose. In the presence of gastrointestinal illness or adrenal crisis, supraphysiologic glucocorticoid doses, for example, double replacement or more, should be parenterally administered. Mineralocorticoid replacement therapy is not required in patients with ACTH deficiency.

E. Gonadotropins: Treatment of pediatric hypogonadotropic hypogonadism usually involves gonadal steroid (testosterone or estrogen/progestin) replacement beginning in the mid-teens, with consideration of the potential effects of these medications on epiphyseal closure and the need for timely replacement to optimize

peak bone mineralization. Gonadal steroid replacement therapy in pediatric patients is aimed toward enabling completion of puberty and does not facilitate fertility; treatments to enable fertility have been described in adults with hypogonadotropic hypogonadism. Testosterone replacement in males is targeted to eventual achievement of normal adult serum testosterone levels, usually using daily topical (patch, gel) testosterone preparations. Estrogen/progestin replacement in females is often initiated with unopposed estrogen treatment (conjugated equine estrogens or estradiol), then transitioned to cycling with oral contraceptives. Monitoring includes examination (height, pubertal staging) and judicious use of bone age and bone densitometry.

IV. ANTERIOR PITUITARY HYPERSECRETION. Clinically relevant pituitary hypersecretion is rarely observed in pediatrics, with hyperprolactinemia being the most common of these conditions.

A. Prolactin: Pediatric hyperprolactinemia is most often due to a pituitary micro- or macroadenoma, that is, a prolactinoma. In some cases, the prolactinoma may cause a mass effect, suppressing secretion of other pituitary hormones and causing visual and neurologic symptoms. Prolactinoma also commonly occurs in patients with *MEN1* mutations. Galactorrhea is a common presenting sign in both sexes; amenorrhea and menstrual irregularity often occur in females. Diagnosis depends on measurement of high PRL levels (e.g., >100 to 200 ng/mL), clinical signs and symptoms, and neuroimaging. Treatment with dopamine agonists, e.g., cabergoline, may normalize prolactin levels and reduce prolactinoma size. However, neurosurgical intervention may be preferable in cases of macroadenoma with evidence of mass effect.

Risperidone, opiates, and cannabis may cause pituitary prolactin hypersecretion without adenoma; treatment involves discontinuation of the causative agent.

B. GH hypersecretion is termed acromegaly in adults and pituitary gigantism in pediatrics (see Chapter 9).

C. ACTH hypersecretion, or Cushing disease, is rare in pediatrics (peak incidence ~14 years old); however, it is more common than primary adrenal causes of Cushing syndrome. The usual cause is a corticotroph microadenoma (basophilic adenoma, stains blue with basic dyes). The classic presentation in children is decreased height velocity in the presence of excessive weight gain. Other typical signs and symptoms

are cushingoid facies, hypertension, unusual fatigue, and emotional lability; psychosis-like behavior may occur. Inappropriate virilization due to hyperproduction of adrenal androgens, often observed in adrenal hypercortisolism, does not occur in Cushing disease. Diagnosis depends on demonstration of elevated serum and/or urine cortisol in the presence of inappropriately normal or elevated baseline or CRF-stimulated plasma ACTH. MRI and bilateral inferior petrosal sinus sampling are performed to localize the microadenoma. Treatment p. 151p. 152usually involves transsphenoidal microadenoidectomy; postoperative radiotherapy may be indicated if cortisol levels remain elevated with detectable ACTH levels. Medical therapy and adrenalectomy are not usually necessary. Posttherapy glucocorticoid replacement is necessary. Pre- and posttherapy deficiencies of other pituitary hormones may occur. *USP8* mutations have been identified in >50% of corticotroph adenomas across all age groups.

D. McCune–Albright syndrome (MAS) is a rare condition (prevalence $1:10^5$ to $1:10^6$) caused by nongermline activating mutations of *GNAS1*, which codes for the α subunit ($G_s\alpha$) of guanine nucleotide-binding protein (G-protein) resulting in constitutive activation of G-protein coupled receptors. The basic features of MAS are polyostotic fibrous dysplasia and multiple café au lait spots in a distinct distribution with variable endocrine hyperfunction depending on the cell lineages affected by the nongermline mutation. Within the pituitary gland, constitutive activation of the GHRH receptor has been observed in approximately 20% of MAS patients, resulting in GH hypersecretion. The increased growth rate resulting from GH hypersecretion may compensate for loss of height potential resulting from gonadotropin-independent precocious puberty related to constitutive activation of the gonadal LH receptor. Although the pituitary GnRH receptor is also G-protein coupled, clinical relevance is unclear because the precocious puberty in MAS is usually gonadotropin independent, although a combined peripheral and central precocious puberty is common during the evolution of this condition.

E. *KISS1* (1q32.1) and ***GPR54*** (19p13) gain of function or activating mutations have been associated with precocious puberty.

F. Multiple endocrine neoplasia type I (MEN I; Wermer syndrome)
MEN1 (11q13.1) codes for the DNA transcription factor, menin. Heterozygous mutations are associated with parathyroid (90%), pancreatic and hypersecreting pituitary tumors (66%); the latter typically involving a prolactinoma, although hypersecretion of GH, TSH, ACTH, FSH, and α-subunit has also been reported. Although MEN1 is congenital, the associated endocrinopathies rarely present clinically during infancy or childhood. Genetic testing should be considered in a child with an affected parent.

G. Pure **TSH** hypersecreting lesions are extremely rare in pediatrics.

H. Other CNS lesions

a. Null cell (*aka* chromophobe) **pituitary adenomas**, containing cells which fail to stain with acidic or basic histochemical dyes, can occasionally hypersecrete GH or ACTH. Such lesions are extremely rare in pediatric patients.

b. Hypothalamic **hamartomas** are not uncommonly found in children with central precocious puberty; a cause and effect relationship has not been demonstrated.

c. Pinealomas have been associated with central precocious puberty.

I. Ectopic pituitary regulatory hormones

Ectopic production of pituitary regulatory hormones may cause excessive production of anterior pituitary hormones; such conditions are extremely rare in pediatrics.

V. ADH DEFICIENCY. Evagination of the ventral diencephalon gives rise to the posterior pituitary gland and stalk, with neuronal connections originating from the primordial hypothalamic areas which form the supraoptic, suprachiasmatic, and paraventricular nuclei. The hormones secreted by the posterior pituitary, ADH (*aka* arginine vasopressin, AVP), and oxytocin, are synthesized in the magnocellular neurons of the hypothalamic supraoptic and paraventricular nuclei. ADH undergoes axonal transport to neurosecretory endings in the posterior pituitary, colocalizing with copeptin and neurophysin II in large dense-core vesicles. Dehydration leads to cell shrinkage and depolarizes the neurosecretory endings causing release of ADH; the same stimulus triggers thirst via signaling to higher cortical centers. ADH released from the posterior pituitary binds to vasopressin V_2 receptors in the renal collecting ducts, enabling aquaporin 2 water channels and consequent

water reabsorption. ADH secretion is also stimulated by cardiac and vascular baroreceptors triggered by an approximately 10% decrease in intravascular volume; this effect takes precedence over regulation of tonicity (serum sodium).

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ADH deficiency is the sole clinically relevant posterior hormone deficiency in pediatrics; most cases are idiopathic. Although oxytocin deficiency may occur, no pediatric clinical disorder has been associated with this condition. ADH deficiency, also known as central diabetes insipidus or CDI, is characterized by the loss of urine concentrating ability resulting in continuous dilute diuresis with increased thirst and fluid intake. In severe cases, inability to maintain adequate fluid intake can result in hypernatremic dehydration, inanition, and death.

A. Gene mutations associated with ADH deficiency

1. ***WFS1*** (4p16) codes for a transmembrane protein located primarily in the endoplasmic reticulum. Homozygous and compound heterozygous mutations are associated with DIDMOAD, *aka* Wolfram syndrome.
2. ***AVP*** (*aka AVP-NPII*, 20p13) codes for both ADH (*aka* AVP) and its carrier protein, neurophysin II (NPII). Heterozygous mutations are associated with familial CDI.

B. Acquired ADH deficiency

1. **Langerhans cell histiocytosis** (**LCH**, *aka* Histiocytosis X, eosinophilic granuloma, Hand–Schüller–Christian disease, Letterer–Siwe disease) is a rare condition occurring across all age groups but most commonly affecting young children (incidence <1:200 000 children). LCH is characterized by clonal proliferation of cells resembling skin Langerhans cells that are genetically related to myeloid-derived precursor dendritic cells; these cells infiltrate tissues, often accompanied by clonal $CD1a^+$ monocytes, as well as macrophages, lymphocytes, eosinophils, and multinucleated giant cells. Involved tissues can be either single system (single organ, bone, skin, node, CNS, etc.) or involve two or more organs or systems (oral cavity, abdominal organs, gut, lung, bone marrow). Activating mutations of the proto-oncogene *BRAF* or deletions in *MAP2K1* have been identified in the majority of cases, suggesting that LCH is a malignant condition. The most

common presentation involves lytic skull lesions, particularly the base of the skull. Posterior pituitary infiltration, characterized by thickening of the pituitary stalk with the loss of the pituitary bright spot on MRI, is associated with ADH deficiency; these solid or cystic lesions may progress to space-occupying lesions. Less commonly, anterior pituitary and hypothalamic involvement, either as a primary focus or extension of a posterior pituitary lesion, may result in anterior pituitary hormone deficiencies. Skin lesions, including congenital reticulohistiocytosis (Hashimoto–Pritzker disease), a seborrheic scalp-line rash (especially post-auricular), and an erythematous candida-like papular rash of the groin and trunk (often misdiagnosed as diaper rash in infants) may be observed. Chemo and/or radiation therapy may be effective in some cases. CDI, hearing loss, neurologic disorders, and bone abnormalities are common permanent sequelae. LCH is distinguished from Erdheim–Chester disease which occurs primarily in adults and involves $CD68^{+}/CD1a^{-}$ histiocyte infiltration.

2. **Brain injury**, especially with basilar skull fracture, can be associated with CDI. In neonates, CDI has been associated with asphyxia, intraventricular hemorrhage, and intravascular coagulopathy.
3. **Postsurgical:** Transient or permanent CDI is not uncommon following intracranial surgery, for example, the removal of a Rathke cleft cyst or craniopharyngioma, because of involvement or disruption of the posterior pituitary and/or infundibulum.
4. **CNS infections** associated with CDI are rarely reported in pediatric patients. In neonates, causative agents include *Listeria* and group B streptococcus.
5. **Adipsic diabetes insipidus**, *aka* adipsic hypernatremia, is a rare disorder with combined ADH deficiency and disordered thirst mechanism. Affected individuals do not experience thirst in response to changes in hydration status or serum osmolality and can develop severe hypernatremia and hyperosmolar syndrome. The most common predisposing conditions across all age groups include craniopharyngioma (postresection) and anterior communicating artery aneurysms, postrupture or surgical clipping. Obesity is a common finding, perhaps related to impaired central control of satiety. A similar condition can occur in children with

ADH deficiency and inability to signal thirst due to severe neurodevelopmental impairment.

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C. Differential diagnosis

1. **Nephrogenic** (*aka* peripheral) **diabetes insipidus** (NDI) is caused by renal resistance to ADH effect. Primary NDI has been associated with mutations of *AVPR2* (Xq28; vasopressin V2 receptor), *AQP2* (12q13.12; aquaporin, homozygous or heterozygous), and a host of other heritable genetic conditions. However, NDI is more commonly secondary and due to drugs (e.g., lithium) or renal injury (e.g., nephrocalcinosis, renal dysplasia, sickle cell anemia, chronic pyelonephritis, sarcoidosis, amyloidosis, and urinary tract obstruction).
2. **Psychogenic** (*aka* habit) **polydipsia** may be symptomatically difficult to distinguish from DI. This is a not uncommon behavioral condition in children, typically 3 to 5 years old, usually normonatremic, benign, and self-resolving. Pathologic cases are rare and can occur at any age, although more commonly in adults and usually in association with significant psychiatric disorders. Signs and symptoms may include anorexia, wasting, water intoxication, hyponatremia and other electrolyte abnormalities, potentially progressing to neurologic impairment, coma, and death.
3. **Diabetes mellitus** (DM), including untreated T1DM and decompensated T2DM, can present with signs and symptoms similar to CDI. The obvious distinguishing features of DM are hyperglycemia and glucosuria, although the presence of DM does not necessarily exclude the rare co-occurrence of CDI, such as in DIDMOAD syndrome and in patients with DM and brain injury.

D. Diagnosis of ADH deficiency

1. **Clinical signs and symptoms:** The hallmark signs and symptoms of pediatric CDI are polyuria (>4 mL/kg/hour) and polydipsia (>2 L/m^2/24 hour), which are constant over a 24-hour period and temporally progressive. The polydipsia can lead to weight loss because of decreased food intake; nocturnal symptoms can lead to bedwetting, sleep disorder, and fatigue. Similar signs and symptoms are observed in NDI and in DM. Symptoms of psychogenic polydipsia are usually more pronounced during the

day.

2. **Severe diabetes insipidus:** Any patient presenting with polyuria, polydipsia, and weight loss requires immediate definitive evaluation including the following tests (preferably using point-of-care-testing [POCT] or STAT laboratory methods):
   - **a.** Serum glucose, urine dipstick: Significant glucosuria with or without ketonuria and serum glucose >200 mg/dL argues for DM; urine-specific gravity is typically elevated, Hemoglobin A_{1c} (HbA_{1c}) will be ≥6.5. Normoglycemia with low urine specific gravity may be consistent with CDI, NDI, or psychogenic polydipsia.
   - **b.** Serum sodium. Elevated serum sodium (>145 mmol/L) with dilute urine (specific gravity <1.005) is diabetes insipidus unless proven otherwise. Psychogenic polydipsia will not cause hypernatremia unless there is concurrent high NaCl intake; such a case of self-induced hypernatremia is usually accompanied by evidence of salt and water retention; for example, edema, hypertension, and weight gain.
   - **c.** For patients diagnosed with DI based on the above assessment, treatment with an ADH analog can be initiated; the therapeutic response may indicate whether the cause is CDI or NDI. Additional diagnostic tests prior to treatment may include concurrent urine and serum osmolality, and an ADH level.
3. **Partial diabetes insipidus:** Patients with partial forms of DI (e.g., partial CDI or mild NDI) and an intact thirst mechanism are often able to maintain sufficient levels of (excessive) fluid intake to avoid significant hypernatremia and dehydration. In such cases, a water deprivation test (Miller test or modification) may be required for diagnosis. This test consists of two sequential parts: a prolonged period of fluid deprivation immediately followed by a test dose of vasopressin.
   - **a.** Part 1:Fluid deprivation is started at midnight and continued in the clinic in the morning (starting at ~08AM) with hourly monitoring of body weight, fluid output, serum and urine osmolalities, and serum Na. The test is terminated when there is a >3% to 5% decline in body weight, no change in two sequential urine osmolality measurements, urine Osm >750 mOsm/kg, serum Osm >300 mOsm/kg (and/or hypernatremia),

or evidence of hypovolemia.

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At the end of the test, an individual without diabetes insipidus will usually have a serum osmolality 285 to 300 mOsm/kg and urine osmolality >500 mOsm/kg (normal maximum urine osmolality is ~1 500 mOsm/kg in older children and adults, lower in infants). In patients with DI, the serum osmolality will be >300 with hypernatremia while urine osmolality will remain <2× serum osmolality. An ADH level obtained at the end of the test will be low in CDI and normal or elevated in NDI.

b. Part 2: At the end of the fluid deprivation period, individuals who have DI based on the above criteria are allowed to drink fluids (limited to 50% of urine output during Part 1) and are given aqueous AVP (pitressin; 8-AVP) 5 units or aqueous desmopressin (DDAVP; 1-[3-mercaptopropionic acid]-8-D-AVP) 1 mcg by subcutaneous injection, with measurement of urine specific gravity or osmolality after 1 hour. If there is no significant increase in urine osmolality, the monitoring period can be extended for another 2 to 4 hours. A lack of response to vasopressin argues for NDI.

c. Pediatric considerations: In children, clinical acumen and judicious modification of the fluid deprivation test procedure is necessary. For instance, infants and young children may have extreme difficulty tolerating prolonged fluid deprivation even in the absence of diabetes insipidus. Fasting hypoglycemia may occur during the fluid deprivation period, and infants and young children with DI can develop hypernatremic dehydration during the initial overnight fluid deprivation. A time limit for Part 1 of the test in infants and young children is typically 7 hours depending on the severity of symptomatology, tolerance and patient body size, age, and clinical status. Surreptitious intake of fluids, including bath and toilet water, may occur particularly during the initial overnight fluid deprivation at home. Inability to urinate on demand or into a suitable container due to age or developmental delay can also be problematic; external devices or urethral catheterization may be necessary. A shorter period of pretest fluid deprivation prior to the clinic procedure or inpatient testing may be indicated in some cases. The test dose

in Part 2 can be scaled to pitressin 5 U/m^2 or DDAVP 0.5 mcg/m^2.

d. Other considerations:

i. Adrenal or thyroid hormone deficiency should be adequately treated prior to water deprivation testing.

ii. Individuals with psychogenic polydipsia may have a prolonged period of continued dilute urine with normal serum measures because of increased total body water and chronic wash-out of the renal concentration gradient; fluid deprivation may need to be extended for a longer time period.

iii. The water deprivation test requires timely performance of all procedures, with availability of POCT or STAT laboratory testing.

iv. The test procedure carries significant risk for patient decompensation and should be conducted in an experienced clinical setting.

v. A common limitation of the water deprivation test is premature termination which can lead to a false diagnosis of inability to concentrate urine. In pediatric patients, premature termination may be unavoidable and diagnosis may not be completely secured; clinical judgment should then prevail as to whether the symptomatology should be treated as DI or whether continued monitoring for progression without treatment is indicated.

4. **Other procedures:** Cranial imaging studies should be performed for all cases of CDI. Other imaging studies, laboratory tests and genetic testing may be indicated based on suspected etiology and other findings.

E. Treatment of ADH deficiency

Physiologic ADH secretion is dynamically responsive to changes in fluid volume; this degree of physiologic regulation is not feasible using pharmaceutical preparations. However, a patient with intact thirst mechanism will be able to maintain fluid and sodium homeostasis if not overtreated. Therefore, in most patients with ADH deficiency and intact thirst mechanism, the selected treatment should be carefully titrated to allow control of symptoms without oversuppression of urination.

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1. **Fluid replacement only** may be a therapeutic option for patients with very mild CDI, intact thirst mechanism and ability to obtain and drink fluids as needed. Limiting factors for this approach are the frequencies of urination and drinking which may interfere with daily activity and sleep. Dietary salt restriction may help by increasing proximal renal tubular water reabsorption. Most cases of mild CDI are progressive and will eventually require medical therapy.
2. **DDAVP** (desmopressin), a synthetic analog of AVP, has a prolonged duration of action (~8 to 12 hours) when compared with the native molecule. Oral tablets are a preferred method of administration; typical dosing for pediatric CDI is 0.2 to 1.0 mg daily, divided into two or three doses; for mild cases, a bedtime dose may be adequate. DDAVP may also be administered via injection, intravenous infusion, and nasal spray. Because of the differences in bioavailability, the oral dose is approximately 10× higher than the intranasal dose; the latter is approximately 10× higher than the parenteral dose.
3. **Pitressin (synthetic 8-vasopressin) aqueous** is typically given via subcutaneous injection, 1 to 10 units two to three times daily. It may also be administered intranasally via spray, dropper, or cotton pledget. Pitressin tannate in oil is no longer marketed in the USA.
4. **Chlorpropamide** 150 mg/m^2 once daily, or 200 to 500 mg daily and **clofibrate** 1 to 2 g/day can enhance ADH secretion in partial CDI; these medications are ineffective in NDI or severe CDI. Chlorpropamide, a sulfonylurea, can cause hypoglycemia.
5. The natriuretic effects of **thiazide diuretics, including chlorothiazide** (30 mg/kg/day or 1.0 g/m^2/day divided tid) **and hydrochlorothiazide** (3 mg/kg/day or 100 mg/m^2/day divided tid) coupled with a low dietary sodium intake can cause volume contraction and a consequent rise in renal tubular reabsorption. Thiazides are often used in NDI and in infants with CDI. There may an additive effect of thiazides with chlorpropamide in partial CDI, and with amiloride (20 mg/1.73 m^2/day) in NDI.
6. **Infants, patients with severe neurodevelopmental**

disability, and patients with adipsic diabetes insipidus may not be able to adequately sense or signal thirst. In such patients, dietary sodium should be limited (breast milk and infant formula are already low in sodium). Strict regulation and monitoring of daily fluid intake and output is often necessary, with parental or direct gastric delivery of fluids if oral intake is insufficient. Medical therapy should be carefully titrated and adjusted against symptomatology and serum sodium levels to avoid over or under treatment. Hypernatremia, hypercoagulability, and thrombosis due to dehydration and hyponatremia due to overtreatment have been reported.

VI. ADH HYPERSECRETION.

Excessive secretion of ADH causing euvolemic hypoosmolar hyponatremia is known as the Syndrome of Inappropriate ADH Secretion (**SIADH**). Excessive ADH secretion leads to inability to excrete free water; an associated decrease in aldosterone secretion augments urinary sodium excretion while elevated atrial natriuretic peptide maintains euvolemia.

A. Causes of SIADH

1. **Genetic:** No genetic abnormalities have been specifically associated with SIADH.
2. **Brain injury** is the most common cause of SIADH in children, including trauma (hemorrhage), thrombosis, intracranial surgery, intracranial malignancies, infections and inflammation (e.g., meningitis, encephalitis, abscess, HIV, porphyria). Intracranial ADH producing tumors are extremely rare, if they occur.
3. A partial list of **pharmaceuticals** associated with SIADH includes: chemotherapeutic agents (vincristine, vinblastine, cyclophosphamide), chlorpropamide, anticonvulsants (carbamazepine, phenytoin, valproate), amiodarone, bromocriptine, and psychotropic agents (tricyclic antidepressants, selective serotonin reuptake inhibitors).
4. **Illicit drugs:** 3,4-Methylenedioxy-methamphetamine (ecstasy) is postulated to affect neurotransmitter regulation of central ADH release, with increased body temperature and perspiration similar to exercise-induced hyponatremia (see below).
5. Positive pressure mechanical ventilation and pulmonary disease (abscess, sarcoid, cystic fibrosis, tuberculosis, asthma, atelectasis) may be associated with SIADH.

6. Although rare in children, **ectopic ADH production** may occur in a variety of malignancies; for example, pulmonary, bone (Ewing sarcoma), leukemia, and lymphoma.

B. Diagnosis of SIADH

1. **Signs and symptoms** of SIADH are primarily attributable to the hyponatremia and may include weakness, lethargy, vomiting, irritability, confusion, and changes in personality. As the serum sodium concentration decreases below 120 mEq/L, seizures and coma may occur. Patients with SIADH are typically euvolemic, without over or under hydration. Most pediatric cases of SIADH are accompanied by clinically evident predisposing risk factors; for example, CNS injury.

   Hyponatremic encephalopathy, with severe headaches, lethargy, nausea, vomiting and seizures, progressing to cerebral edema with herniation is the most serious consequence of hyponatremia; children may be at greater risk for this occurrence than adults. Menstruation and hypoxia are additional risk factors. Noncardiogenic pulmonary edema (Ayus–Arieff syndrome) may also occur.

2. **Diagnostic testing:** Hyponatremia with low serum osmolality (<285 mmol/kg), coupled with hypertonic urine compared with plasma (urine osmolality >250 mmol/kg, urine Na usually >30 mEq/L) and fractional excretion of Na (FeNa) >0.5% is consistent with SIADH [FeNa = 100 × urine (Na/Cr) × serum (Cr/Na), with Na in mmol/L and Cr in mg/dL]. Other causes of hyponatremia should be excluded (e.g., hypothyroidism, adrenal insufficiency). ADH levels will be elevated relative to serum Na, with low plasma renin activity. Low serum uric acid levels are also characteristic.

3. **Differential diagnosis**
   - **a.** Pseudohyponatremia is due to high levels of lipids, protein, or glucose in the serum sample. In these cases, direct measurement of serum osmolality will be usually normal or elevated despite the hyponatremia and low calculated serum osmolality.
   - **b.** Hyponatremic dehydration resulting from gastrointestinal loss.
   - **c.** Hypervolemic hyponatremia may occur in association with heart failure, cirrhosis, and nephrotic syndrome due to renal resistance to or deficiency of atrial natriuretic peptide and

consequent renal water retention; FeNa is usually <0.5%.

d. Acute decrease in intravascular volume (>10%) will result in increased ADH secretion via baroreceptor response. Subsequent provision of low sodium (hypotonic) fluid can result in hyponatremia.

e. *AVRP2* (Xq28) mutation causing constitutive activation of the renal vasopressin V2 receptor has been associated with nephrogenic syndrome of inappropriate antidiuresis in which ADH secretion is normal or decreased.

f. Adrenal insufficiency can cause hyponatremia partly because of depletion of intravascular volume and consequent ADH secretion.

g. Reset Osmostat is an uncommon condition reported in association with midline cranial malformations or injury, resulting in chronic mild hyponatremia which does not require treatment and is usually resistant to treatment attempts.

h. Water intoxication is a rare cause of hyponatremia even in the presence of psychogenic polydipsia because there is a large renal capacity to excrete free water, and human dietary salt intake is usually generous. However, this condition may occur in infants fed overdiluted formula or excess water because breast milk, commercial formula, and baby foods have relatively low salt content.

i. Renal salt wasting is characterized by high urine output, elevated plasma renin activity and aldosterone, elevated uric acid and hypovolemic hyponatremia.

j. Exercise-induced hyponatremia due to loss of sodium and water (perspiration) coupled with redistribution of free water. This condition, which may be more common during menstruation, can lead to Ayus–Arieff syndrome.

k. Exogenous vasopressin, including overzealous treatment of CDI and overuse of DDAVP for treatment of nocturnal enuresis in children without diabetes insipidus.

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C. Treatment of SIADH

Note: The following treatments may or may not apply to other causes of hyponatremia.

1. General goals of treatment include short-term correction of serum

sodium (sNa) to 125 mmol/L, especially if there is evidence of encephalopathy, followed by more gradual correction to normal sNa levels. Too rapid correction of hyponatremia has been associated with central pontine myelinolysis presenting several days after correction of the hyponatremia and resulting in severe permanent neurologic disability or death. Therefore, correction of hyponatremia should be carefully monitored to achieve not more than a 5 to 10 mmol/L increase in sNa over each 24-hour period.

2. A commonly used formula for estimation of sodium deficit is the difference between desired and current serum sodium level multiplied by total body water (TBW). In infants and children, TBW is approximately 0.75 and 0.60 × body weight (kg), respectively. This estimate should only be used at initiation of treatment because it does not account for therapeutic provision of sodium, water, and medications.
3. Discontinue causative agents and treat contributory conditions.
4. Fluid restriction. This may be adequate for children with less severe hyponatremia.
5. Hypertonic saline (3% NaCl), 1 to 2 mL/kg over 10 or more minutes will usually raise sNa by 1 to 2 mmol/L. However, hypertonic saline is not recommended in children unless there is significant evidence of encephalopathy. Isotonic or hypotonic fluid infusion is also not recommended. Although the fluid may be hypertonic relative to serum, it is hypotonic relative to urine, thereby providing free water which can worsen the hyponatremia.
6. Furosemide will increase renal free-water excretion and may be useful during the initial treatment; for example, together with hypertonic saline. However, chronic use may result in hypokalemia which could worsen the hyponatremia by causing intracellular movement of sodium.
7. Hypokalemia should be corrected if present.
8. Urea, administered orally, causes an osmotic diuresis and has been successfully used for chronic treatment of SIADH. However, palatability is a limitation.
9. Demeclocycline, a tetracycline derivative that can cause NDI, has been used for treatment of SIADH with variable efficacy; most patients respond within 2 to 3 days. Adverse effects include photosensitivity, nephrotoxicity, and renal failure; pediatric use is not recommended.

10. Lithium inhibits aquaporin-2 synthesis and can cause NDI. Although effective after several days in the majority of patients with SIADH, pediatric use is not recommended because of the risk for chronic renal failure.
11. Oral V_2 receptor antagonists (vaptans) block renal ADH action and may be a drug of choice for treatment of SIADH.

VII. TALL STATURE

A. Definition:

Childhood tall stature is defined as length (<2 years old) or height (≥2 years old) ≥95th percentile (≥+2 SD) for age and sex when compared with appropriate population norms. The etiology of childhood tall stature can be divided into two categories: (1) conditions with normal or decreased final adult height relative to the population and/or genetic potential and (2) those conditions that result in adult tall stature.

1. **Childhood tall stature with normal or decreased final adult height**
   a. **Exogenous obesity** in an otherwise healthy child is often associated with childhood tall stature, sometimes accompanied by earlier onset of adrenarche or central precocious puberty. Final adult height is usually normal or decreased relative to genetic potential (especially in females) depending on pubertal timing.
   b. **Hyperthyroidism**, untreated, can cause a dramatic increase in height velocity and bone age. However, pubertal timing and final adult height are usually unaffected.
   c. **Central precocious puberty** and other exposure to excessive endogenous androgens or estrogens can cause rapid childhood growth and childhood p. 158p. 159tall stature with early epiphyseal fusion and adult short stature. **Exogenous exposure to estrogens or androgens**, most often resulting from transdermal exposure to a parent or other individual using topical preparations, can result in a similar situation and can also trigger central precocious puberty.
   d. Childhood tall stature with normal adult height may be observed in several genetic conditions including Bannayan–Riley–Ruvalcaba syndrome (*PTEN*, 10q23.31), deletion 22q13, Pallister–Killian syndrome (mosaic tetrasomy or

isochromosome 12p) and in some individuals with Sotos and Beckwith–Wiedemann syndromes (next section).

2. **Childhood tall stature with adult tall stature**
   a. **Familial tall stature.** Most tall children with adult tall stature have tall parent(s) and a concordant calculated midparental height. In most such pedigrees, the tall stature is related to normal human variation. However, familial tall status can also be due to heritable abnormalities in both the parent(s) and child.
   b. **GH hypersecretion (pituitary gigantism)** (see Chapter 9).
   c. **Klinefelter** syndrome (47, XXY) is the most common sex-chromosome aneuploidy in males, with an incidence of 1 to 2 per 1 000 live births. Affected individuals have primary hypogonadism, azoospermia and infertility with small, fibrotic testes and variable occurrence of other features including gynoid habitus, gynecomastia, cognitive and behavioral abnormalities. 47, XXY and the less common variant 48, XXXY are associated with normal to modestly increased stature, perhaps related to increased *SHOX* dosage; 48, XXYY is associated with final height >6 feet while short stature is observed in 49, XXXXY.
   d. **Marfan syndrome** is caused by heterozygous mutation of *FBN1* (15q21.1) which codes for fibrillin, a key connective tissue component. Affected individuals have tall stature, arachnodactyly, joint hyper-extensibility, kyphoscoliosis, ectopia lentis, and aortic medionecrosis with increased risk for aortic valve prolapse and aortic dilatation. *FBN1* mutations have also been associated with other clinical presentations and syndromes, not all of which include tall stature.
   e. **Homocystinuria** is caused by mutation of *CBS* (21q22.3) causing cystathione β-synthase deficiency and resulting in elevated levels of homocysteine which may interfere with *FBN1*, resulting in a marfanoid habitus and tall stature. Affected individuals lack other features of Marfan syndrome but may have intellectual disability and increased risk for thromboembolism. Pyridoxine responsive and nonresponsive forms have been associated with specific *CBS* mutations.
   f. **Sotos syndrome,** *aka* cerebral gigantism, due to sporadic mutation of *NSD1* (5q35.3) is characterized by dolicocephaly, prominent forehead, downslanted palpebral fissures, mild to

severe learning disability, and somatic overgrowth. Head circumference and height are typically >2.5 SD starting in infancy; final adult height is variably increased. *NSD1* mutations may also be found in some cases of Beckwith–Wiedemann syndrome.

g. **Beckwith–Wiedemann syndrome,** an autosomal dominant condition with macrosomia, childhood tall stature, and variable adult tall stature, is usually associated with imprinting defects of 11p15.5, including genes which are paternally (*IGF2*, *KCNQ1OT1*) and maternally (*H19*, *CDKN1C*, *KCNQ1*) expressed. Other features include anterior earlobe pits/creases, hemihyperplasia of body segments or organs, visceromegaly, adrenal cortical cytomegaly, renal abnormalities, omphalocele, macroglossia, neonatal hypoglycemia, and increased risk for embryonal tumors; for example, Wilms tumor, neuroblastoma, hepatoblastoma, and rhabdomyosarcoma. A variant form is associated with *NSD1* mutation.
h. **Weaver** (*aka* Weaver-Smith) **syndrome**, associated with heterozygous mutation of *EZH2* (7p36), resembles Sotos syndrome, and also includes hypertelorism, micrognathia, wide philtrum, deep horizontal chin groove, and deep-set nails.
i. **Simpson–Golabi–Behmel syndrome** is an X-linked recessive condition associated with mutation of *GPC3* (Xq26.2; codes for the proteoglycan glypican-3). p. 159p. 160The phenotype strongly resembles Beckwith–Wiedemann syndrome, with additional features including supernumerary nipples, cardiac abnormalities, hand malformations, and variable intellectual impairment.
j. **Aromatase deficiency** (***CYP19A1***; 15q21.2) results in inability to convert androgens to estrogen. Female fetuses (and their pregnant mothers) will be inappropriately virilized because of failed placental conversion of DHEAS to estrogen, the excess DHEAS undergoes peripheral conversion to testosterone. Affected individuals of both sexes have delayed skeletal maturation, eunuchoid habitus, low bone mineral content, and tall stature, reflecting the role of estrogen in bone mineralization

and epiphyseal closure. A similar phenotype occurs with **homozygous mutation of the estrogen receptor** (***ESR1***, 6p25).

B. Evaluation

Although the statistical distribution of tall stature should be similar between male and female children, the majority of patients referred for evaluation of tall stature are female (and the majority of children evaluated and treated for short stature are male). In most cases, the cause of childhood tall stature is obvious on clinical history and examination. Elements of an evaluation for tall stature may include:

1. Medical history and physical examination: Family history, parent and sibling heights, birth history, growth patterns, other medical conditions, dysmorphic features.
2. Thyroid axis (T_4, T_3, TSH), GH-IGF axis (IGF-I, IGFBP-3, random and postglucose GH).
3. Homocysteine levels (usually with methionine, cysteine).
4. Testosterone, estradiol, 17-hydroxyprogesterone, FSH, LH for patients presenting with evidence of sexual precocity or inappropriate virilization.
5. Genetic testing for specific conditions.
6. Bone age radiograph for calculation of predicted adult height. Bone age may underestimate final adult height in hyperthyroidism, obesity, and benign premature adrenarche; and may overestimate final adult height in precocious puberty.

C. Treatment of tall stature

1. **Childhood tall stature resulting in normal or decreased final adult height**
   a. Treatment of the underlying and any associated conditions as clinically indicated.
   b. For conditions in which final adult height may be compromised, treatment of the underlying condition (e.g., precocious puberty treated with GnRH agonists). GH and/or aromatase inhibitors (e.g., anastrozole, letrozole) have also been used to preserve final adult height; efficacy data for these ancillary treatments are not conclusive.
2. **Childhood tall stature resulting in adult tall stature**
   a. Treat any underlying pathology or associated conditions, if feasible.

b. Estrogen treatment with induction of menarche has been used for female childhood tall stature; limited data indicate a small reduction in final adult height relative to genetic potential. Testosterone treatment for male childhood tall stature could have a similar effect to hasten epiphyseal fusion, but such treatment is rarely requested or indicated.

c. Estrogen treatment has been used for treatment of tall stature in both males and females with aromatase deficiency. No effective treatment has been identified for individuals with the very rare condition of estrogen receptor deficiency.

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14 Short Stature and Growth Hormone Therapy

Philippe F. Backeljauw

I. INTRODUCTION

Any infant, child, or adolescent with unexplained short stature and/or growth failure has a good reason to be evaluated by a pediatric endocrinologist. The workup of such a patient must be based foremost on a detailed history and carefully executed physical examination. Additional investigation may have to include radiographic and laboratory testing. This chapter introduces some of the key aspects of the regulation of the hypothalamic–pituitary–growth plate axis, discusses normal and abnormal growth, and reviews the evaluation of growth failure and the treatment of growth hormone deficiency (GHD) and a variety of other growth disorders.

II. THE PHYSIOLOGY OF THE HYPOTHALAMIC–PITUITARY–GROWTH PLATE AXIS

A. Growth hormone (GH). Human GH is produced in and secreted by the cells (somatotropes) situated in the anterior part of the pituitary gland, and is a 22-kDa 191-amino-acid protein made up of a core of four helices with two disulfide bonds between cysteines 53 to 165 and 182 to 189, respectively. The gene for human GH (*GH1*) is located on chromosome 17, and is part of the GH gene family that also encodes for human placental lactogen and placental GH. In addition, GH is structurally related to the hormone prolactin (PRL), secreted by anterior pituitary lactotrope cells, and for which the *PRL* gene is located on chromosome 6. Both GH and PRL evolved from a common precursor gene. GH secretion from the somatotropes is produced in a pulsatile manner and reflects the influence of several different regulatory peptides, including two from the hypothalamus: GH-releasing hormone (GHRH) and somatostatin (somatotropin release-inhibiting factor). The former, GHRH, acts via the GHRH receptor, a member of the G-protein–coupled receptor family, and stimulates GH

secretion. Analog derivatives of GHRH can be used as diagnostic agents in the evaluation of GHD. The other hypothalamic peptide, **somatostatin, inhibits GH secretion**. A variety of other nonpeptide hormones further affect GH secretion, including estrogens, androgens, glucocorticoids, and thyroid hormones. Stress conditions, sleep, hypoglycemia, and fasting, as well as exercise all influence endogenous GH secretion. An additional regulator of GH secretion is the 28-amino-acid **ghrelin**, a peptide secreted in small amounts by the hypothalamus (among other organs), but in larger quantities by the stomach. Ghrelin is the endogenous ligand for the GH secretagogue receptor and releases GH together with GHRH in a synergistic manner. The efficacy of ghrelin as a growth-promoting peptide is believed to be poor, although mutations in the ghrelin receptor have been implicated in the etiology of GHD and short stature.

GH is found in the fetal pituitary at approximately 60 days of gestation, and its concentration increases throughout pregnancy. Circulating fetal GH is entirely of fetal origin because **maternal GH does not cross the placenta**. The highest fetal serum GH concentrations are found during mid-gestation, after which they decrease toward birth. In term newborns, GH concentrations remain elevated for the first 2 days of life, after which they decrease over several weeks to reach "adult range" concentrations at 3 months of age. The slow wave phase of sleep-associated p. 162p. 163maximal GH release (stages 3 and 4) is only observed after 3 months of life. Normal 24-hour GH production rates range from 0.25 to 0.5 mg/m^2, with the highest serum GH concentrations seen in puberty.

B. GH signaling and action. Secreted GH is bound by GH-binding protein, the cleaved extracellular portion of the GH receptor. The binding of GH to the GH receptor induces a conformational change of the latter, resulting in activation of the JAK/STAT signaling pathway. With a mature hypothalamic–pituitary–growth axis, GH has both growth-promoting/anabolic and metabolic effects: respectively, stimulation of postnatal bone growth and development of muscle mass, as well as lipolytic effects. Most of the growth-promoting and anabolic effects of GH are mediated through the production of insulin-like

growth factors (IGFs), predominantly IGF-I (see below).

GH does not play a major role in prenatal growth and does not influence fetal IGF-I production; an effect of GH on fetal IGF-I production is only noticeable during the last segment of gestation.

C. Insulin-like growth factors. The anabolic actions of GH are mainly mediated through the IGFs, a family of small peptides originally called somatomedins. Two major IGFs are identified: IGF-I, a 70 amino-acid single-change peptide with more than 40% homology to proinsulin, and IGF-II—structurally closely related to IGF-I. Like insulin, both IGFs have A- and B-chain connected by disulfide bounds, and this explains why both molecules also bind to the insulin receptor. At the same time, insulin can bind to the receptor for IGF-I, the type 1 IGF receptor, which is closely related to the insulin receptor. Studies have shown that the type 1 IGF receptor is capable of binding to both IGFs with high affinity. The affinity of insulin for the type 1 IGF receptor is approximately 100-fold less. IGF-II preferentially binds to the type 2 IGF receptor.

The concentration of IGF-I is under strong influence of GH, and serum IGF-I measurements are used as a marker of GH secretion/concentration/activity. In addition to stimulating tissue growth, IGF-I provides direct feedback to the hypothalamic and pituitary glands and hereby controls the release of GHRH and somatostatin, as well as the release of GH. The IGF-I peptide itself is mainly found in bound form: to different IGF-binding proteins (IGFBP-1 through IGFBP-6). These IGFBPs distribute IGF-I throughout the body. The most important binding protein for IGF-I is IGFBP-3, which further complexes with another protein called acid-labile subunit (ALS). The resulting **IGF-I/IGFBP-3/ALS is called the ternary complex** and makes up the largest reservoir for circulatory IGF-I.

III. NORMAL GROWTH

Figure 14-1 illustrates schematically the role that GH and IGF-I have in pre- and postnatal growth. As noted, IGF-I is involved both in prenatal and postnatal growth, whereas GH is mainly involved in postnatal growth. Linear growth is most impressive during prenatal life so that at the end of gestation the mean birth length is around 50 cm. Birth size is further regulated by both maternal and placental factors. Postnatally, a neonate’s growth rate is determined by its own genetic potential (parental heights)

and the physiologic milieu. During the first year of life, linear growth is approximately 25 cm/year. This decreases to about 10 cm/year in the second year, and about 7.5 cm/year in the third year. During the childhood years and prior to the onset of puberty, children grow the slowest (minimum growth velocity is ±5 cm/year). During puberty, growth velocity again increases. Girls enter puberty approximately 2 years before boys, but they do not have as strong a growth spurt as seen in boys. Those differences result in a 13-cm difference in mean adult height between males and females. For the assessment of a patient's longitudinal growth, the addition of height velocity curves is very helpful, but the differences in the timing and cadence of puberty need to be taken into account. Cross-sectional reference growth charts are available for specific short stature syndromes such as Turner syndrome (TS), trisomy 21, and several forms of skeletal dysplasia.

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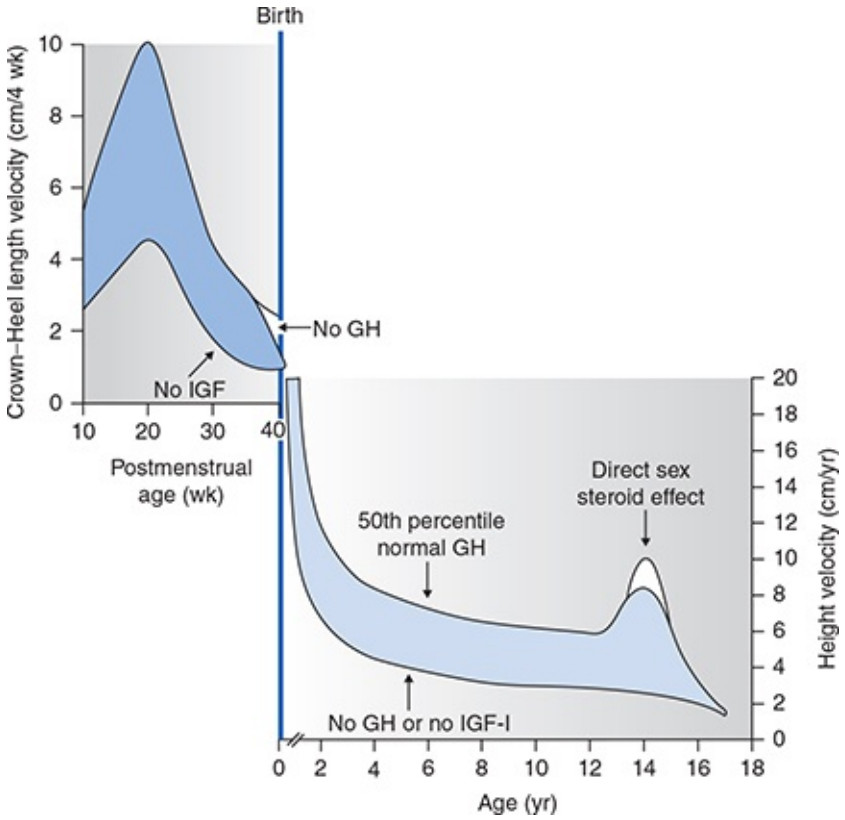

Figure 14-1. The role of GH and IGF-I in pre- and postnatal growth. The upper line of the height–velocity curve in both panels approximates the 50th percentile in boys. Different scales are used for prenatal growth and postnatal height velocity. The lower line in the postnatal height–velocity curves indicates the expected growth rate in children totally lacking GH. Clinical evidence

suggests that a similar line can be drawn for children with severe IGF-I deficiency. The shaded region thus reflects IGF-dependent growth. Prenatally, the lower line reflects the best estimate of intrauterine growth in the absence of IGF-I. IGF-dependent growth in prenatal life is largely independent of GH. GH, growth hormone; IGF, insulin-like growth factor. (From Rosenfeld RG. Insulin-like growth factors and the basis of growth. *N Engl J Med* 2003;349:2184–2186.)

IV. AUXOLOGY

During the first 2 to 3 years of life, children are measured in the supine position, whereas standing heights are measured beyond that age. The upper:lower segment ratio is 1.7:1 in neonates and decreases by 0.1 for every year of age. At 7 years of age, this ratio becomes 1:1 and remains so afterward (it will be slightly below 1 in adults). With normal health, the arm span is less than the height in boys up to 10 years and in girls up to 11 years of age. The arm span is approximately 5 cm greater than the height in adult males and about 1.2 cm in adult females.

It is also helpful to calculate an estimate of **midparental height (MPH)**, that is, the patient's genetic potential for adult height. To do so, one adds the height of the parents and subtracts 13 cm for girls or adds 13 cm for boys, followed by dividing by 2. The MPH can be plotted to the right of the growth chart so that a child's height curve can be compared to what should be his or her genetic potential. The **target height range** will then be defined as ±2 standard deviation score (SDS) around the MPH. One must seriously consider the possibility of an underlying pathologic process if a child's growth pattern deviates from that of his or her sibling(s) or that of the parents: thus, below the 3rd percentile on the growth chart, or greater than 2SDS below the MPH curve.

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V. DIFFERENTIAL DIAGNOSIS OF SHORT STATURE AND GROWTH FAILURE

Figure 14-2 shows a schematic overview of the differential diagnosis of short stature. For the abnormal short stature, one can differentiate between disproportionate and proportionate short stature. In the latter group, one can distinguish between patients who have prenatal onset of short stature versus patients with postnatal onset of short stature. The last group will include patients with organ system disease, as well as patients with endocrine disorders.

VI. VARIATIONS OF NORMAL OF GROWTH AND DEVELOPMENT

A. **Familial/genetic short stature**. These patients usually have a family history of short stature and a normal birth weight. Their growth curve should parallel the normal percentile curves, but length or height will plot below the 3rd percentile for chronologic age, as they grow with a normal annual height velocity. Their predicted adult height and MPH will both be below the 3rd percentile. They should not develop a significant bone age delay or advancement. Their onset of puberty is normal. A detailed history and physical examination will not reveal any evidence for organic or emotional causes of short stature. Because some forms of familial short stature can have a pathologic cause, an evaluation may still be in place for those children who fall significantly below the growth chart, whose height is more than 2SDS below their MPH curve, and/or who have a specific genetic pattern of short stature in the family.

B. **Constitutional growth delay** (usually associated with constitutional delay of maturation). These patients often have a family history of constitutional delay of growth and maturation. Their physical examination is normal. They have a normal nutrition history, but it is not uncommon for them to have a low body mass index. Their height plots out below the 3rd percentile for age, but they tend to develop delayed skeletal maturation. Puberty is also often delayed. Despite this, their annual height velocity tends to be normal throughout childhood. All this still allows them to have a normal adult height prediction. Evaluation of the GH–IGF-I axis will not yield any abnormalities. As with patients with familial short stature, constitutional growth delay is not associated with an organic or emotional cause for growth failure. These patients tend to have a growth pattern that begins to deviate from their target height growth curve during the first couple of years of life.

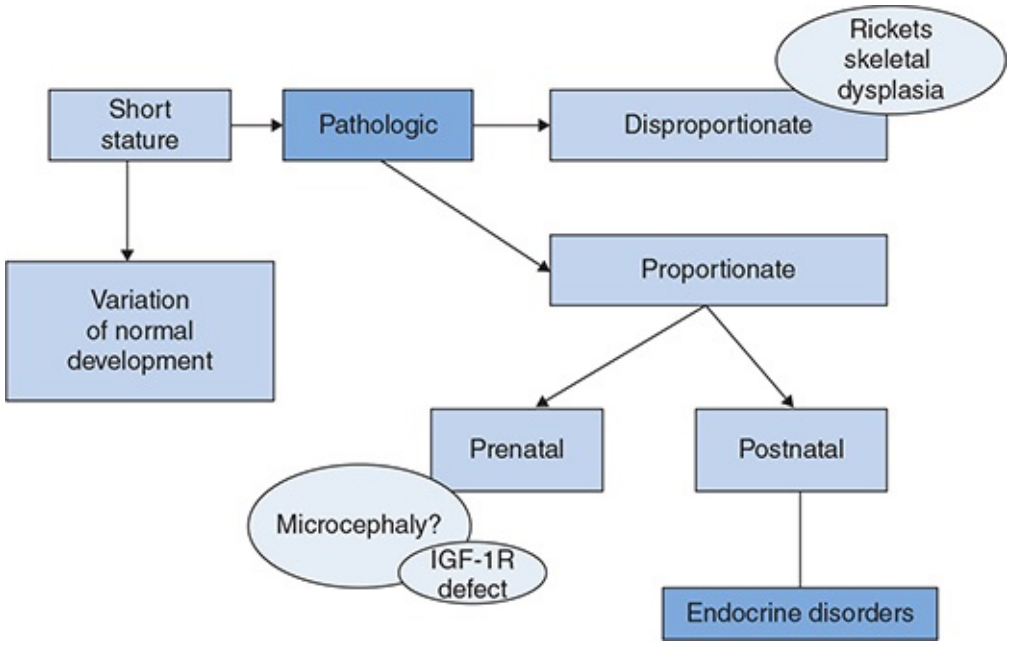

Figure 14-2. Schematic overview of the differential diagnosis of short stature. IGF-1R, insulin-like growth factor 1 receptor.

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VII. PATHOLOGIC SHORT STATURE

A. Disproportionate short stature

1. **Osteochondrodysplasia (skeletal dysplasia)**
   The osteochondrodysplasias make up a large and heterogeneous group of disorders characterized by abnormalities affecting the size or shape of the skeleton (long bones, vertebrae, and skull). These bone and cartilage abnormalities can be confirmed with x-ray evaluation when typical features often allow for the diagnosis of a specific phenotype. With the advent of molecular diagnostics, most of these disorders are now characterized genetically.
2. **Achondroplasia:** This is the most common form of skeletal dysplasia with a frequency of 1 in 26 000 births. It is transmitted in an autosomal dominant manner, but close to 90% of patients are caused by a new mutation. The etiology is a mutation in the gene for the fibroblast growth factor receptor 3 (FGFR3). Patients homozygous for this mutation have a severe form of skeletal dysplasia, which can result into respiratory insufficiency and death in infancy. Milder forms are diagnosed because of progressive

growth failure in the first couple of years after birth, although significant short stature may not be detected until 2 years of age. Mean adult height is 131 and 124 cm, respectively, for males and females. In addition to short stature due to short proximal upper and lower extremities (rhizomelia), other skeletal abnormalities include megalocephaly, low nasal bridge, lumbar lordosis, and a short trident hand. On x-ray, these patients have small, cuboid-shaped vertebral bodies with short pedicles, a progressive narrowing of the lumbar interpeduncular distance, and small iliac wings with narrow sciatic notches. Hydrocephalus and spinal cord compression may develop as the result of a small foramen magnum and from kyphosis, stenosis, or intervertebral disc anomalies.

3. **Hypochondroplasia:** Although these patients may present as having a "fruste" form of achondroplasia, the disorder is caused by a completely different mutation of the FGFR3 gene. These patients' short stature and rhizomelia are less pronounced, they lack the characteristic facial phenotype of achondroplasia, and their mean adult height is between 120 and 150 cm. Patients may have genu varum and lumbar hyperlordosis. Milder forms of hypochondroplasia are often not diagnosed or diagnosed late. Radiologic findings also include diminished interpeduncular distance between L1 and L5, with milder flaring of the pelvic bone and narrowing of the sciatic notches.

   Although GH therapy has been prescribed to patients with achondroplasia, and especially to those with hypochondroplasia, and some patients may have demonstrated modest improvements in height, these disorders **have not been recognized as indications for GH therapy by the US Food and Drug Administration**. Therefore, GH therapy should not be routinely recommended for these patients.

4. **Other osteochondrodysplasias.** Many other types of osteochondrodysplasia have been described, including epiphyseal dysplasia, metaphyseal dysplasia, dysplasias with increased or defective bone mineralization, spondylometaphyseal dysplasia, and acromelic/acromesomelic dysplasias. With careful assessment of body proportions including head circumference, arm span, sitting height, and determination of the upper/lower body segment ratio, most of these patients can be diagnosed during the childhood age range. Investigations should include both clinical and radiologic

evaluation to determine which part of the skeleton is additionally involved. Confirmation of the specific diagnosis is achieved with molecular testing.

5. **Disproportionate short stature associated with rickets**
   Children with different forms of rickets may also present with poor growth/short stature. Characteristic radiographic findings of all types of rickets may include widening, cupping, and splaying of the epiphysis; generalized decreased bone mineralization; and loss of the definition of the zone of provisional calcification at the transition of epiphysis to metaphysis. Pathognomonic findings in infants and toddlers include frontal bossing, craniotabes, rachitic rosary, widening of the wrists, and leg bowing.

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   a. **Vitamin D deficiency rickets** is a common cause of subnormal growth. Vitamin D deficiency can be due to lack of sunlight exposure without vitamin D supplementation, but is often associated with malnutrition, malabsorption, or organ disease, such as chronic renal failure or liver disease.
   b. **Hypophosphatemic rickets,** or phosphopenic vitamin D-resistant rickets, is due to decreased renal tubular reabsorption of phosphate. Patients will have short stature, leg bowing, and other signs of rickets. Males are usually more affected than females. Phosphopenic rickets can not only be caused by renal tubular pathology such as in **Fanconi syndrome** (phosphaturia, glucosuria, aminoaciduria, and proximal renal tubular acidosis), but may also be encountered as a congenital disorder caused by a mutation in the *PHEX* gene (phosphate regulating endopeptidase homolog, X-linked). This form of rickets is called **X-linked hypophosphatemic rickets** and is associated with renal phosphate wasting at birth. The development of a clinically apparent phenotype occurs in the first years of life. Finally, hypophosphatemic rickets can also result from the production of a phosphaturic factor (FGF23) by certain tumors, often of mesynchymal in origin.

B. Proportionate short stature

1. **Intrauterine growth retardation (IUGR) or smallness for gestational age (SGA)**
   Approximately 3% of all newborns have a birth weight and/or birth

length ≤2 SDS below the mean in relation to the gestational age for the same sex. In about 40% of these SGA babies, no specific etiology can be identified. Catchup growth will occur postnatally in most of these children during the first 2 years of life, but about 10% to 15% of children born SGA will fail to reach the normal growth percentiles by that age. It has been estimated that **10% of adults born SGA will have an adult height below −2SDS**. Several studies treating SGA children with GH have demonstrated improvements in adult height, and GH therapy for children born SGA who fail to show adequate catchup growth is now approved in several countries. Some IUGR has been associated with mutations of the type1 IGF receptor, especially if microcephaly is also part of the picture. On the other hand, IUGR can be caused by intrinsic abnormalities of the fetus, the mother, or by placental insufficiency.

2. **Specific forms of IUGR**

   Russell–Silver syndrome represents a heterogeneous group of patients who present initially with IUGR, and continue to have postnatal growth failure. Children often have a small and triangular face, as well as evidence of congenital hemihypertrophy. The head circumference is normal. Other characteristics may include clinodactyly, delayed closure of the fontanelle, and premature adrenarche. A molecular basis for Russell–Silver syndrome is maternal uniparental disomy for chromosome 7 (in 5% to 10% of patients). Many other Russell–Silver syndrome patients have epigenetic changes, for example, DNA hypomethylation of the imprinting control region on chromosome 11p15, a defect that includes both the *H19* and *IGF-II* genes (in up to 60% of patients). These patients often manifest increased IGF-I and IGF BP-3 concentrations, suggestive of resistance to IGF-I.

3. Other forms of prenatal-onset proportionate short stature are due to *CDKN1C* mutations which have been associated with **Beckwith–Wiedemann syndrome** and **IMAGe syndrome** (without the adrenal insufficiency), as well as **Russell–Silver syndrome** variants. True **IMAGe syndrome** patients have IUGR, metaphyseal dysplasia, congenital adrenal hypoplasia, and, in males, genitourinary abnormalities. The phenotype for CDKN1C-related short stature is clearly evolving. Dysfunction of the GH/IGF axis is a feature of **3-M syndrome**, an autosomal

recessive form of growth failure with IUGR and postnatal growth restriction, as well as a triangular face, with flat cheeks and full lips, a short chest, and large fleshy heels. It is known to be caused by mutations in at least three genes (*CUL7*, *OBSL1*, and *CCDC8*).

4. **Proportionate short stature with postnatal onset**
   a. **Nutritional causes of growth failure**

      Impaired growth can be secondary to malnutrition. On a worldwide basis, this is the most common cause of growth failure in children. Two specific forms p. 167p. 168of malnutrition or undernutrition have been recognized.

      In **marasmus**, there is muscle mass wasting and depletion of body fat stores, leading to a weak appearance (thin arms, thighs, and buttocks). Marasmus leads to decreased weight and height for age, a relatively large head, severe constipation, bradycardia, hypotension, hypothermia, thin sparse hair, and dry skin. Marasmus is the more common form of protein-energy malnutrition, caused by inadequate intake of all nutrients. When protein-energy malnutrition is also associated with edema, patients have **kwashiorkor**: muscle atrophy, often normal body fat amounts, but with peripheral edema (anasarca). In kwashiorkor, the inadequate protein intake is the dominant factor, but caloric undernutrition may be associated. Kwashiorkor children may have normal or near-normal weight for age, generalized edema, pitting edema of the lower extremities, rounded cheeks, skin atrophy and dry skin/hair, hyperpigmentation, hepatomegaly (fatty infiltration of the liver), hypothermia, and abdominal distension. The association in these patients of an **increased GH with a decreased IGF-I** points toward the presence of a degree of GH insensitivity. Children may have hypercortisolemia. Liver metabolism and excretion of toxins by the liver is also impaired, and gluconeogenesis is reduced, which puts these patients at risk for hypoglycemia. Alternatively, glucose intolerance has also been documented.

   b. **Chronic organ system disease**

      i. **Gastrointestinal disease and malabsorption.** Poor

growth often accompanies patients with malabsorption or chronic inflammatory bowel disease (ulcerative colitis and Crohn disease). Whenever a patient presents with unexplained growth failure, inflammatory bowel disease, as well as gluten-sensitive enteropathy (celiac disease), need to be considered in the differential diagnosis. The associated malabsorption and **malnutrition will lead to decreased IGF-I concentrations**. The abnormal growth seen in patients with inflammatory bowel disease is due to a combination of factors: malabsorption of nutrients, decreased appetite, chronic inflammation, subnormal trace mineral concentrations, and even glucocorticoid therapy.

ii. **Cardiovascular system.** Growth retardation can be a consequence of chronic heart disease associated with cyanosis or congestive heart failure. The degree of hypoxia is correlated with the severity of the postnatal growth failure, and may be aggravated by the increased energy demands of heart failure. Patients with congestive heart failure may also have decreased food intake contributing to impaired statural growth. Cyanotic heart disease and compromised cardiac function may manifest through IUGR.

iii. **Renal disease.** A large number of disorders that affect renal function can lead to clinically significant growth retardation: renal tubular acidosis in young children, Fanconi syndrome, uremia, and nephrotic syndrome (protein loss). Glucocorticoid therapy can further inhibit growth. If these patients develop decreased renal function at a young age, they can be expected to have cumulative growth impairment over several years. **GH therapy has been approved** for the treatment of growth failure associated with renal disease and can be helpful in improving linear growth before renal transplantation.

iv. **Hematologic disorders.** Chronic anemia (e.g., sickle cell disease) may be associated with growth failure. This is also the case with thalassemia, which may be further complicated by endocrine insufficiency because of chronic transfusion and secondary hemosiderosis. Concentrations of IGF-I may be decreased, and hypothyroidism and

hypogonadism can contribute to a more severe growth impairment.

v. **Pulmonary disease.** Patients with **cystic fibrosis** often have significant growth failure because of impaired pulmonary and pancreatic function. Contributory factors to the poor growth include hypoxia, malabsorption, decreased appetite, chronic catabolism, and the development of glucose intolerance and diabetes. In addition, increased energy expenditure and glucocorticoid-induced growth failure contribute to a poor height outcome. In children with chronic asthma, the use of the **glucocorticoids** may contribute to impaired growth, even if medication is administered via inhalers.

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vi. **Infection.** In many parts of the world, especially in the developing countries, chronic infection and infestation with intestinal and systemic parasites leads to nutritional impairment and growth failure. Patients with chronic immunodeficiency syndromes often have significant growth failure.

c. Other causes of poor growth

Children with **inborn errors of protein, carbohydrate, and lipid metabolism** often have growth failure. Examples include glycogen storage diseases, mucopolysaccharidoses, and mucolipidoses. Some of these disorders also have a skeletal dysplastic component.

Children with **psychosocial or psychoemotional growth failure** fail to thrive and grow normally because of extreme socioeconomic or emotional deprivation. These patients often have decreased GH and IGF-I concentrations, as well as delayed skeletal maturation. Because stress is an important contributing factor, this condition is seen in patients from abusive homes. Removal from the harmful environment often leads to a rapid resolution of the endocrine disturbances, including correction of the growth failure.

Voluntary restriction of nutrition can also lead to growth failure as seen with excessive dieting. **Anorexia nervosa** is an eating disorder characterized by decreased

weight and fear of gaining weight, a strong desire to remain thin, and self-induced food restriction. There are two categories of anorexia nervosa, which are defined by symptoms observed during a 3-month period. The restricting type is characterized by marked weight loss through dieting, fasting, and excessive exercise. The other type consists of binge eating followed by purging (bulimia nervosa).

Involuntary caloric restriction can be observed in patients with attention deficit disorder (ADD) treated with **stimulant medications that decrease appetite**, and be associated with growth delay. When followed until near-adult height, height attainment appears to be within the normal range. Although many children with ADD treated with stimulant medications have some degree of growth attenuation, the rate of height loss appears to be relatively small and reversible.

Other medications that have a negative impact on growth include glucocorticoids: they interfere with the integrity of the GH/IGF-I axis by increasing somatostatin tone, decreasing GH secretion, decreasing GH-induced IGF-I production in the liver, increasing protein catabolism, and potentially increasing the production of IGF-I inhibitors (e.g., IGFBP-2). At the growth plate level, glucocorticoids decrease cell proliferation and matrix production, decrease local production of IGF-I, and decrease the expression of the GH and the type 1 IGF receptor.

d. Genetic/chromosomal causes of growth failure

i. Turner syndrome: Short stature is the single most common physical abnormality in individuals with TS. Untreated TS girls achieve an average adult height approximately 20 cm below that of normal women. The growth failure observed in patients with TS is due to several factors: (a) mild-to-moderate growth retardation in utero, (b) slow growth during infancy compared to the expected target height percentile, (c) delayed onset of childhood component of growth, (d) slow growth during childhood, and (e) failure to experience the pubertal growth spurt. The poor growth of TS infants may be further exacerbated by feeding difficulties. Because of the decreased or absent pubertal growth spurt, linear growth can be prolonged in untreated TS females (until the late teenage years or early

20s). TS girls also have a stocky appearance due to a relatively greater reduction in body height than body width; they are also somewhat overweight. Scoliosis and kyphosis not infrequently contribute to the decreased adult height. The major determinant of growth failure in TS patients is **haploinsufficiency of *SHOX*** (short stature homeobox-containing gene on the X-chromosome). GH therapy is now considered standard of care for TS girls, and should begin as soon as growth failure is observed. To stimulate normal development, initiation of estrogen replacement should p. 169p. 170begin around 11 to 12 years of age. **Low doses of estrogen** should be used to protect adult height potential whether or not the patient is on GH treatment. Incremental dose increases may be done about every 6 months to mimic the normal cadence of puberty progression until the adult dosing range is reached (usually in 2 to 3 years). The addition of the anabolic nonaromatizable steroid **oxandrolone** (at doses from 0.03 and 0.05 mg/kg/day), adds approximately 2 to 4 cm of height gain, when such treatment starts around 8 to 10 years of age. Timing, route, and dose of recommended estrogen options are depicted in Table 14-1.

TABLE 14-1 Timing, Route, and Dose of Recommended Estrogen Options

Preparation	Pubertal Initiation Dose	Adult Dosing
Transdermal estradiol	3–7 μg/d	25–100 μg/d
Oral micronized 17-β estradiol	0.25 mg/d	1–4 mg/d
Oral ethinyl estradiol	2 μg/d	10–20 μg/d
Depot IM estradiol	0.2 mg/mo	2 mg/mo

ii. **SHOX deficiency.** Patients with deficiency of the *SHOX* gene show a wide variety of phenotypic features with variability in the severity of the presentation. Patients with *SHOX* gene haploinsufficiency (e.g., *SHOX* deletion) usually have skeletal abnormalities as well as short stature.

In **Leri–Weill dyschondrosteosis**, disproportionate short stature with shortening of the middle segments of the long bones of the arms and legs, and Madelung deformity of the wrist is classical. The short stature in these patients can be variable with affected individuals ranging in adult height from 135 cm to normal for their gender. When patients are homozygous for *SHOX* gene deficiency, they develop **Langer mesomelic dysplasia**, with much more severe short stature, and severe (mesomelic) shortening of the limbs. Finally, *SHOX* gene mutations have been identified in approximately **2% of children with idiopathic short stature (ISS)**. GH therapy can be helpful in these patients as well as in other patients with *SHOX* gene haploinsufficiency.

iii. **Noonan syndrome (NS).** Although children with NS can have a similar phenotype to TS (short stature, neck webbing, and gonadal failure—in males), the etiology is different. Slightly more than half of NS children have dominant-negative mutations in the ***PTPN11* gene** which encodes the nonreceptor protein tyrosine phosphatase signaling molecule SHP-2. Less common mutations in genes encoding other signaling molecules have also been identified (*KRAS*, *RAF1*, *SOS1*, *BRAF*, and *NRAS*). The incidence of NS is reportedly between 1 and 1 000 and 1 in 2 500 live births. Transmission is thought to be autosomal dominant with many cases arising spontaneously. Most NS patients have short stature. Pubertal delay, unlike with TS, is only seen in certain NS patients. In males, microphallus and cryptorchidism are common findings, and puberty is frequently incomplete. Girls with NS have normal fertility. Other similarities with TS include webbing of the neck, kidney malformations, and eyelid ptosis. In contrast to TS patients, the **cardiac anomalies tend to involve the right side of the heart,** and the neurobehavioral anomalies include global developmental delay and seizures, whereas TS patients most often have nonverbal learning deficits. NS children respond to GH therapy, and NS is now also an approved indication for such therapy in the United States.

iv. **Prader–Willi syndrome (see Chapter 16)**

v. **Down syndrome.** Trisomy 21 is found in approximately 1 in 600 live births. This makes this diagnosis the most common chromosomal disorder associated with growth retardation. At birth, the average weight p. 170p. 171of a Down syndrome neonate is about 500 g below normal. Infants are also 2 to 3 cm shorter than normal newborns. Down syndrome is further characterized by postnatal growth failure and a delayed, poor pubertal growth spurt. Although **GH therapy** has been tried in Down syndrome, this is **not an approved indication** for such therapy. There are no convincing data available indicating that the GH therapy improves the neurologic or intellectual well-being of these children.

vi. **18q deletion syndrome.** Patients with a deletion of the long arm of chromosome 18 are usually below −2SDS for height. The phenotype is characterized by short stature, developmental delay (mild-to-severe, seizures, autistic behaviors), and hypotonia. There are some reports suggesting that GHD is common in18q deletion syndrome, but the provocative testing was not always done in a rigorous manner, and studies were done in a limited number of patients.

vii. **Other genetic syndromes associated with short stature**. Many other syndromes may be associated with short stature, varying from moderate to profound. These include Bloom, Cornelia de Lange, Donohue, Rubinstein–Taybi, Johanson–Blizzard, and Aarskog syndromes to name but a few. Patients with Seckel syndrome represent a genetically heterogeneous autosomal recessive condition caused by mutations in *ATR*, *RBBP8*, *CENPJ*, *CEP152*, and *CEP63* genes. Patients with Seckel syndrome have IUGR as well as severe postnatal growth failure in combination with microcephaly and micrognathia. **Progeria patients** (Hutchinson–Guilford syndrome) are known for a characteristic phenotype appearing by 2 years of age that

consists of progressive loss of subcutaneous fat, alopecia, joint limitation, and congestive heart failure. Skeletal hypoplasia results in severe growth retardation, which can be seen from 6 months of age on. **Cockayne syndrome** will also be characterized by **premature senile appearance**. Growth failure in these patients is seen from 2 years of life on. This autosomal recessive disorder is further characterized by retinal degeneration, photosensitivity of the skin, and hearing impairment.

e. Endocrine causes of short stature

i. Hypothyroidism

The most common manifestation of untreated acquired hypothyroidism is growth failure. Postnatal growth retardation can also be seen in infants with congenital hypothyroidism if the diagnosis is not made in the newborn period and the patient does not receive prompt treatment with thyroid hormone supplementation. In the acquired form of hypothyroidism, poor growth may be present for several years before it becomes clinically apparent. Because of this, evaluation of the hypothalamic–pituitary–thyroid hormone axis is crucial for any child presenting with short stature. Thyroid hormone replacement therapy usually restores normal growth velocity, but in cases of long-standing growth failure, catchup growth may not entirely occur, and long-standing hypothyroidism may therefore be associated with permanent loss of height potential. A particularly interesting presentation of long-standing hypothyroidism known as the **Van Wyk–Grumbach syndrome** is characterized by the combination of hypothyroidism with precocious puberty. Whereas chronic hypothyroidism is usually associated with delayed pubertal maturation, boys with Van Wyk–Grumbach syndrome may have enlarged testes as a result of a **stimulatory effect of thyroid-stimulating hormone (TSH) on the follicle-stimulating hormone (FSH) receptor**. Girls with Van Wyk–Grumbach syndrome may present with ovarian cysts. The reason why some of previously hypothyroid patients do not reach their height potential is due to a rapid increase in skeletal maturation observed during the first 12 to 18

months of thyroid hormone supplementation, especially in patients in the pubertal age range who experience a rapid cadence of pubertal progression.

ii. **Glucocorticoid excess and Cushing syndrome.** As discussed previously for exogenous exposure to glucocorticoid medication, endogenous p. 171p. 172hypersecretion of glucocorticoids has an inhibitory effect on linear growth. Growth attenuation may be the only presenting sign of Cushing syndrome in childhood because many children may be lacking the clinical symptoms associated with hypercortisolism. Opposite to this, Cushing syndrome is unlikely to be the explanation for abnormal weight gain in children because patients with glucocorticoid oversecretion have growth failure versus patients with exogenous obesity, in whom linear growth will be normal or even accelerated.

iii. **Pseudohypoparathyroidism.** Children with pseudohypoparathyroidism are most often short and have truncal obesity. They can also present with short metacarpals, round facies, mental retardation, and subcutaneous calcifications. This represents the classic phenotype of the **Albright osteodystrophy**. The short stature in these patients can be further accentuated by the development of mild hypothyroidism as a result of TSH resistance.

iv. **Diabetes mellitus.** Growth failure can be observed in children with diabetes mellitus especially with poor control of the patient's glycemia. In severe cases, a patient can develop **Mauriac syndrome** when the diabetes is associated with severe growth failure and hepatomegaly (caused by excessive hepatic glycogen deposition). Delayed puberty can further contribute to poor pubertal growth in their second decade of life. Other growth attenuating issues may play a role in these patients because they are at increased risk to develop celiac disease and autoimmune thyroiditis with hypothyroidism. Improved diabetes control

reduces the prevalence of delayed puberty and poor growth in patients with diabetes mellitus.

v. **Growth failure due to defects in the GH–IGF-I–growth plate axis**

Deficiency in the secretion of GH, either due to hypothalamic dysfunction or a defect in the pituitary gland, results in IGF-I deficiency and is an important cause of growth failure in childhood. However, classic GHD is a fairly uncommon cause of short stature, with an incidence estimate in the range from 1 in 4 000 to 1 in 30 000 to 60 000 children. The true incidence of severe GHD is likely in the lower range of this estimate, but milder degrees of GHD may be more common (partial GHD). IGF-I deficiency as a result of GH resistance is even less common, but milder degrees of GH resistance may be the cause of poor growth in a cohort of patients labeled as having ISS. Because we are able to determine the molecular basis of short stature in more patients, we find that both GHD and GH resistance encompass a broader spectrum of phenotypes of these disorders than initially proposed.

f. Hypothalamic dysfunction

i. **Congenital malformations** of the brain and hypothalamus often lead to GH insufficiency, sometimes in association with other pituitary hormone deficiencies. Examples include anencephaly and holoprosencephaly, of which the spectrum ranges from cyclopia to hypertelorism. Children with clefts of the lip and palate who grow poorly need an evaluation for GHD.

ii. **Septo-optic dysplasia (SOD, De Morsier syndrome)** patients have at least two of the following three features: midline forebrain defect (absent septum pellucidum or corpus callosum), optic nerve hypoplasia, and hypopituitarism. Only about 30% of patients have the complete triad, whereas >60% have some degree of hypopituitarism, and this can vary from isolated GHD to panhypopituitarism. Mutations in several genes have been associated with SOD, with those involving *HESX1* being the best known, although still only accounting for a small number of SOD diagnoses.

iii. **Molecular defects of the GHRH receptor** have been identified in 10% of patients with familial recessive isolated GHD and in up to 3% of isolated GHD patients. Their phenotype includes reduced GH concentrations, abnormal response to a provocative stimuli, and low serum IGF-I, resulting in proportionate short stature apparent from the first year of life. These patients respond well to GH replacement therapy. Mutations in GHRH itself have not been reported so far.

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iv. **Hypothalamic trauma** can be seen after birth, such as with breech delivery, forceps use, prolonged labor, or abrupt delivery. Traumatic brain injury (TBI) (see Chapter 6) in later life has been recognized as a cause of acquired hypopituitarism of varying degrees in both adults and children. Primary injury following TBI often results in disruption of the hypothalamic–pituitary–adrenal axis and antidiuretic hormone production and release, with implications for both acute management and survival. Secondary injuries, occurring hours to weeks after TBI, result in both temporary and permanent alterations in pituitary function. GHD and disturbances in pubertal development are the more common, but any part of the hypothalamic–pituitary axis can be affected.

v. **Inflammation and infiltration of the hypothalamus** can be seen with histiocytosis, sarcoidosis, tuberculosis, and other infiltrative disorders. Although diabetes insipidus (DI) is the most common hypothalamic–pituitary consequence of Langerhans cell histiocytosis, anterior pituitary deficiencies are seen more frequently in those patients with multisystem disease. Most of the hormone deficits will develop within 6 years after the diagnosis of DI, which itself may even precede the diagnosis of histiocytosis. Hypothalamic and pituitary dysfunction has also been reported after infectious diseases of the central nervous system (meningitis and encephalitis).

vi. **Tumors of the hypothalamus:** Craniopharyngioma is the most common childhood tumor affecting the

hypothalamic–pituitary axis. Midline brain tumors, such as germinoma, meningioma, and optic nerve glioma, are a major cause of hypothalamic dysfunction. The latter is seen more in females (60% to 70%) and is associated with neurofibromatosis type 1 in more than half of the cases. Cystic lesions in the area include Rathke cleft cysts, arachnoidal cysts, and craniopharyngiomas. Rathke cleft cysts are benign, small (<5 mm), and common (seen in 20% of routine autopsies).

vii. **Hypothalamic irradiation:** Endocrinopathies develop in many patients following radiation therapy, and may occur after doses as low as 20 Gy. Children who receive pituitary as well as nonpituitary cranial radiation are at risk. The most common abnormality is GHD, followed by gonadotropin deficiency, hyperprolactinemia, adrenocorticotropic hormone (ACTH) deficiency, and central hypothyroidism. Two to five years after irradiation, **100% of children** receiving more than 30 Gy over 3 weeks will have an abnormal GH response to insulin-provocative testing.

g. Pituitary dysfunction

i. **Genetic abnormalities resulting in combined GHD.** Patients with *PROP1* mutations make up one of the more common groups of pituitary insufficiency. Homozygous patients have a deficit of GH, TSH, PRL, and gonadotrophins, but the time of onset and severity of hormone deficiency varies. The evolving nature of hormone insufficiency suggests a progressive decline in pituitary function. Mutations in the *POU1F1* gene are less common and lead to pituitary hypoplasia with GH, PRL, and TSH deficiencies. Other molecular abnormalities of pituitary development include *LHX3* gene mutations (GHD as well as TSH, LH, FSH, and PRL deficiencies), *LHX4* (GHD as well as TSH and ACTH deficiencies), the previously mentioned *HESX1* (SOD), among several others.

ii. **Genetic abnormalities resulting in isolated GHD.** Isolated GHD IA results from deletions or mutations of the *GH1* gene that totally block GH synthesis or secretion, and is inherited in an autosomal recessive manner. All patients

have profound congenital GHD. Patients are immunologically intolerant of GH and typically develop anti-GH antibodies when treated with GH therapy. A less severe form of autosomal recessive GHD (isolated GHD IB) is likely to also result from mutations of the GH1 gene, presumably resulting in a GH molecule that retains some function but could be unstable. Mutations in the GHRH receptor also lead to GHD 1B. Isolated GHD II is transmitted in an autosomal dominant manner, and has abnormalities of p. 173p. 174the GH1 gene that function in a dominant-negative manner. Patients with autosomal dominant isolated GHD have substantial variation in the severity of their GHD, resulting in variable height deficits.

iii. **Tumors of the pituitary gland.** Craniopharyngiomas comprise a major cause of pituitary insufficiency. These tumors represent 5% to 15% of intracranial tumors in children and are the most common neoplasm of the hypothalamic–pituitary region in this age group, accounting for up to 80% of tumors in this location. At diagnosis, most craniopharyngiomas have a combined intra- and suprasellar location, and almost half also have hypothalamic involvement. Although they are benign lesions, they are very destructive because of their aggressive growth and high relapse rate after treatment. The management of craniopharyngiomas is therefore very complex, and includes surgery with or without radiotherapy.

iv. **GH neurosecretory dysfunction.** There likely exists a group of patients with GH neurosecretory dysfunction: children are characterized by short stature and poor growth, but have normal serum GH concentrations with stimulation testing, reduced 24-hour serum GH concentrations, and low serum IGF-I. Some of these children may be very well GHD, and benefit from GH therapy. Other patients may fall in the group of patients who will later turn out to have constitutional delay of growth and maturation, and this diagnosis may then reflect an inability to provide such patients with diagnostic testing of sufficient sensitivity.

h. **Growth hormone insensitivity syndrome (GHIS).** Resistance or insensitivity to GH is characterized by the finding of low IGF-I in the face of GH sufficiency. The conditions causing GH insensitivity lead therefore to primary IGF deficiency, in contrast to GHD which causes a secondary IGF-I deficiency.

i. **GH receptor abnormalities (Laron syndrome) (see Chapter 15)**

j. **GH receptor signaling defects.** Mutations in *STAT5b* (a component of the JAK-STAT signaling pathway) have been described in a few patients with GHIS. These children may have **associated immune defects** (likely because STAT5b is involved in the signaling of multiple cytokines), recurrent pulmonary infections, and eczema. Serum PRL may also be elevated.

k. **IGF-I gene defects.** Severe primary *IGF-I* gene deficiency has been reported in a few patients only. It is characterized by severe intrauterine and postnatal growth failure. Additional clinical features include microcephaly, mental retardation, and sensorineural deafness. It is possible that milder forms of such IGF-I deficiency are more common and could account for some cases of ISS. Recently, some more mildly affected patients have been characterized.

l. **ALS deficiency.** Deficiency of the ALS component of the IGF-I/IGFBP-3/ALS ternary complex has been reported as a cause of short stature. Markedly, reduced concentrations of IGF-I and IGFBP-3 have been observed in cases involving mutations of the *ALS* gene. Given this, the degree of growth failure is actually quite modest in ALS deficiency, especially when compared with other molecular defects of the GH–IGF axis. Analysis of heights within individual families has suggested that having two affected alleles results in about 2SDS of height loss, whereas having one affected allele results in a loss of almost 1SDS of height.

m. **Idiopathic short stature.** ISS is a diagnosis given to a patient with a height more than 2SD below the corresponding mean height for a given age, sex, and population group, without evidence of systemic, endocrine, nutritional, or chromosomal abnormalities. Children with ISS have normal birthweight and

are **not GH deficient**. Consequently, ISS describes a heterogeneous group of children consisting of many presently unidentified causes of short stature. In situations where, in an ISS patient, a specific genetic diagnosis is suspected (e.g., NS), the gene(s) of interest should be examined. Online resources such as *Genetest* (www.genetests.org) identify laboratories capable of performing these tests. Several countries, including the United States, have **approved GH therapy** for ISS (defined as height greater than 2.25SDS below the mean for age and sex).

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VIII. EVALUATION OF THE SHORT CHILD

A. Step 1—Identifying potentially affected children

1. **Further evaluation is indicated for children with the following auxology:**
   - **a.** Severe short stature (height < −3SDS)
   - **b.** Severe growth deceleration (height velocity SDS < −2 over 6 to 12 months)
   - **c.** Height < −2SDS and height velocity < −1SDS over 12 months
   - **d.** Height < −2SDS and history of SGA
   - **e.** Height deflection < −2SDS below target height percentile without explanation
   - **f.** Height < −1.5SDS and dysmorphic features and/or disproportionality
2. **Risk factors**
   - **a.** History of a brain tumor, cranial irradiation, or other documented organic pituitary abnormality
   - **b.** Incidental finding of pituitary abnormality on magnetic resonance imaging (MRI)

   If any of the above exist, proceed to step 2; if not, follow clinically and return to step 1 in 6 months.

B. Step 2—Screening for GHD/IGF deficiency and other diseases

Detailed history and review of systems have been completed. Detailed nutritional history was obtained. Physical examination completed. Consider ordering from a laboratory panel, including assessment of bone age, thyroid function, chromosomes (in females), and

nonendocrine screening tests (consider complete blood count, creatinine, erythrocyte sedimentation rate, celiac panel, and inflammatory bowel disease screen), and treat any diagnosed conditions as needed. *And*:

1. Order an IGF-I (and an IGFBP-3 in younger patients).
2. If IGF-I and/or IGFBP-3 are above the mean, follow clinically and return to step 1 in 6 months.
3. If IGF-I and/or IGFBP-3 are low, proceed to step 3; but if the MRI is abnormal, GH stimulation is optional.
4. If height < −2.25SDS, proceed to step 3 regardless of the screening tests.

   Figure 14-3 shows the mean serum concentrations of IGF-I for boys and girls.

C. Step 3—Testing of GH secretion

This step can be bypassed if a clear GHD risk factor and a severe IGF-I deficiency identified. If not, perform two GH stimulation tests. **We use clonidine and arginine** (Table 14-2), but other options include insulin, glucagon, levodopa, and propranolol.

1. If peak GH on both tests is <10 ng/mL, go to step 4.
2. If GH >10 and height is <−2.25SDS, consider GH treatment for ISS (step 5).

D. Step 4—Evaluating the pituitary

E. Perform MRI

Consider testing the hypothalamic-pituitary-adrenal axis with an **ACTH stimulation test** or other appropriate test. This is essential in all **cases of organic GHD** and should be considered on a case-by-case basis in other children.

F. Testing in the neonate. The diagnosis of GHD in a newborn is particularly challenging. The presence of a **micropenis** in a male newborn should always be addressed by an evaluation of the GH axis. GH should always be measured in the presence of **neonatal hypoglycemia** in the absence of a metabolic disorder or other obvious risk factors. All patients with recurrent or persistent hypoglycemia should be evaluated for GHD. **A GH of <20 mg/L at the time of true hypoglycemia** may suggest GHD in the newborn (a value <10 mg/L strongly suggests it). The use of standard GH stimulation tests is not recommended in newborns, with the exception of the **glucagon test**. Ahead MRI is essential when the diagnosis of GHD is suspected, and results may be available sooner than with

serum assays. Ahead **IGFBP-3 level** is of great value for the diagnosis of GHD in infancy because IGF-I values may not be helpful. Serum IGFBP-3 can be the test of choice in suspected neonatal GHD.

IX. Therapy

Daily subcutaneous administration of GH has been the standard of care since recombinant human GH has been available in 1985. GH injections are best administered in the evening because of the potential better mimicking of the endogenous GH physiology via the higher GH concentrations overnight. The dosage of GH should be expressed in p. 175p. 176 p. 176p. 177 milligrams (or micrograms; μg) per kilogram per day, although consideration should be given to dosing in μg per square meter of body surface per day—especially in obese patients or in older adolescents. GH is routinely prescribed in the range of **25 to 50 μg/kg/day**. On this regimen, the typical GH-deficient child accelerates linear growth from a pretreatment height velocity of 3 to 4 cm/year to 10 to 12 cm/year in year 1 of therapy, and 7 to 9 cm/year in years 2 and 3. Because it is generally accepted that prolonged supraphysiologic concentrations of IGF-I should be avoided, annual monitoring of serum IGF-I should be part of the routine follow-up care of the GH-deficient child receiving GH therapy (Table 14-3). Titration of the GH dose to p. 177p. 178 **maintain IGF-I within age-dependent normal limits** is physiologically sound and standard practice in adults. Periodic monitoring for scoliosis worsening, tonsil hypertrophy, papilledema, and slipped capital femoral epiphyses should be performed as part of the regular physical examination during the follow-up visits. Although GH therapy has had an excellent track record from a safety perspective, recent reports from epidemiologic studies in Europe have shown that GH therapy may carry risks of long-term morbidities (see Chapter 12). Results from the European Union's Safety and Appropriateness of GH treatment in Europe study about the long-term mortality indicated that mortality rates were increased in adults treated as children with GH, particularly in those who had received higher GH doses. Although the **study has a number of limitations** (e.g., mortality cases were extracted from the general French population, rather than from untreated short persons with similar short stature diagnoses,

SGA-related comorbidities were not taken into account), GH prescribers must balance the rationale for GH therapy with the limitations of the these data sets.

There are two schools of thought about the duration of treatment. One adheres to stopping GH therapy when near-adult height is achieved (height velocity <2 cm/year, and/or bone age >15.5 years in boys and >13.5 years in girls). Alternatively, therapy can be discontinued when height is in the "normal" adult range (above −2SDS) or when the patient is pleased with the height achieved. After attainment of adult height, retesting of the GH/IGF-I axis, using the adult GHD diagnostic criteria, should be undertaken by the pediatric endocrinologist. Standard GH stimulation tests can be performed 1 to 3 months off GH therapy. It is very likely that in the near future, GH therapy will be prescribed using long-acting GH preparations. Compliance is a problem in up to 75% of teenagers, and height velocity is reduced in the children with poor treatment adherence. The early publications of phase II and phase III trials have shown that **long-acting GH** can induce sustained physiologic IGF-I concentrations, improve linear growth in children, and ameliorate body composition in adults. One sustained-release depot GH consisting of microparticles containing GH incorporated into sodium hyaluronate has already been approved for use in GHD in Europe. The safety and efficacy seems to be similar to daily GH, at least over 1 to 2 years of therapy, but long-term data are needed.

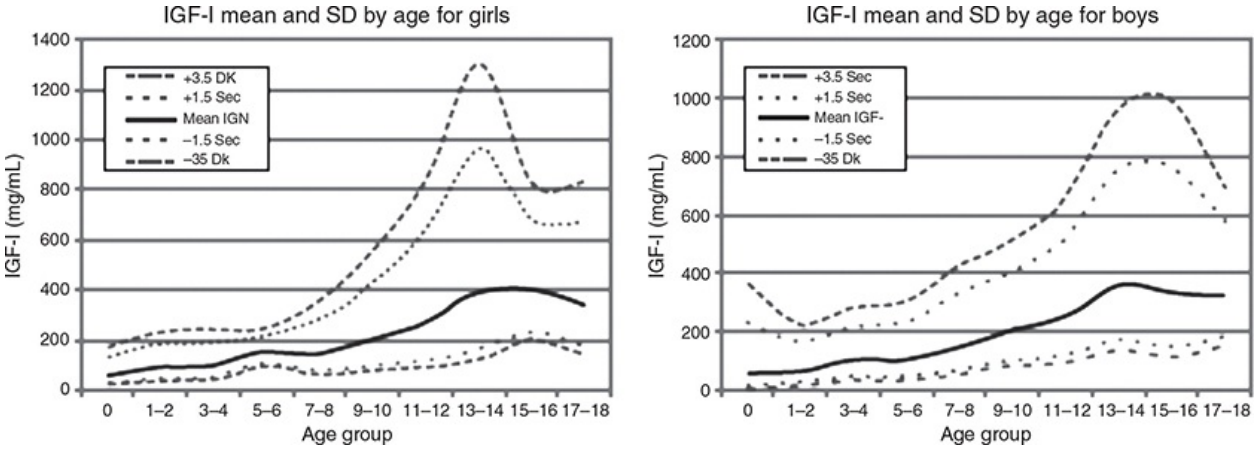

Figure 14-3. Mean serum IGF-I concentrations for boys and girls. IGF-I, insulin-like growth factor I; SD, standard deviation.

TABLE 14-2 GH Stimulation Tests

Stimulus	Dosage	Sampling for GH (min)	Comments (Side Effects)
L-DOPA (PO)	<15 kg: 125 mg 15–30 kg: 250 mg >30 kg: 500 mg	0, 30, 60, 90, 120	Nausea
Clonidine (PO)	0.15 mg/m^2 (or 4 μg/kg)	0, 30, 60, 90, 120, 150	Tiredness, postural hypotension Higher GH peaks (>20 ng/mL
Arginine HCl (IV)	0.5 g/kg (max 30 g) 10% arginine HCl in 0.9% NaCl over 30 min	0, 15, 30, 45, 60, 90	Peak GH usually 60 min after starting IV arginine
Insulin (IV)	0.05–0.1 IU/kg	0, 15, 30, 45, 60, 75, 90, 120	Hypoglycemia; requires supervision[a] Peak GH after 60 min
Glucagon (IM, SC)	0.03 mg/kg (max 1 mg)	0, 30, 60, 90, 120, 150, 180	Nausea, emesis Peak GH after 120 min

Tests should be performed after an overnight fast. It is generally recommended by some authorities that peripubertal children be "primed" with sex steroids (e.g., ethinyl estradiol, 50 to 100 μg/day for 3 consecutive days prior to testing; or depot testosterone, 50 to 100 mg, 2 to 7 days prior to testing). Patients should be biochemically euthyroid at time of testing.

[a]Insulin-induced hypoglycemia is a potential risk of this procedure, which is designed to lower the blood glucose by at least 50% (glucose nadir after 15 to 30 minutes). Documentation of appropriate lowering of blood glucose is recommended. If GH deficiency is suspected, the lower dose of insulin may be advisable, especially in infants and if high suspicion for hypopituitarism. Dextrose 50 solutions and glucagon should be available.

GH, growth hormone; IM, intramuscular; IV, intravenous; PO, orally; SC, subcutaneous.

TABLE 14-3 Elements of Monitoring GH Therapy

- Close follow-up with a pediatric endocrinologist every 3–4 mo
- Determination of growth response (change in height *Z*-score, height velocity)
- Monitoring of serum IGF-I concentrations
- Screening for potential adverse effects
- Evaluation of compliance/treatment adherence
- Consideration of dose adjustment based on IGF-I values, growth response, and comparison to growth prediction models

GH, growth hormone; IGF-I, insulin-like growth factor I.

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15 Laron Syndrome

Zvi Laron

I. INTRODUCTION

Laron syndrome (LS; OMIM#262500), synonymous with severe congenital growth hormone (GH) insensitivity, is a rare autosomal recessive hereditary disease first described in 1966. It is estimated that there are approximately 500 patients in the world that are partly undiagnosed.

The great majority of patients come from consanguineous families originating from the Mediterranean, Middle East, and South Asia areas or their descendents. A large cohort lives in South and Central America, the majority descendents of Jews who fled the inquisition in 1492 and called "Conversos."

A. Genetic defects

LS is caused by deletions or mutations in the GH receptor gene. The most frequent deletion is of exons 5 and 6. At present, 60 mutations have been reported, most in the extracellular domain of the receptor. Few are "de novo" mutations. Only subjects homozygous for the molecular defects have the disease.

B. Diagnosis

Owing to the lack of binding of the circulating GH to its receptor, a state of GH insensitivity results characterized by high levels of serum GH and low to undetectable serum insulin-like growth factor 1 (IGF-1), which do not increase after 7 days of daily subcutaneous human growth hormone (hGH) injection (2.5 mg) (the IGF-1 generation test). The final and more exact diagnosis is obtained by genetic analysis.

C. Clinical features

The main clinical features resemble those of congenital-isolated GH deficiency.

D. Gestation and delivery

Pregnancy and delivery are usually normal. Birth weight is normal, but birth length is reduced.

E. Infancy and prepubertal period

LS children have a typical facial appearance, a protruding forehead,

with subnormal head circumference, sparse hair, small face, and chin, resulting in a saddle nose (Fig. 15-1).

Postnatal growth velocity slows progressively and, if untreated, reaches a −4 to −10 standard deviation score (SDS) height deficit. Bone age is retarded. Hands and feet are small (acromicria) as are the internal organs (organomicria). Progressive obesity is another typical feature.

Infants and children with LS have a high-pitched voice because of a narrow oropharynx.

F. Sexual development

Genitalia are small, and puberty is delayed, mainly in males; but LS patients reach full puberty, and the reproductive potential is normal.

G. Carbohydrate metabolism

Infants with LS have symptomatic or asymptomatic hypoglycemia, which is attenuated by IGF-1 treatment by stimulating somatostatin and suppressing insulin secretion.

With increasing obesity, a relative insulin resistance develops that leads to glucose intolerance, during or after puberty, and in mid-adult age even to type 2 diabetes mellitus with its complication if not properly treated.

Figure 15-1. Typical appearance of a 2-year-old girl with Laron syndrome. Note also sparse hair, protruding forehead, saddle nose, and small chin.

H. Lipid metabolism

The progressive obesity is accompanied by hyperlipidemia, causing fatty liver and leading to sleep apnea. In contradistinction to simple obesity, LS patients have elevated serum adiponectin levels, indicating an abnormal adipose tissue metabolism. Most adult patients require treatment with statins.

I. Muscle mass and force

The long-term IGF-1 deficiency leads to a decrease in the muscle mass and muscle force.

J. Cardiopulmonary system

The cardiac muscle mass and left ventricle output are reduced, so is the pulmonary maximal aerobic capacity. If not treated, adult LS patients develop coronary heart and peripheral vascular diseases.

K. Nervous system

In untreated patients, the brain as measured by head circumference is small, and in part of the patients, magnetic resonance imaging revealed various degrees of diffuse parenchymal loss and a small cerebellum. Further findings are lack or small sinuses and development of spinal stenosis in adult patients. In few patients, epilepsia has been reported.

With advancing age, part of the patients develop peripheral neurologic complaints and gait difficulties.

L. Intellectual function

Most LS patients have a wide range of psychological defects. As a result, only very few reach college or university training. Accordingly, the occupations of most patients are of lower levels. Few have severe mental defects.

M. Social problems

Because of their severe growth retardation, obesity, and possible neuropsychological deficits, part of the patients have difficulty to find jobs and marital partners. With few exceptions, all LS patients have sexual relations.

N. Cancer

Of great interest is the recent finding that homozygous LS patients are protected from developing malignancies, even after long-term IGF-1 treatment.

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O. Longevity and mortality

Life span is normal, provided the metabolic and cardiovascular complications are diagnosed early and treated. Reports of death have been reported because of untreated hypoglycemia in early infancy, coronary heart disease, and accidents in adults.

II. TREATMENT

The only treatment of LS is daily recombinant IGF-1 administration that not only stimulates linear, acral, and organ growth but also increases the adipose tissue mass. Mean growth velocity in the first year of treatment is 8 cm/year compared to 10 to 12 cm in GH-deficient children treated with hGH. Linear growth catch-up and changes in the U/L ratio show a change in height SDS from −6.1 ± 1.3 to −4.6 ± 1.2 SDS ($P < 0.001$), without change in the U/L ratio. IGF-1 increases normal head circumference to normal size. A single daily subcutaneous injection of recombinant IGF-1 (150 to 220 μg/kg to children) resulted in the same growth-promoting effects as two daily injections and causes fewer adverse effects. To avoid hypoglycemia, the injection has to be given with the largest daily meal. IGF-1 treatment increases androgen secretion and stimulates penile growth, but less testicular growth. IGF-1 treatment also causes a significant increase in the red blood indices, with an increase in blood

hemoglobin.

At present, there is only one IGF-1 preparation for clinical use, Increlex (Ipsen), in vials containing 40 mg/4 mL. This concentration makes it difficult to administer exact doses in babies.

IGF-1 treatment is approved only until the end of linear growth, that is, achievement of adult stature. Because short-term treatment of adults with LS reduced slightly body lipids, these LS patients also deserve treatment to strengthen the muscular and skeletal system and some metabolic disturbances. The drug, IGF-1, is very expensive so the majority of children with LS worldwide are not treated because of a lack of national insurance programs and the low-economic class of the patients' families.

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16 Prader–Willi Syndrome

Mario Carcamo and Norman Lavin

I. ETIOLOGY: Prader, Labhart, and Willi first reported a unique pattern of abnormality in nine children in 1956. This rare genetic neurodevelopmental disorder has an estimated prevalence of 1 in 15 000 to 1 in 25 000. The genetic changes in this disorder are due to lack of expression of the paternally expressed genes on chromosome l5q11–q13. Of these individuals, 70% have a deletion of the long arm of chromosome 15. Approximately 25% have maternal uniparental disomy (UPD), where the subject inherits both copies of chromosome 15 from the mother and none from the father. The remaining are due to mutations of the imprinting center or to a chromosome translocation of proximal l5q.

A. Phenotype and intellectual capacity

Patients with Prader–Willi syndrome (PWS) have the following phenotype: eyes have an almond-shaped appearance to palpebral fissures, upslanting and/or strabismus; thin upper lip; light brown hair; fair skin that is sun sensitive; small hands and feet; small penis and cryptorchidism in males; and hypoplastic labia minora and clitoris in females. Body weight varies from failure to thrive in the first few months of life to obesity that becomes apparent after 2 to 4 years of age. Decreased growth velocity from childhood to adolescence is universal. Other phenotypes have been associated with other genetic abnormalities, and intellectual capacity is decreased (intelligence quotient [IQ] 60 to 70) in the majority of patients. Patients with PWS with paternal 15q11–q13 deletion are associated with lower full-scale IQ and verbal IQ, but higher performance IQ.

II. GENETIC DIAGNOSTIC METHODS: The goal of testing is to identify the absence of a paternal contribution in the critical region of chromosomes 15q11–q13. The preferred and most cost-effective method is DNA methylation, which identifies the methylation pattern on the long arms of both copies of chromosome 15. In the patient with PWS, only the methylated (inactive) region is detected. This abnormal pattern is seen whether there is a deletion of the paternal chromosome 15 or there is

another explanation such as two copies of maternal chromosome 15 (maternal UPD). When the DNA methylation study is abnormal, the next test, fluoresence in situ hybridization or a chromosome microarray is performed to detect a deletion of the critical area, which explains about 70% of the abnormal results. The deletion is too small to be reliably detected with conventional or even high-resolution chromosome analysis. When there is no deletion, then UPD, which explains about 25% of all cases, is the most likely explanation. This is especially common when there is advanced maternal age, and UPD occurs after a Trisomy 15 conception is “rescued” with loss of the paternal chromosome 15, leaving two maternal copies. Genetic counseling will be needed when an imprinting control center mutation is identified as the recurrence risk for PWS is 50% in this situation. Parental testing to rule out a deletion, when one has been identified in an affected child, is not routinely offered to asymptomatic parents. The recurrence risk is generally low for a second affected child with PWS when a deletion or UPD has been identified in an affected sibling. However, prenatal testing with an amniocentesis and DNA methylation testing should be offered in all subsequent pregnancies because, rarely, gonadal mosaicism for a deletion has been found in an apparently unaffected father. Prenatal diagnosis can also be considered when there is polyhydramnios and poor intrauterine growth or small male genitalia.

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III. **NATURAL HISTORY: PERINATAL PERIOD:** Prenatal hypotonia is associated with decreased fetal movements, breech presentation, and polyhydramnios. At birth, weight, length, and body mass index are less than their unaffected siblings. Infantile hypotonia is present in all infants after birth. This causes poor suck, poor reflexes, and weak cry. Hypotonia is central in origin. Frequent difficulty in feeding and lethargy results in failure to thrive requiring gavage feeding or the use of special nipples. Lavin and Carcamo utilize growth hormone (GH) in the newborn period to help with feeding, thus preventing the need for a gastrostomy tube. Without GH treatment, difficulty feeding usually lasts several weeks, occasionally months. Hypotonia improves over time, but mild hypotonia remains as the child becomes an adult. Delayed motor development affects the great majority of children with PWS. Language milestones are also affected; learning and intellectual difficulties are variable with

moderately lower IQ, few of them have normal IQ. Nutritional phases have been described by Millevet et al. as follows: phase 1a from 0 to 9 months of age (hypotonia and difficulty feeding); phase 1b from 9 to 25 months of age (improved feeding and appetite); phase 2a from 2.1 to 4.5 years of age (weight increases without appetite increase or excess calories); phase 2b from 4.5 to 8 years of age (increased appetite and calories); phase 3 from 8 years to adulthood (hyperphagia occurs, and they rarely feel full); and phase 4 (adulthood appetite is no longer insatiable). The majority of children become overweight with all associated complications. Different approaches to treat obesity have been attempted, including restrictive diet and increased physical activity.

IV. CLINICAL FEATURES AND TREATMENT

A. Sleeping-related disorders: Many factors contribute to obstructive sleep apnea (incidence of 50% to 100%), including hypotonia with ventilatory restriction (aggravated by obesity), adenotonsilar hypertrophy, narrow upper airway, and sticky saliva. Central sleep apnea also has been reported in nonobese PWS children. Hypoventilation also leads to chronic elevation of PCO_2. Obstruction of the upper airway can lead to systemic hypertension, cardiovascular disease, and pulmonary hypertension. PWS children have a higher incidence in frequency and intensity of serious respiratory infections compared with healthy children. Infants are more likely to experience central sleep apnea (43%) when compared with older children (5%). In contrast, obstructive sleep apnea is more prevalent in older children. Sleep disorders and an increase in daytime sleepiness (narcolepsy 35%) are common. Owing to a high prevalence of sleep-related difficulties, a sleep study and an ear, nose, and throat evaluation are recommended in general and especially before and during treatment with GH.

B. Growth and GH treatment: At birth, both weight and length are significantly decreased. Prematurity and postterm infants are also very common. Short stature is almost universal after birth. Very young children with PWS seem to have impaired hypothalamic GH-releasing hormone secretion with a normal GH pituitary reserve. The levels of insulin-like growth factor 1 (IGF-1) are reduced in the majority of children with PWS when compared with obese children who have normal or slightly elevated IGF-1 levels. Low levels of GH and IGF-1 have been found in PWS of normal weight. Decreased levels of IGBP-

3 have been reported as well. Many studies have shown a decreased GH secretion with low peak response to stimulation tests, defined as a peak GH level of <10 μg/L. Between 48% and 100% of children fulfill the criteria of GH deficiency. The degree of GH deficiency varies from mild to severe. The prevalence before 18 months of age is 27% compared with older children which is 81% according to one study. If individuals are not treated with GH, the average height for males will be approximately 155 cm and 148 cm for females. GH therapy has demonstrated a significant improvement in height, body mass index (decrease in fat mass), muscle mass, gross motor skills, strength, agility, cognitive scores, and language acquisition. Children younger than 6 months of age also have shown benefit. There are some concerns of GH treatment in children with PWS with high serum levels of IGF-1, but the lack of acromegalic symptoms indicates no increase in IGF-1 bioactivity. Reports of rare deaths in children with PWS have been associated with increased obesity, obstructive airway, and acute or p. 183p. 184chronic infections. In a recent report, the mortality in PWS in a population cohort in the United Kingdom seems to be declining (1.25%). Despite theoretical risks of the use of GH, the multiple benefits outweigh the risks. The **consensus guidelines for Recombinant Human Growth Hormone Therapy in PWS**, published in 2013 by the Endocrine Society, are presented as follows:

1. After genetic confirmation of the diagnosis of PWS, rhGH treatment should be considered and, if initiated, should be continued for as long as demonstrated benefits outweigh the risks.
2. GH stimulation testing should be considered as part of the therapeutic decision-making process for infants and children with PWS.
3. Adults with PWS should have an evaluation of the GH/IGF axis before rhGH treatment.
4. Before initiation of rhGH therapy, patients with PWS should have a genetically confirmed diagnosis and expert multidisciplinary evaluation.
5. Exclusion criteria for starting rhGH in patients with PWS include severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis.
6. Scoliosis should not be considered a contraindication to rhGH

treatment in patients with PWS.

7. Infants and children with PWS should start with a daily dose of 0.5 mg/(m^2/day) subcutaneously with subsequent adjustments toward 1.0 mg/(m^2/day) according to clinical response and guided by maintenance of physiologic levels of IGF-1.
8. Adults with PWS should receive a starting dose of 0.1 to 0.2 mg/day based on age, presence of edema, prior rhGH exposure and sensitivity, and concomitant oral estrogen use. Subsequent dosage titration should be based on clinical response, age, and sex-appropriate IGF-1 levels in the range of 0 to +2 SDS (standard deviation score).
9. Selection of patients with PWS for rhGH therapy and dosing strategy should not depend on the genetic class of PWS.
10. IGF-1 levels in patients with PWS on rhGH treatment should be maintained within the upper part of normal range (maximum +2 SDS) for healthy, age-matched normal individuals.
11. Clinical outcome priorities should vary, depending on the age and the presence of physical, mental, and social disability.
12. Monitoring of rhGH treatment in patients with PWS should address specific benefits and risks of treatment.
13. Patients with PWS receiving rhGH must be followed carefully for potential adverse effects.
14. Treatment with rhGH must be in the context of appropriate dietary, environmental and lifestyle interventions necessary for care of all patients with PWS.
15. Cognitive impairment should not be a barrier to treatment with rhGH for patients with PWS.

C. Obesity and related complications: Most children with PWS start to gain weight between 2 and 4 years of age. Appetite increases significantly usually at 4 years of age in the majority of children. Obesity is manifested as central (abdomen and buttocks) adiposity. The decrease in activity and the decrease in lean body mass are contributing factors. Adipose tissue dysfunction has been reported in children with PWS. There is a decrease in progenitor cell content in the stromal vascular fraction of adipose tissue and an impairment of lipolytic response to β-adrenergic agonists in PWS adipocytes. There is also an increase in plasma inflammatory cytokines (tumor necrosis factor α, monocyte chemoattractant protein 1, and interleukin 8).

Interestingly, the first two abnormalities in the adipose tissue seem to be partially restored by GH therapy. The etiology of hyperphagia still remains undetermined. Structural abnormalities have been found in postmortem hypothalamic areas, especially low oxytocin cell number. The orexigenic hormone ghrelin produced in the stomach has been found to be elevated during fasting and postprandial periods. The hormone peptide YY produced in the gastrointestinal tract has been reported to be elevated during fasting, but has an attenuated and delayed postprandial response especially p. 184p. 185to high-fat meal content. Other findings include lower levels of leptin, a decrease in postprandial insulin secretion, and a blunted suppression of ghrelin in patients with PWS on treatment with GH. These findings suggest that the GH action is, in part, responsible for reducing the adiposity and improving insulin sensitivity. Studies have shown that children not in the period of hyperphagia still have increased levels of ghrelin, therefore, preceding hyperphagia and obesity. Pharmacologic agents that lower the levels of ghrelin have been used, like a long-acting somatostatin analog. Studies have found no benefit on appetite or weight reduction. The use of metformin in a small study (21 patients) improved a sense of satiety, and a decreased anxiety about food. Obesity management is challenging. Early understanding by the parents about hyperphagia and weight gain is important to implement the following objectives: early intervention of a low-calorie, well-balanced diet, and strict supervision to access of food, as well as regular physical activity. The physical activity is difficult to manage because of poor muscle tone, decrease resting metabolic rate, hypersomnolence, and obesity, but some studies have shown that exercise programs improve body composition. Medical treatment has been attempted using anorexigenic agents with little benefit in hyperphagia or weight loss. Restrictive bariatric surgery had similar results with no change in appetite or long-term weight reduction; furthermore, the high incidence of morbidity and mortality has made this a contraindication. One most recent study of the Mini-gastric bypass appears to provide an effective weight reduction without nutritional impairment or weight regain, and no postoperative complications were reported. Type 2 diabetes has become more prevalent in teenage-young adults (about 25%). The treatment is similar to other type 2 diabetes patients, including weight loss if

possible, increased exercise, and use of metformin and insulin if necessary.

D. Skeletal abnormalities: Scoliosis is one of the most frequent findings (30% to 70%) that is probably related to obesity and hypotonia. Kyphosis is frequently associated with scoliosis. Orthopedic evaluation and X-ray of the spine are recommended before and during treatment with GH; the progression of scoliosis during GH treatment is not an absolute indication to stop therapy. It most likely represents the natural history of the condition. Most patients with scoliosis present with lumbar or thoracolumbar curves (types 5 and 6) when compared with idiopathic scoliosis (types 1, 2, and 3). Surgical treatment is indicated only in the most severe cases. Unfortunately, the frequency and severity of complications is higher than in idiopathic scoliosis (infections, pneumonia, risk of paraplegia, and other complications). Blount disease (growth disorder of the tibia in which the lower leg turns inward) is a rare condition seen in PWS. Osteoporosis and osteopenia have been well established. Most recently, in a 9-year longitudinal study in children with PWS on GH treatment, the total and lumbar spine bone mineral density (BMD) remained stable in prepubertal children, but decreased during adolescence. The authors suggest starting sex hormone therapy at 11 years of age in girls and 14 years of age in boys if they have not shown progression to puberty.

E. Other endocrine abnormalities

1. **Hypothyroidism:** This has a prevalence of 25% of subjects. Thyroid function is usually normal in the newborn period. The majority present after 2 years of age. Periodic screening for hypothyroidism is recommended before and after treatment with GH.
2. **Adrenal insufficiency:** Hokken-Koelega et al. in 2008 found a high prevalence of central adrenal insufficiency in PWS subjects. Two subsequent studies by other investigators, using a high- or low-dose adrenocorticotropic hormone test or insulin-tolerance testing, found normal cortisol response. This area is still controversial, but we should pay attention during the first 9 months of therapy with GH because GH treatment can precipitate adrenal crisis in a patient with subclinical adrenal insufficiency.
3. **Hypogonadism:** This is usually present since birth in both sexes. In males, the penis is small with a hypoplastic scrotum.

Cryptorchidism is present in 80% to 90%. In females, the clitoris and labia minor are also small; at puberty, amenorrhea and oligomenorrhea are common. Infertility is common for both sexes.

p. 185p. 186The hypogonadism is due to hypothalmic or primary gonadal abnormalities at least in males. The use of human chorionic gonadotropin is recommended in males with undescended testis as a form of therapy; 23% can lower the testis to a stable position in the scrotum or for preparation for orchidopexy to improve surgical outcome. Hormonal treatment will be required for almost all subjects for induction and maintenance of puberty; delayed mental development should not be a contraindication during adolescence or in young adults. Even though there is no consensus in the approach of induction and maintenance of puberty, there are indications that early hormone replacement may prevent the decrease in BMD. In females, oral preparation and transdermal estrogen preparation have been used and well tolerated even in subjects with skin picking behavior. In males, testosterone replacement therapy should be gradually increased especially in subjects with aggression.

4. **Premature adrenarche:** This can occur in up to 15% of patients.
5. **Precocious puberty:** Although uncommon, it has been reported in 3.6% of children with PWS.

F. Behavior and psychiatric aspects: There is a progression of behavior difficulties starting in early childhood, including rigidity in daily routines, temper tantrums, oppositional behavior, perseverant speech, and compulsive behavior–like skin picking. In later childhood, food-seeking behavior, associated with lying and stealing food has been noted. During the adolescent years, they can get involved in dangerous situations because of overconfidence. Children and adults especially are more prone to a variety of conditions, such as compulsive behavior, depression, and anxiety. Psychosis and bipolar disorders are more prevalent in the UPD genotype. The management and treatment is usually complex and difficult. Parents, health care providers, and psychologists should be involved in the care of abnormal behaviors from early childhood to avoid or slow the progression of symptoms. Psychiatric intervention may be needed in severe cases of anxiety, depression, or psychosis.

G. Other manifestations: Eye evaluation is recommended; some of the most common conditions seen in PWS are myopia, strabismus, and hypermetropia. Dental care is necessary because of increased frequency of caries. Many factors are responsible, such as abnormal enamel, decreased saliva production, and increased saliva thickness. Children with PWS have a decreased reaction to pain, less febrile episodes, lack of manifestation of illness, and decreased thirst, and some are more prone to dehydration. Seizures have been associated with PWS, with higher prevalence than the general population. The most common type is generalized tonic–clonic. The median age of onset is 4 to 5 years (ranging from 1 month to 14 years). Most of the subjects have a favorable response to therapy (84%) except those with brain abnormalities. A study of 180 children with PWS followed for 13 years had a prevalence of congenital defects higher than the normal population (22%). The most frequent were heart defects, renoureteral malformations, vertebral anomalies, hip dysplasia, clubfoot, and agenesis/hypolasia of the corpus callosun.

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SECTION 3

Adrenal Disorders

17

The Adrenal Cortex and Mineralocorticoid Hypertension

Naftali Stern, Etty Osher, and Michael L. Tuck

I. CUSHING SYNDROME

A. General principles

Cushing syndrome (CS) refers to a diverse symptom complex resulting from excess cortisol and other steroid hormones produced by the adrenal cortex, mainly androgens (endogenous) or to sustained administration of glucocorticoids (exogenous). Clinical manifestations in CS vary considerably from subclinical, subtle, or mild to florid disease. The clinical features of classical CS initially described included central obesity (90%), hypertension (85%), glucose intolerance (80%), plethoric facies (80%), purple striae (65%), hirsutism (65%), menstrual dysfunction (60%), muscle weakness (60%), bruising (40%), and osteoporosis (40%) with typical spontaneous vertebral fractures as a result of the preferential loss of trabecular bone, ankle edema (60%), and renal colic (20%).

Less common features include mental changes, hyperpigmentation, acne, hypokalemic alkalosis, venous thromboembolism, increased intraocular pressure, cataracts, and central serous chorioretinopathy (more common with exogenous glucocorticoid, in particular, topical steroids). **Endogenous CS**

comprises three distinct pathogenic disorders: pituitary (68%), adrenal (17%), and ectopic (15%).

1. **Pituitary CS (Cushing disease):** Most cases are intrasellar microadenomas (<1 cm in diameter) that produce excessive amounts of adrenocorticotropic hormone (ACTH). In 5% to 10%, pituitary lesions are large and often invasive macroadenomas (>1 cm in diameter) with extrasellar invasion. Pituitary ACTH-secreting carcinomas with extrapituitary metastases causing CS are extremely rare.
2. **Adrenal CS** results from autonomous cortisol production by an adrenal tumor (adenoma or carcinoma) or by adrenal hyperplasia. Adrenal CS is associated with suppressed plasma levels of ACTH.
   a. **Adrenal adenomas** usually evolve gradually. Dehydroepiandrosterone sulfate (DHEA-S) levels are typically suppressed as a result of suppression of ACTH secretion. It has been shown that similar to macrododular adrenal hyperplasia, adrenal adenomas can express ectopic receptors for and respond to, in terms of cortisol secretion, hormones such as gastric inhibitory polypeptide (GIP), vasopressin, β-adrenergic agents, serotonin, luteinizing hormone (LH)/chorionic gonadotropin, and perhaps leptin or interleukin-1.

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   b. Functioning (steroid-secreting) **adrenal carcinoma** is rare and typically evolves rapidly and is often associated with excessive secretion of adrenal androgens, leading to prominent androgenic symptoms in women. *It is now recognized that some adrenal cortical cancers reflect hereditary disorders:* The Li–Fraumeni syndrome is caused by mutated TP53, a tumor suppressor gene, resulting in soft-tissue sarcomas, osteosarcoma, premenopausal breast cancer, brain tumors, and adrenal cortical carcinomas. The **Beckwith–Wiedemann syndrome** is the most common congenital overgrowth disorder (1 in 10 500 live births) with predisposition to the emergence of adrenal cancer and other tumors, depending on the specific (epi)genetic defect involved.
   c. **ACTH-independent bilateral adrenal nodular hyperplasia** is an uncommon group of disorders manifesting as CS.

i. **Macronodular adrenal hyperplasia** is characterized by nodules whose diameter is greater than 1 cm. In most, the etiology is unknown, but in a few cases, the nodules have been shown to express increased numbers of receptors normally found on the adrenal gland, or ectopic receptors (aberrant) that they can stimulate cortisol production. This condition may be associated with food-dependent hypercortisolism caused by GIP receptors on the adrenal glands. Food intake stimulates GIP, which binds to the ectopic receptors expressed in the adrenal cortex, where it stimulates growth and cortisol secretion. Treatment with long-acting somatostatin has been helpful in some patients. In other cases, anomalous activation of adrenal growth and steroidogenesis is mediated through β-adrenergic receptors, LH receptors, or V1a receptors. ***Familial forms of macronodular hyperplasia with autosomal dominant inheritance underlie significant fraction of the cases, including*** multiple endocrine neoplasia type 1 (MEN1), familial adenomatous polyposis, fumarate hydratase gene mutations, and inactivating mutations of probable tumor suppressor gene and armadillo repeat containing 5 gene (*ARMC5*). In ARMC5 cases, there is aberrant G-protein–coupled receptors expression and paracrine production of ACTH.

ii. **Micronodular hyperplasia: Primary pigmented adrenal nodular dysplasia** (PPNAD) is a rare disorder in which adrenal pigmented hyperplasia leads to mild and/or cyclic hypercortisolism associated with other endocrine and nonendocrine tumors, such as acromegaly, sertoli cell tumor, and myxoma (Carney complex). *PRKAR1A* is the gene that most frequently causes PPNAD and Carney complex.

3. **Ectopic CS** results from autonomous ACTH production from an extrapituitary tumor, with elevated plasma levels of ACTH.

The tumors are divided into two main groups: highly malignant carcinomas of which the most common is small-cell lung carcinoma, with excessively high circulating ACTH, and a more indolent group of neuroendocrine tumors originating in bronchial and pancreatic tissues. Rarely, neuroendocrine tumors

produce corticotropin-releasing hormone (CRH), leading to excess pituitary ACTH secretion.

B. Clinical features, correlates, and clues

1. **Age and sex:** Adrenal carcinoma is more common in children; pituitary CS is frequently seen in women of child-bearing age; and ectopic CS is more common in adult males and usually presents after 40 years of age.
2. **Obesity,** hypertension, and plethoric facies are common.
3. The **metabolic syndrome** that includes many of the findings characteristic of Cushing (central obesity, hypertension, dyslipidemia, insulin resistance, and atherosclerosis) has been often termed Cushing phenotype.
4. Evidence of **severe hyperandogenism**/virilization (hirsutism, clitoromegaly, and temporal balding) is most common in adrenal carcinoma.
5. **Hypokalemic alkalosis,** myopathy, and sometimes hyperpigmentation occur most often in ectopic CS, a form of the disease in which the more typical clinical features of hypercortisolism are often absent.

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6. **Cognition**—Learning, cognition, and memory (especially short-term memory) are impaired by hypercortisolism.
7. **Infection and immune function**—Glucocorticoids inhibit immune function, and thus increase propensity for infections. Bacterial infections are common, and opportunistic infections are typically seen with severe hypercortisolism (cortisol >40 μg/dL) as in ectopic ACTH syndrome.
8. **Periodic (cyclic) CS,** with predictable cycles of high and normal cortisol levels, can occur in any of the subtypes of CS and should be considered in patients with Cushingoid features when testing fails to demonstrate hypercortisolism.
9. The **natural history** of CS can be variable, but if it is unrecognized or untreated, fully manifested disease has a 5-year mortality of 50%. Milder forms of this condition may smolder for years.

C. Diagnostic evaluation

Because of a variety of adrenal diagnostic procedures, a stepwise evaluation is carried out in three phases: confirmation of

hypercortisolism, differentiation among the three forms of CS, and localization procedures (Table 17-1).

1. Screening tests for the confirmation of CS

Screening for CS is recommended in patients with multiple and progressive features suggestive of hypercortisolism, patients with unusual features for age (hypertension, osteoporosis, and diabetes), unexplained resistant hypertension on the background of hypokalemia or recent emergence of the metabolic syndrome or weight gain, new-onset hirsutism after the second decade of life, and children with slow growth or arrest. According to the Endocrine Society recommendations, 24-hour (24h) urine cortisol, 1-mg overnight dexamethasone suppression test, 2 mg/day for 48 hours dexamethasone suppression test and midnight cortisol/salivary test have similar accuracy. Unless exceptionally high cortisol values are seen, no single positive test should be taken as sufficient proof for the diagnosis of CS. Two positive tests require further workup, that is, performance of tests intended to differentiate among the various forms of true hypercortisolism. A single positive test requires careful clinical consideration and, when appropriate, further follow-up and laboratory reassessment.

TABLE 17-1 Diagnostic Evaluation of CS

A. Confirmation of hypercortisolism
- **a.** Overnight dexamethasone suppression test or standard 2-day, 2-mg test
- **b.** Urinary steroid excretion test (urinary free cortisol, 17-hydroxycorticosteroids)
- **c.** Salivary midnight cortisol or midnight serum cortisol
- **d.** CRH after low-dose dexamethasone suppression test

B. Differentiation of CS
- **a.** Plasma ACTH level
- **b.** High-dose dexamethasone suppression test
- **c.** Metyrapone test

C. Localization
- **a.** Adrenal CT
- **b.** MRI scan (adrenal and pituitary)
- **c.** Inferior petrosal sinus sampling (IPSS)
- **d.** Chest CT
- **e.** Octreotide scintigraphy

In the diagnosis of CS and its etiologies, final interpretation depends on the integration of results from several tests; no single procedure can reliably diagnose this syndrome.
ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CS, Cushing syndrome; CT, computed tomography; MRI, magnetic resonance imaging.

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a. **Overnight 1-mg dexamethasone suppression test**
Dexamethasone suppression test is the “test of choice” in subjects with adrenal incidentaloma.
   i. **Interpretation.** In general, though, **normal subjects should suppress plasma cortisol levels to <1.8 *μ*g/dL, following 1 mg of dexamethasone** administered on the previous night. **Levels between 2 and 7 *μ*g/dL may be difficult to interpret**, because they are commonly seen in subjects with mental depression or with alcohol- and stress-induced adrenocortical activation, referred to, collectively, as **pseudo-Cushing disorders**. Additional forms of testing are, therefore, recommended under these circumstances. Thus, **low cortisol levels following administration of dexamethasone do not entirely exclude the diagnosis**. Constitutive variation in the metabolic clearance of dexamethasone and acceleration in dexamethasone metabolism by alcohol and drugs, such as nifedipine, rifampin, hydantoin, carbamazepine, phenobarbital, tamoxifen, and topiramate, because of the induction of CYP3A4 enzymes, which also metabolize dexamethasone, can lead to false-negative results. Suppression of cortisol can be also incomplete in chronic renal failure because of decreased cortisol clearance, or in high-estrogen states (pregnancy, consumption of estrogen-containing drugs). On the other hand, decreases in cortisol-binding globulin (CBG) or albumin, which occur in some patients with hyperthyroidism and commonly in the critically ill or nephrotic patient, are associated with decreased serum cortisol. Also, when possible, estrogen-containing drugs should be withdrawn for 6 weeks before testing.

b. **Urinary free cortisol (UFC) excretion** is a screening choice for the initial diagnosis of hypercortisolism. The measurement is made on 24h collections of urine, using creatinine, and total

volume as estimates of the adequacy of the collection. It represents a direct measurement of cortisol that is not bound to plasma protein and is a reliable and useful test for assessing cortisol secretion rate as long as the assay methods and normal ranges are well defined. High-performance liquid chromatography–based methods provide a more specific way to assess UFC than immunoassays, with an upper range that is 40% lower. The role of liquid chromatography–tandem mass spectrometry (LC–MS-MS)–based UFC remains presently controversial because initial assessment in one study revealed that it may yield false-negative results, whereas others find that it performs better than the combination of any other two screening tests. UFC is elevated in 95% of CS patients, but only if several samples are assayed. High water intake will elevate the UFC, as will the drug carbamazepine. Incomplete urine collection, low urine output, and renal failure (creatinine clearance <60 mL/minute) may cause false-negative results. Some authorities advocate reliance on UFC levels exceeding three times the upper limit of the normal range as a proof of true hypercortisolism, but because specificity of detection increases with raised cutoff values, sensitivity is much diminished. In early or mild disease where small increases in cortisol production at the circadian nadir occur, an increase in UFC may not be detected. Therefore, repeat testing over time and consideration of at least one additional screening test is indicated.

c. **Standard 2-day, 2-mg test.** This test provides essentially the same type of information as is derived from the shorter, overnight, 1-mg dexamethasone suppression test, but offers the opportunity to examine, in addition to serum cortisol, the urinary excretion of cortisol. It may also have higher specificity than the shorter overnight test.
    i. **Interpretation.** Normal subjects show suppression of 24h urinary cortisol excretion to <10 μg (27 nmol)/24h. Proper suppression of serum cortisol is considered by most as a better tool in this setting, but it suffers from the same practical limitations outlined for the 1-mg dexamethasone overnight test. The performance of this test is significantly enhanced if dexamethasone is also measured. In normal

subjects, serum cortisol should decline to 1.8 μg/dL, 6 hours after the last dexamethasone dose (last dose at 3 A.M.; sample collected at 9 A.M.).

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d. **Late-night salivary cortisol.** The concentration of cortisol in the saliva is correlated with free or biologically active cortisol levels in serum or plasma. A sampling device is available with which saliva can be collected by chewing on a cotton tube for 2 to 3 minutes. This commercially available device is best used at the patient's home, followed by delivery to a reference laboratory the next morning. Cortisol in the saliva is quite stable and can be sent for determination over several days. Testing is done at bedtime up to 11 or 12 P.M., but timing may actually affect the result because the true nadir of circulating cortisol typically takes place at midnight or even later. A salivary cortisol >4.3 nmol/L (~1.6 ng/mL) is suggestive of true hypercortisolism, but variations in reference values among laboratories and methods (e.g., radioimmunoassay vs. tandem mass spectrometry) requires attention. False-positive cases have been noted in men aged 60 years or older, particularly in obese, hypertensive, and/or diabetics subjects and in critically ill patients. Increased midnight cortisol can be detected in subjects smoking or using licorice (both of which contain the 11-hydroxysteroid dehydrogenase type 2 inhibitor glycyrrhizic acid). Late-night salivary cortisol depends on diurnal variation and hence results in subjects with irregular sleep patterns such as after recent long flights, shift workers, or insomnia may be misleading.
    i. **Diurnal variation of circulating cortisol.** Plasma cortisol values are highest from 6 to 8 A.M., declining during the day to <50% to 80% of morning values from 10 P.M. to midnight. This rhythm is typically lost very early in the course of CS. Diurnal variation–based tests are not suitable for shift workers or subjects with potentially altered diurnal rhythm due to insomnia, irregular sleep, and jet lag.
e. **Midnight serum cortisol** seems intuitively to be a direct measure of circulating cortisol. This test has been largely replaced by the measurement of late-night salivary cortisol,

which is conveniently done in the patient's home.

i. **Procedure.** Sampling is best performed with an indwelling needle and with basal conditions maintained for 30 minutes prior to sampling. Because cortisol is secreted in pulsatile bursts, multiple samples are taken: sampling for cortisol is done at 30-minute intervals between 10 P.M. and midnight. Patients should be in the supine position before and during the study.

ii. **Interpretation.** A midnight plasma cortisol of 7.5 μg/dL or greater strongly suggests a diagnosis of CS. Values of 5.0 μg/dL or less are unlikely to be CS, and values of 2.0 μg/dL nearly exclude Cushing. This test has value in moderate cases of hypercortisolism (where UFC is normal), especially in distinguishing pseudo-Cushing, in which a normal diurnal pattern can be retained. A timed or spot UFC to creatinine ratio at midnight can also be used to establish the presence of hypercortisolism. Also, a midnight "sleeping" plasma cortisol of 1.8 μg/dL or greater is shown to have a 100% diagnostic sensitivity for CS, but specificity at this level is apparently low. In general, it has been difficult to obtain a nonstressed late-night cortisol measurement.

2. **Ruling out pseudo-CS**

Additional testing may be required when tests listed above are inconclusive, inconsistent, or raise the possibility of pseudo-Cushing.

a. **CRH after low-dose dexamethasone suppression test.** This test was developed to distinguish between patients with pseudo-Cushing and those with CS, particularly those with Cushing disease. The test is based on the premise that suppression of ACTH by dexamethasone is more profound in normal subjects and depressed patients than in patients with Cushing disease, such that following proper suppression with dexamethasone, serum cortisol cannot be stimulated by CRH in these patients, but only in subjects with Cushing disease.

i. **Choice of patients.** This test should be considered only for subjects who show normal suppression following dexamethasone administration but in whom CS continues to be seriously suspected because of clinical considerations or

other anomalous (positive) screening test(s) for Cushing states.

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ii. **Procedure.** Give 0.5 mg dexamethasone at 6-hour intervals for 2 days, as of 12 A.M. on day 1. **The CRH stimulation test is initiated at 8 A.M., 2 hours after completion of the last dexamethasone dose (6 A.M.)**. Both human and ovine CRH are available and can be administered as an intravenous bolus of 1 μg/kg body weight or as a fixed dose of 100 μg intravenously.

iii. **Interpretation.** A measurable serum cortisol response to CRH (e.g., cortisol level >1.4 to 2.5 μg/dL measured 15 minutes after CRH administration) identifies patients with CS compared to those with pseudo-Cushing conditions, with a sensitivity of approximately 90%, but with much lower specificity, ranging overall around 70%, in reports published thus far.

Desmopressin test is a potential alternative to the CRH-dexamethasone test, in that it helps distinguish between patients with pseudo-Cushing and those with CS, mainly in cases of mild hypercortisolism and normal ACTH levels. It is more convenient than the dexamethasone-CRH test. It may also be useful in the postsurgical follow-up of Cushing disease.

3. **Differential diagnosis of CS: Is hypercortisolism ACTH dependent?**

   a. **Plasma ACTH**

      i. **Basal plasma ACTH.** Improvements in the measurement of plasma ACTH using the immunoradiometric assay (IRMA) offer good sensitivity and specificity in the differential diagnosis of CS. Samples should be taken at 8:00 A.M. under basal condition. Because ACTH is rapidly degraded by circulating peptidases, samples must be chilled and plasma separated, aliquoted, and frozen immediately. The concomitant measurement of ACTH and cortisol offers a rational approach to the differential diagnosis of CS, in that it establishes in a simple preliminary manner whether hypercortisolemia, once established and if present at the

time of testing, is ACTH dependent.

a) **Ectopic or pituitary Cushing.** Whenever basal levels of ACTH are measurable (ACTH values >20 pg/mL) in a patient with high levels of plasma cortisol, ectopic or pituitary Cushing (ACTH dependent) forms of CS should be suspected. Plasma ACTH is sometimes very elevated in **ectopic CS**, most often because of lung carcinoma, but can be only mildly elevated or normal in patients with bronchial carcinoid tumors. Patients with **pituitary CS** have elevated baseline plasma ACTH values in about half the cases; this elevation is often mild to moderate (50 to 250 pg/mL), with the remainder of patients having levels within the normal range. An important pitfall with ectopic secretion of ACTH relates to the high specificity of the currently used ACTH assays, which may miss even very high levels of slightly modified ACTH molecules formed by the ectopic tissue, which still retains significant bioactivity.
b) **Adrenal CS.** Undetectable levels of ACTH (below 10 pg/mL, and particularly <5 pg/mL), in the presence of increased plasma cortisol levels suggest the diagnosis of adrenal CS (ACTH independent).

b. **High-dose (8-mg) dexamethasone suppression test.** Administration of large dosages (8 mg/day for 2 days) of the potent synthetic glucocorticoid dexamethasone will suppress urinary or plasma cortisol by >50% of baseline in pituitary but not in adrenal or ectopic CS. The **test distinguishes pituitary CS from other causes in approximately 85%** of cases. Some practitioners maintain that the high-dose dexamethasone suppression test has been made obsolete by the availability of reliable methods for the measurement of plasma ACTH, pituitary imaging, and inferior petrosal sinus (IPS) sampling. The inconvenience of the latter procedure, pitfalls in measuring plasma ACTH, and the high rate of pituitary and adrenal incidentalomas (up to 10% of the general population) comprise sufficient grounds for continued performance of this test.

i. **Procedure**

a) **Baseline.** Collect 24h urine samples for UFC and

morning plasma cortisol and ACTH.

b) **Day 1.** Administer dexamethasone, 2 mg orally (PO) every 6 hours (q6h). Collect 24h urine sample for UFC.

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c) **Day 2.** Administer dexamethasone, 2 mg PO q6h. Collect 24h urine sample for UFC.

ii. **Interpretation.** Suppression to >50% of baseline plasma cortisol and UFC on day 2 indicates lack of complete autonomy of ACTH secretion, and is therefore compatible with pituitary Cushing disease or, occasionally, bronchial carcinoid tumor; failure to suppress on 8 mg/day implies adrenal or ectopic CS. **Anomalous responses** to high-dose dexamethasone suppression include the following.

a) Suppression in ectopic Cushing because of bronchial tumors of low-grade malignancy

b) Lack of suppression of cortisol in subjects harboring a large pituitary macroadenoma.

This test has a diagnostic sensitivity and specificity of 80% to 85%, so as many as 15% of pituitary Cushing subjects will not be detected by this test. More recent criteria have been established that improve diagnostic accuracy. A decrease from baseline levels in UFC of >90% and in 17-hydroxycorticosteroid excretion of >64% will detect 100% of patients with pituitary Cushing and exclude most ectopic cases.

c. **The 8-mg overnight dexamethasone suppression test.** This test can be used in place of the 2-day dexamethasone suppression test because it probably has similar accuracy and specificity.

i. **Procedure**

a) Obtain a plasma cortisol at 8 A.M. as baseline, then give 8 mg of dexamethasone at 11 P.M. and draw another blood sample for plasma cortisol at 8 A.M. the next morning.

ii. **Interpretation**

a) More than a 50% reduction in plasma cortisol from the baseline level strongly indicates Cushing disease (pituitary).

d. **CS with measurable to high ACTH levels: ruling out**

ectopic ACTH-secreting tumor

i. **CRH stimulation test.** Upon its release from the hypothalamus, CRH selectively stimulates the pituitary corticotrope cells to increase ACTH; this is followed by a rise in cortisol. Both human and ovine CRH are available and administered as an intravenous bolus of 1 μg/kg body weight or as a fixed dose of 100 μg intravenously. Blood samples for cortisol and ACTH are collected at times −10, 0, 5, 10, and 15 minutes relative to the injection of CRH. This dose increases ACTH and cortisol levels in up to 90% of patients with pituitary CS, because most pituitary ACTH-secreting tumors have CRH receptors. Patients with ectopic or adrenal CS have no ACTH or cortisol response to CRH. This test differentiates ACTH dependent from ACTH-independent CS but might not always distinguish pituitary (eutopic) from ectopic causes, mostly because some pituitary patients do not respond to CRH. Still, proposed cutoff levels indicative of a pituitary origin are an increase of 35% to 50% above baseline for ACTH, and 14% to 20% for cortisol 15 minutes following the administration of CRH.

e. **CS with borderline ACTH (5 to 20 pg/mL)**

In the absence of a clear finding on magnetic resonance imaging (MRI) scan (negative or shows a very small lesion [5 mm or less; incidentaloma?]), with equivocal levels of plasma ACTH, the differential diagnosis includes Cushing disease (pituitary) or an ectopic ACTH-secreting tumor, usually a bronchial carcinoid, that might be radiologically occult and have equivocal ACTH levels. Under these circumstances, CRH testing and, as a second phase, IPS sampling with CRH are helpful.

f. **Limitations of testing procedures for CS**

In some cases, an abnormal overnight dexamethasone suppression test, an elevated plasma ACTH level, and precise localization of the tumor suffice indicate ectopic, pituitary, or adrenal CS. In other cases, the high-dose dexamethasone test might be needed to establish the etiology of hypercortisolism

p. 193p. 194or measurement of ACTH during CRH

and IPS sampling. A host of pitfalls (e.g., periodic cortisol production, unreliable laboratory sources, improper handling or transport of ACTH samples, variation in dexamethasone metabolism and cortisol clearance rate, missed doses, inaccurate or incomplete urine collection during dexamethasone suppression) surround these tests. Periodic hormonogenesis in CS with episodic phases of eucorticalism requires repeat testing over time. Depression, alcohol ingestion, and stress produce false-positive results (pseudo-Cushing) in basal cortisol and ACTH in the dexamethasone suppression tests. Also, an occasional case of adrenal or ectopic CS displays normal dexamethasone suppression. Increasingly often, cases of CS are detected in the course of the workup of an adrenal incidentaloma on computed tomography (CT) scan, osteoporosis, or unexplained weight gain.

g. Localization procedures

i. **Pituitary CS. MRI** of the pituitary is the initial procedure of choice because it detects 50% to 85% of pituitary ACTH-secreting microadenomas, with current estimates of resolution reaching as low as 2-mm tumor size. ACTH-secreting pituitary tumors typically (95%) generate a hypointense signal on MRI with no postgadolinium enhancement. Because a minority of ACTH-producing microadenomas (5%) display an isointense signal postgadolinium, care should be taken to obtain pregadolinium images. The sensitivity of CT scanning in the localization of pituitary Cushing disease is much lower and has been estimated at approximately 40% to 50%, thus rendering CT a suitable choice only if an MRI is contraindicated. Because of the significant rate (10%) of pituitary incidentalomas measuring up to 6 mm in the general population, caution should be exercised in assuming that the presence of such lesions on MRI establishes the presence of pituitary Cushing disease; **biochemical studies must support the diagnosis.**

ii. **Adrenal CS** is suspected in a subject with suppressed plasma ACTH, blunted ACTH response to CRH, and lack of suppression of urine or plasma steroids by high-dose dexamethasone testing.

CT scan of the adrenal is the initial test of choice and reliably identifies most tumors because the surrounding tissue is suppressed and atrophied. One or more lesions can be seen, and they may be unilateral or bilateral. **Adrenal adenoma** or cortisol-producing benign nodules are typically round and of homogeneous density; have a smooth contour, appear well demarcated, and measure <4 cm in diameter. They usually have low unenhanced CT attenuation values of <10 Hounsfield units (HU), which increases by 60 and 120 (arterial and portal phases, respectively) after the injection of the contrast material, reaching a peak of <37 to 40 HU, followed by a third phase washout effect, recorded at 15 minutes, where a 50% or larger decline in the peak density takes place. **Adrenal carcinoma**, on the other hand, is typically unilateral and of nonhomogeneous appearance, larger in size and with higher unenhanced CT attenuation values (>10 HU), rising to >40 HU and showing, 15 minutes after contrast administration, a contrast washout of <50%. The combination of unenhanced CT with <20 HU and size <4 cm or an unenhanced CT with < 10 HU alone successfully separated adenomatous from nonadenomatous lesions in one study.

MRI complements the CT scan in some cases but does not offer greater sensitivity for small adrenal lesions. Adenomas are classically isointense with liver on both T1- and T2-weighted MRI sequences and display evidence of lipid on chemical shift MRI. In contrast, adrenal carcinoma is typically hypointensive compared with liver on T1-weighted MRI, but generates high-to-intermediate signal intensity on T2-weighted MRI.

iii. **Ectopic CS.** Thin-cut CT or MRI studies of the chest, abdomen, and pelvis localize 70% to 90% of ectopic ACTH-secreting tumors. Importantly, most of these lesions reside in the chest.

Full lung CT and MRI scans detect a high percentage of ectopic ACTH-secreting tumors in the thorax, such as bronchial carcinoid and

small-cell carcinoma of the lung, and are, therefore, the procedures of choice. Detection of these lesions is important because thoracic neuroendocrine tumors (bronchial carcinoid or thymoma) and thyroid medullary carcinoma–producing ACTH can be cured with surgery. Clinical outcome in subjects harboring small-cell lung carcinomas is usually rapidly progressive. Ectopic CRH-secreting tumors have been described, but they usually also contain ACTH, so the tumor behaves in a paracrine rather than endocrine mode. Because some of these ectopic CRH lesions do cause hypercortisolism, it is important to note that they will give a false-positive result on IPS ACTH sampling, because the tumorous CRH utilizes the pituitary ACTH.

a) **Octreotide scintigraphy.** Some ACTH-secreting neuroendocrine tumors express somatostatin receptors type 2 and/or 5 and may, therefore, be detected by radiolabeled somatostatin analogs-based imaging (e.g., 111-In octreotide scan: OctreoScan; 111-In pentetreotide: ^{111}In-DTPA^{0}) or more advanced and sensitive method Ga 68 somaostatin analog-linked (e.g., ^{68}Ga-DOTA-NOC) positron emission tomography CT. However, the likelihood of correct localization of an ectopic ACTH-producing tumor missed by current CT techniques through the performance of an octreotide scan is fairly low. This is also why a positive scan requires confirmation by CT or MRI. Although it is not strictly specific for neuroendocrine tumors (false positives may include breast cancer and lymphoma), a positive somatostatin analog-based scintigraphy in the setting of ectopic ACTH secretion likely indicates the presence of a neuroendocrine tumor and may occasionally suggest potential therapeutic response to somatostatin analogs.

b) **IPS sampling**

   IPS sampling is the **most reliable means of distinguishing pituitary from nonpituitary ACTH**

hypersecretion. Sampling for ACTH venous gradients during petrosal sinus catheterization in the areas of pituitary venous drainage may detect a central or eutopic etiology of ACTH. Samples can be drawn before and/or after 100 μg of CRH administered intravenously. Correction for prolactin level in the samples obtained may assist in identifying problems related to localization of the draining catheter and dilution. Administration of CRH may not be necessary if blood samples are obtained closer to the pituitary, from the cavernous sinuses instead of the petrosal sinuses. Such techniques are limited to few specialized centers and require a skilled invasive radiologist. Samples for ACTH are obtained simultaneously from each IPS before as well as 2 to 3 and 5 to 6 minutes after CRH.

An IPS to peripheral (P) ratio >2.0 to 3.0 confirms the presence of a pituitary ACTH-secreting tumor. Subjects who have an IPS/P ratio 1.8 or less are assumed to have an ectopic source. CRH testing is needed because up to 15% of pituitary tumors will not show an abnormal basal gradient. Correct preoperative lateralization of an ACTH-secreting microadenoma to the right or left hemisphere of the pituitary gland can be accomplished much less frequently than was initially believed, probably because of asymmetric venous drainage in many pituitary glands.

The procedure carries some risk, including false-positive and false-negative results. Direct procedure-related risks are not common but include, besides inguinal and jugular hematomas or transient arrhythmias, rare serious consequences such as perforation of the right atrium, cavernous sinus thrombosis, and cerebrovascular events (0.2%), sometimes with permanent brainstem damage. Hence, IPS should be reserved for clearly equivocal cases, such as normal pituitary MRI or the presence of very small pituitary lesions and/or atypical response to dexamethasone and/or CRH.

D. Treatment

1. **Pituitary CS**

Transsphenoidal adenomectomy or **hypophysectomy** is the treatment of choice in the majority of patients with pituitary CS. Selective removal of pituitary microadenomas yields an immediate remission rate of 80% to 85%, but remission p. 195p. 196is <50% for invasive tumors. Surgical damage to anterior pituitary function is rare. Mortality is low, and complications occur in approximately 5% of patients, including diabetes insipidus (usually transient), cerebrospinal fluid rhinorrhea, and hemorrhage. Postoperative hypoadrenalism (requiring glucocorticoid replacement therapy) is expected. No consensus on the criteria for remission exists, or whether perioperative glucocorticoids change the results. Morning (8 A.M.) cortisol levels which decline to <2 μg/dL within 24 to 72 hours indicate successful removal of the tumor; postoperative (within 7 days) cortisol concentrations are <5 μg/dL; or UFC concentrations <10 to 20 μg/day indicate remission. Immediate reoperation if postoperative hypocortisolism does not occur is advocated by some, usually resorting to subtotal or total hypophysectomy, but spontaneous delayed decline in serum cortisol in some patients renders this approach questionable. Within the first 5 to 10 postoperative years, significant **recurrence is seen**, resulting in long-term surgical cure of 60% to 70%. Patients in remission experience gradual resolution of the signs of CS and slow recovery of hypothalamic–pituitary–adrenal (HPA) axis function for a year or more.

Pituitary x-irradiation is an **optional form** of therapy for patients with pituitary Cushing disease who are either not candidates for surgery or who have failed surgery. The type of radiation chosen depends on the site of the lesion as well as on available expertise. Conventional fractionated external beam radiotherapy delivers a total dose of 45 Gγ over 3 to 4 weeks. The more sophisticated intensity-modulated radiotherapy allows further dose adjustment for tumor contours and spares neighboring vital structures. Radiosurgery (“Gamma knife surgery”), which delivers radiation in a single setting, is suitable if the adenoma is not close

to the optic pathway and achieves remission in 54% to 83% of patients followed up for 5 years. The best and fastest results have been reported in children, but despite early reports of low response rate in adults, long-term remission rates in adult subjects who failed surgical attempts may exceed 80%. There is a long lag period before correction of hypercortisolism (6 to 60 months), but symptoms can be controlled in the interim with enzyme inhibitors. Radiation therapy with protons or α particles yields a higher remission rate and a shorter lag phase. Hypopituitarism and late relapse can occur.

2. **Adrenal CS**

   Unilateral adrenal adenomas are removed by surgery and have a high remission rate. Because the contralateral adrenal gland is suppressed, glucocorticoid replacement is necessary for several months or years until adrenal function returns (see Section II).

   a. **Adrenal carcinoma.** Surgery is the treatment of choice. The transabdominal approach is preferable because it enables assessment of the extent of the disease and removal of involved organs and because recurrence rate may be higher in subjects undergoing laparoscopic adrenalectomy. For residual disease or inoperable carcinoma, **mitotane** can be used as a palliative drug. Further, mitotane may prolong recurrence-free survival in patients with radically resected adrenal cortical carcinoma and is presently recommended even in apparently disease-free subjects following surgery. Starting dose is 250 mg four times a day (qid) and with gradual increase to tolerance levels should be assisted by monitoring mitotane levels to achieve, whenever possible, therapeutic levels (14 to 25 μg/mL). Severe gastrointestinal effects (nausea, vomiting, and diarrhea) occur in 80% of patients. Central nervous system toxicity (somnolence, dizziness, and vertigo) is common because mitotane is fat soluble. Hypothyroidism can develop and require thyroid hormone replacement. Hypercholesterolemia, which usually requires treatment with HMG-CoA reductase inhibitors, often develops as the dose of mitotane is increased toward the effective range. Because hypoadrenalism can occur and because mitotane enhances cortisol clearance and increases CBG, serum cortisol *and* UFC should be monitored. In advanced or recurrent disease, chemotherapy consisting of **etoposide,**

doxorubicin, and cisplatin can be added to mitotane, achieving benefit in up to half of subjects treated.

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b. **Macronodular hyperplasia**: If the mechanism/hormone which underlies the increased secretion of cortisol is identified, specific medical treatment may be attempted (e.g., propranolol for β-adrenergic–dependent secretion), but satisfactory control is often hard to achieve. Unilateral or bilateral adrenalectomy may be required with poor control or excessively large adrenal masses.

3. **Ectopic CS**
   a. **Surgery.** The removal of the ACTH-secreting tumor is the treatment of choice, but is usually not feasible because of the nature of the underlying process (e.g., carcinoma of the lung). Adrenalectomy can be considered in cases of indolent yet inoperable tumors, such as some medullary carcinomas of the thyroid.
4. **Medical treatment as an adjunct form of treatment in CS**
   a. **Adrenal enzyme inhibitors** are useful in **reducing hypercortisolism in otherwise uncontrolled forms of CS** and additionally, in preparation for surgery, if tissue fragility is particularly prominent.
      i. **Metyrapone,** an 11-hydroxylase inhibitor, at an average dose of 250 to 500 mg three times daily, provides an effective means of normalizing cortisol levels. This agent can lead to increases in deoxycorticosterone (DOC), which has sufficient mineralocorticoid activity to cause hypertension and hypokalemia, and accumulation of androgenic precursors any cause or worsen hirsutism and acne. This agent is not generally helpful in Cushing disease where feedback disinhibition of ACTH secretion leads to compensatory rise in ACTH.
      ii. **Aminoglutethimide,** which blocks the conversion of cholesterol to δ-5-pregnenolone, can also be used starting at 250 mg qid, up to 2 g daily. Because hypoadrenalism can result, monitoring of therapy (plasma cortisol and UFC) is mandatory. Aminoglutethimide also enhances the metabolism of dexamethasone and can cause

hypoaldosteronism.

iii. **Adrenolytic agents** such as mitotane (medical adrenalectomy) can be used when control cannot be obtained with metyrapone or aminoglutethimide. Mitotane is administered either alone or in addition to the enzyme inhibitors. It is primarily used in adrenal cortical carcinoma, either alone or in combination with chemotherapy (etoposide, adriamycin, and cisplatin).

iv. **Ketoconazole,** an antifungal agent, is perhaps the **first choice** for antiadrenal therapy, because it is an effective and simple means to control hypercortisolism. This agent blocks steroidogenesis at several levels, the most important being the 20,22-desmolase catalyzing the conversion of cholesterol to pregnenolone. Doses range from 600 to 1 200 mg/day. **It may cause hypogonadism.** Patients have been maintained on this agent for years with good responses. Because ketoconazole blocks early (as well as late) in the steroid pathway (cholesterol side-chain cleavage enzyme), there is no accumulation of other potentially toxic steroids. Therapy can be combined with other agents (metyrapone and aminoglutethimide). In many cases, it does not elicit increase in ACTH in Cushing disease and may be useful in this setting. Owing to **potential liver toxicity**, the Food and Drug Administration warning on this agent has been issued in 2013, and the European Medicines Agency has restricted access to the agent to physicians specialized in treating CS.

v. **Etomidate** is an intravenous substituted imidazole anesthetic drug that blocks the last step of cortisol synthesis (11β-hydroxylation) and may be useful in the acute setting in hospitalized patients with severe hypercortisolemia.

b. Agents used to suppress ACTH secretion

i. **Cabergoline,** a D_2 receptor agonist, was shown to achieve some success in Cushing disease because corticotroph adenoma often expresses D_2 receptors.

ii. **Pasireotide,** a newer somatostatin multireceptor analog with affinity predominantly for sst_1, sst_2, sst_3, and particularly for sst_5 receptor subtypes, has shown some

effect in subjects with Cushing disease but often leads to hyperglycemia caused by suppression of insulin secretion.

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c. Glucocorticoid receptor antagonism: Mifepristone, a dual glucocorticoid and progesterone receptor antagonist, which is **more commonly used to induce medical abortion**, can be used to alleviate severe and otherwise uncontrollable effects of glucocorticoid excess. It increases ACTH and cortisol concentrations in patients with Cushing disease and is presently approved in the United States only for the treatment of hyperglycemia related to CS in patients who cannot be treated surgically. It is not approved for Cushing disease, just for otherwise uncontrollable CS.

II. ADRENAL INSUFFICIENCY

A. General principles

Adrenal (or **adrenal cortical**) **insufficiency** can be caused by:

1. Primary disease at the adrenal level, involving destruction of >90% of the steroid-secreting cortex (Addison disease).
2. Destructive process at the hypothalamic–pituitary level, leading to CRH or ACTH deficiency (or both).
3. Long-term suppression of the **HPA axis** by exogenous or endogenous glucocorticoids followed by inappropriate withdrawal.

B. Chronic adrenal failure (Table 17-2)

1. Primary adrenal failure

a. Etiology. Primary adrenal failure evolves only when there is nearly complete destruction or infiltration of the adrenal glands.

i. Autoimmune adrenalitis accounts for approximately 70% of cases, 50% of whom present with additional forms of autoimmune endocrinopathy, p. 198p. 199that is, **polyglandular autoimmune syndrome type I or II**. Polyglandular autoimmune syndrome type I, also known as **polyendocrinopathy-candidiasis-ectodermal dystrophy**, is an autosomal recessive disorder with mutations in the autoimmune regulator gene and is seen in childhood in association with 100% adrenal

failure, hypoparathyroidism, and mucocutaneous candidiasis. This condition may also be associated with hypogonadism and malabsorption. Females are affected slightly more frequently than men. In the more common type II polyglandular autoimmune syndrome, which usually comprises type 1 diabetes mellitus, autoimmune hypothyroidism, primary hypogonadism, and pernicious anemia, autoimmune adrenal insufficiency is a major component. Approximately 50% of cases are familial with autosomal recessive, autosomal dominant, or polygenic heredity and a female to male preponderance of approximately 3:1 (see Table 17-2).

TABLE 17-2 Etiology of Chronic Adrenal Insufficiency

Primary

Idiopathic adrenal atrophy (autoimmune adrenalitis, with or without other components of the polyglandular autoimmune syndrome type 1 or 2)

Granulomatous diseases
- Tuberculosis
- Histoplasmosis
- Sarcoidosis

Neoplastic infiltration

Hemochromatosis

Amyloidosis

Following bilateral adrenalectomy

Congenital and genetic hypoadrenalism

ACTH-resistance syndromes

Secondary

Tumors
- Pituitary tumor
- Craniopharyngioma
- Tumor of the third ventricle

Pituitary infarction and hemorrhage

Postpartum necrosis (Sheehan syndrome)

Hemorrhage in tumors

Granulomatous diseases
- Sarcoidosis

Following hypophysectomy

Steroid withdrawal

ACTH, adrenocorticotropic hormone.

ii. **Infectious disease** is another cause, and disseminated **tuberculosis**, the leading cause of chronic adrenal failure in the first half of this century, now accounts for approximately 5% of cases. The adrenal glands are usually 100% infiltrated. Rifampin accelerates cortisol metabolism, so higher dose steroid replacement therapy may be needed. Almost all fungal infections, an exception being candidiasis, can destroy the adrenal gland. **Histoplasmosis** is the most common cause in the United States, and **South American blastomycosis** is the most common cause in South America. Because ketoconazole, but not fluconazole or itraconazole, inhibits steroid biosynthesis, it may worsen adrenal insufficiency in someone being treated for a fungal disease. **HIV/AIDS can be associated with adrenal necrosis, but AIDS by itself does not cause adrenal insufficiency.** The usual cause of adrenal insufficiency in AIDS is an associated opportunistic infection, especially cytomegalovirus and tuberculosis. Hyponatremia in AIDS is usually caused by inappropriate secretion of antidiuretic syndrome. Hyperkalemia is often related to trimethoprim therapy. Antifungal treatment (ketoconazole), which inhibits steroidogenesis or concomitant treatment for tuberculosis (rifampin), which accelerates cortisol metabolism, may precipitate hypoadrenalism in these predisposed subjects.

iii. **Bilateral adrenal hemorrhage** is being increasingly recognized as a cause of adrenal failure. Initially described in association with severe bacterial infections (e.g., Waterhouse–Friderichsen syndrome in meningococcemia), it is now often seen in very ill patients, particularly **in association with anticoagulant therapy**. A CT scan shows the classic finding of **bilateral enlargement of the adrenals**. The patient may present with subtle findings of low-grade fever, hypotension, and anemia. The adrenal gland has a rich arterial blood supply drained by

only a single adrenal vein. **ACTH-induced increase in adrenal blood flow with stress may overwhelm its venous drainage, with subsequent hemorrhage.** Patients who have coagulopathies or who are predisposed to thrombosis can also develop adrenal hemorrhage. Heparin-associated thrombosis-thrombocytopenia syndrome is associated with adrenal vein thrombosis. The primary **antiphospholipid antibody syndrome** (lupus anticoagulant) can also be a cause of adrenal insufficiency.

iv. **Bilateral metastatic infiltration** of the adrenal glands is common, especially from breast cancer (54%), bronchogenic carcinoma (44%), renal malignancies (31%), melanoma (30%), and stomach or colon carcinoma (14% to 20%). However, most metastatic lesions do not cause adrenal insufficiency.

v. **Adrenoleukodystrophy and adrenomyeloneuropathy** are X-linked causes of adrenal insufficiency in men and are associated with demyelination of the central and peripheral nervous system. In adrenoleukodystrophy (X-ALD), mutations in the *ALD* gene, which encodes a peroxisomal membrane protein named adrenoleukodystrophy protein (ALDP), and the synthesis of a defective ALDP result in impaired β-oxidation of very–long-chain p. 199p. 200fatty acids (VLCFAs). Consequently, VLCFAs accumulate preferentially in lipids, primarily in the nervous system and in the adrenal cortex. The very–long-chain fats are thought to infiltrate the adrenals or act as toxins to the adrenal gland, blocking ACTH action. The screening diagnostic test is the measurement of VLCFA concentration in the plasma. Dietary treatment with monosaturated fatty acids is marginally effective. **ALD** is the more severe form, occurring in childhood and advancing to coma and other severe neurologic complications. In **adrenomyeloneuropathy**, which is the milder form seen in adults, approximately 30% of patients develop adrenal insufficiency. Specific drug therapy aimed to induce the expression of homolog proteins that show some functional

redundancy with ALDP, such as ABCD2, may alter these pathways.

vi. **ACTH-resistance syndromes** can be induced by mutations that inactivate ACTH receptor action or impair adrenal cortical function or development. Severe forms of the "common" variants of **congenital adrenal hyperplasia**, such as severe to **21-hydroxylase deficiency**, represent one such example. The **triple A syndrome** includes adrenal insufficiency, achalasia, and alacrima and is caused by a mutation in the gene encoding the protein ALADIN, which is part of the nuclear pore complex. The **POEMS** syndrome involves polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin lesions. Mutations in the nuclear receptors **DAX1** and **steroidogenic factor-1** (Ad4BP and *NR5A1*), which play an important role in adrenal development and function, can lead to adrenal hypoplasia. Mutations in **StAR**, a protein that facilitates the transport of cholesterol into the mitochondria, lead to **congenital adrenal lipoid hyperplasia** with hypoadrenalism and hypogonadism.

vii. **Drugs**

a) **Steroidogenic inhibitors:** Some drugs that are not only known to directly inhibit steroidogenesis, but have been actually used to lower cortisol secretion in CS, including keotonazole and etomidate and related agents such as the antimycotic drug fluconazole, can also cause adrenal insufficiency. Suramin, used as an antiparasitic drug as well as in HIV and prostate cancer patients, also inhibits steroidogenesis.

Accelerators of cortisol metabolism, such as phenytoin barbiturates and rifampin, can rarely induce hypocortisolemia.

Inhibitors of CRH or ACTH production/release, including progestins such as megestrol acetate used to raise appetite and mood in cancer patients (which possesses some glucocorticoid activity) and high doses of medroxyprogesterone acetate or opioids, can lower cortisol and induce hypoadrenalism, especially upon the withdrawal of the

former agents.

Immune checkpoint inhibitors, which are presently used to treat certain cancer types such as melanoma, can induce hypophysitis with secondary hypoadrenalism. The best known example is ipilimumab, an anticytotoxic T-lymphocyte–associated antigen 4 antibody, but hypoadrenalism has been also reported with the programmed death 1 antibodies nivolumab and pembrolizumab. In some cases, primary adrenal insufficiency has also been described.

viii. **Systemic amyloidosis** with renal failure can also cause adrenal insufficiency.

2. **Secondary adrenal insufficiency**
   a. **High-dose or prolonged glucocorticoid** administration is the most common cause of secondary or "central" adrenal insufficiency. It is often referred to as tertiary hypogonadism because of the hypothalamic suppression in this condition.
   b. **Common anatomic causes of secondary adrenal insufficiency** include **tumors of the pituitary** gland, compression of the pituitary gland, or pituitary tumor **hemorrhage** (pituitary apoplexy), either spontaneous or during treatment with dopamine agonists. ACTH deficiency is more common in large pituitary tumors and in nonfunctioning macroadenomas than in growth hormone–secreting adenomas. Besides primary pituitary tumors, **metastatic malignancies,**

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craniopharyngiomas, meningiomas, and other tumors may interfere with the ACTH axis. In these diseases, there is usually evidence of other pituitary hormone deficiencies. **Lymphocytic hypophysitis, sarcoidosis, histiocytosis X**, and **hemochromatosis** can destroy the pituitary or hypothalamus. **Postpartum pituitary necrosis** (Sheehan syndrome) and pituitary stalk damage by trauma can cause adrenal insufficiency. Blunt head trauma is a recently recognized cause of hypopituitarism, including secondary hypoadrenalism, and partial-to-complete ACTH deficiency may persist for months to years.

   c. **Genetic diseases leading to developmental abnormalities of the pituitary**, such as mutations of the

PROP1, HESX1, or LHX4 genes, can reduce ACTH and other pituitary hormones. Mutations of **pro-opiomelanocortin (POMC)** or prohormone-convertase 1, which converts POMC to ACTH can underlie impaired synthesis of active ACTH and induce, in parallel lack of α-melanocyte-stimulating hormone (αMSH), leading to the development of increased appetite and early severe obesity. The **TPIT gene** is a transcription factor necessary for differentiation of the corticotroph cell and POMC production, and mutations in this gene may be the most common genetic cause of neonatal isolated ACTH deficiency and hypoadrenalism.

d. **Congenital defects can lead to ACTH deficiency,** such as **septo-optic dysplasia**, a midline brain structure developmental abnormality.
e. **Nonglucocorticoid drugs can also induce suppression of the HPA axis,** for example, the progestational agent Megace (megestrol acetate) and etomidate, a drug used for sedation and anesthesia. Very rarely, Megace used at high doses, can actually cause iatrogenic Cushing syndrome, probably through interaction with glucocorticoid receptors.
f. **Successful removal of ACTH-secreting pituitary adenoma or adrenal cortisol-secreting tumor** is usually followed by secondary hypoadrenalism resulting from long-standing suppression of the normal corticotrophs. Hypoadrenalism may persist for several months up to many years.
g. **Isolated ACTH deficiency** may appear in patients who have lymphocytic hypophysitis, presumably an autoimmune disease, which is often linked to recent or current pregnancy. A rare association of hypoadrenalism with glucocorticoid-responsive alopecia and impaired cognitive function with amnesia linked to hippocampal changes has been also reported.

3. **Signs and symptoms**
   a. **Symptoms of primary and secondary adrenal insufficiency** result from glucocorticoid deficiency and include weakness, hypoglycemia, anorexia, weight loss, and gastrointestinal discomfort spanning from mild diffuse tenderness to chronic or acute forms of abdominal pain,

vomiting, and diarrhea. Gastrointestinal symptoms are more dominant in primary than in secondary hypoadrenalism, but weight loss is a consistent finding seen in all true cases of adrenal insufficiency. Decreased libido and the loss of pubic and axillary hair are more typical in women, in whom the adrenal is a more dominant source of androgens. With protracted hypoadrenalism, mental changes spanning from memory impairment and unexplained mood changes to depression and psychosis can be seen. Diffuse muscle and joint pain are common. Primary adrenal disease also involves loss of mineralocorticoid-secreting tissue, leading to hypoaldosteronism with sodium wasting, salt craving, hypovolemia, overt or orthostatic hypotension, hyperkalemia, and mild metabolic acidosis. Because the pituitary gland is intact in primary adrenal insufficiency, the lack of cortisol will result in a compensatory increase in ACTH, leading to mucocutaneous **hyperpigmentation** because ACTH binds to the melanocyte receptor 1, which is responsible for pigmentation. The **hyperpigmentation** can be diffuse but is usually spotty, being noted around the lips and buccal membranes and in exposed or pressure areas, for example, the knuckles, knees, feet, elbows, and belt and brassiere lines. Multiple freckles and generalized tan may be seen along with areas of vitiligo in autoimmune adrenalitis. **Hyperkalemia** occurs in 61% of primary disease, and **hyponatremia** is even more common, p. 201p. 202because of the combined effect of loss of aldosterone secretion and absence of the physiologic inhibitory effect of cortisol on antidiuretic hormone secretion, leading to water retention. Secondary hypoadrenalism, on the other hand, is accompanied by hyponatremia but not by hyperkalemia.

b. **Symptoms of secondary adrenal insufficiency.** Clinically, secondary adrenal insufficiency can be quite subtle, presenting only as weakness and fatigue. It does not cause hypoaldosteronism, because the renin-angiotensin system is intact to control aldosterone production from the zona glomerulosa. **Two clinical features** can help distinguish primary from secondary adrenal disease: **(a) hyperkalemia** is

not found in secondary disease, but **hyponatremia is common** and **(b) hyperpigmentation** is also not present in secondary disease, because ACTH and MSH levels are low.

Additional clues of secondary adrenal insufficiency are concomitant symptoms of hypogonadism and hypothyroidism, reflecting deficiencies in LH, follicle-stimulating hormone, thyroid-stimulating hormone, and growth hormone.

C. Acute adrenal crisis

1. **Etiology.** Chronic adrenal insufficiency can evolve into acute adrenal crisis precipitated by severe infection, trauma, or surgery.
2. **Clinical presentation** includes high fever, dehydration, nausea, vomiting, and hypotension that evolves rapidly to circulatory shock. Hyperkalemia and hyponatremia are seen if mineralocorticoid deficiency is present. Elevated blood urea nitrogen and sometimes hypercalcemia reflect extracellular fluid loss.

D. Suppression of the HPA axis

Chronic glucocorticoid therapy results in suppression of the HPA axis. Individual susceptibility to HPA suppression, with regard to steroid dosage and duration of therapy, is variable. HPA suppression can manifest in several ways, such as weakness, fatigue, depression, and hypotension occurring upon cessation of glucocorticoid therapy. Acute adrenal crisis can ensue during major stressful situations when glucocorticoids have not been appropriately increased. HPA suppression can present as undue prostration during or following relatively minor intercurrent stress or ailments, such as mild upper respiratory viral infection. Subjects may present with no overt clinical manifestations and only subclinical or biochemical evidence of HPA suppression (blunted cortisol response to exogenously administered ACTH). The following situations should be considered as producing HPA suppression:

1. Any patient who has taken prednisone at a dosage of 15 to 30 mg daily for 3 to 4 weeks. Suppression of the HPA axis can last for 8 to 12 months after cessation of glucocorticoid therapy.
2. Any patient who received prednisone at a dosage of 12.5 mg daily for 4 weeks. HPA suppression can last for 1 to 4 months after cessation of therapy.
3. Any patient who has been treated with glucocorticoids and exhibits a subnormal response to the ACTH test, regardless of dose and

duration of therapy.

4. Occasional cases include subjects receiving glucocorticoid-containing inhalations, dermatologic preparations or intra-articular injections.
5. Any patient with CS who underwent surgery for removal of an adrenal adenoma or carcinoma or transsphenoidal removal of ACTH-secreting pituitary adenoma.

E. Diagnosis of adrenal insufficiency

1. **8 A.M. serum cortisol, plasma ACTH, and plasma renin activity (PRA).** Unless the patient has low CBG (a fairly uncommon condition), serum cortisol ≤3 μg/dL is practically indicative of hypoadrenalism. The ACTH IRMA is a valuable ancillary tool, because ACTH concentration often rises even before significant drops in plasma cortisol occur in primary adrenal failure. When serum cortisol is low, *properly collected and transported* plasma ACTH levels should be clearly elevated in primary adrenal insufficiency. A plasma ACTH >50 to 100 pg/mL indicates primary adrenal insufficiency. Low cortisol levels associated with low ACTH concentrations are indicative of secondary hypoadrenalism, and secondary hypoadrenalism is also suggested by the combination of low cortisol levels with inappropriately "normal" plasma ACTH. ACTH level <30 pg/mL is particularly p. 202p. 203supportive of the diagnosis of secondary adrenal failure. PRA is typically increased in primary but not in secondary hypoadrenalism. *When 8 A.M. serum cortisol is higher than 3 μg/dL, additional testing will be required to confirm the presence of hypoadrenalism.*
2. **Rapid ACTH stimulation test (cosyntropin [Cortrosyn] test).** Cosyntropin is a potent and rapid stimulator of cortisol and aldosterone secretion. The cosyntropin test can be used on an inpatient or outpatient basis, and time of day and food intake does not alter test results. In a previously undiagnosed patient, it can, and indeed should, be performed even in the emergency room, whereas glucocorticoid replacement with dexamethasone is initiated concomitantly.

a. Procedure

i. Draw blood for baseline serum cortisol, renin, aldosterone, and ACTH. Aldosterone, renin, and ACTH will help

differentiate primary from secondary adrenal hypofunction.

ii. Inject 250 μg of cosyntropin either intravenously or intramuscularly. For intravenous injection, dilute cosyntropin in 2 to 5 mL of 0.9% sodium chloride and inject over 2 minutes.

iii. Obtain repeat samples for serum cortisol (and aldosterone) 30 and 60 minutes following ACTH administration.

b. Interpretation. A normal adrenal response to ACTH consists of a rise in serum cortisol to 18 μg/dL or greater. A higher cutoff of 20 μg/dL is also used to increase the sensitivity of the test. A normal response effectively rules out primary adrenal insufficiency. Patients with secondary adrenal insufficiency usually show a blunted response to cosyntropin but occasionally have a normal response. Baseline ACTH levels in primary adrenal insufficiency are high, generally >50 to 100 pg/mL, whereas levels in secondary adrenal insufficiency are low or normal (10 pg/mL or less).

Plasma ACTH level exceeding twice the upper limit of upper limit of the normal range is indicative of primary hypoadrenalism. An elevated PRA or concentration in combination with an (inappropriately) normal or low serum aldosterone concentration suggests primary adrenal insufficiency.

3. **The low-dose (1-μg) ACTH test.** This test is more sensitive and accurate than the 250-μg dose of ACTH in detecting partial adrenal gland insufficiency, especially in patients with secondary adrenal deficiency. The 250-μg dose of ACTH produces massive pharmacologic concentrations of ACTH, exceeding blood concentrations of 10 000 pg/mL, which is way above the ACTH level seen even under extreme conditions in real life. Therefore, the 250-μg dose tends to test only for maximum adrenocortical capacity and overrides any more partial loss of cortisol function. The 1-μg cosyntropin test should replace the 250-μg dose because it is more likely to detect partial or more subtle forms of adrenal insufficiency, particularly secondary adrenal insufficiency resulting from pituitary tumors or chronic glucocorticoid treatment. Two important limitations of this test should be considered, however: (a) standard 1-μg cosyntropin packaging is not commercially available at the present time, and care must be taken to produce the

1-μg dose accurately by serial dilutions and (b) the test may be unreliable in the first few weeks after acutely induced secondary hypoadrenalism (e.g., after pituitary surgery), because the evolution of impaired adrenal reserve (cortisol response to ACTH) under these conditions requires some time, yet the HPA axis may already be severely damaged as a result of ACTH deficiency. This qualification obviously applies to the 250 μg test as well.

4. **Single-dose metyrapone test**
   a. **Purpose. Metyrapone** activates the HPA axis by blocking cortisol production at the 11-hydroylase step and lowering cortisol levels. This test is used to establish or confirm the diagnosis of adrenal insufficiency and is particularly useful when secondary adrenal insufficiency is suspected. Often, patients with hypothalamic or pituitary disease have mild symptoms and a normal rapid ACTH stimulation test. Metyrapone is an inhibitor of 11β-hydroxylase, the adrenal enzyme responsible for catalyzing the conversion of 11-deoxycortisol p. 203p. 204(compound S) to cortisol —the last step in cortisol synthesis. Following metyrapone administration, cortisol synthesis is blocked, levels of cortisol fall, and ACTH release is stimulated, as is the production of adrenal steroids proximal to the enzymatic block as 11-deoxycortisol accumulates.
   b. **Procedure**
      i. **Metyrapone,** 2 to 3 g as a single dose, depending on body weight (<70 kg, 2 g; 70 to 90 kg, 2.5 g; >90 kg, 3 g), is given at midnight with a snack to minimize the nausea accompanying metyrapone.
      ii. Serum cortisol and 11-deoxycortisol are collected the following morning at 8 A.M.
   c. **Interpretation.** A normal response is an increase in serum 11-deoxycortisol of >7 μg/dL; patients with primary or secondary adrenal insufficiency exhibit <5 μg/dL. Cortisol levels should fall below 5 μg/dL to confirm adequate metyrapone blockade. An abnormal metyrapone test in a subject with a near-normal response to the rapid ACTH stimulation test suggests **secondary adrenal insufficiency**. The metyrapone dose needs to be increased in patients who are taking phenytoin

(Dilantin), which enhances clearance of metyrapone. Adverse effects of metyrapone include gastric irritation, nausea, and vomiting. The overnight (single-dose) metyrapone test is generally safer than the standard multiple-dose metyrapone test; however, caution must be applied, especially with patients in whom primary adrenal disease is likely, because adrenal crisis can be precipitated. *Hospitalization with proper monitoring of the patient's condition is suggested for this test.* It is advisable to demonstrate some responsiveness of the adrenal cortex to ACTH before initiating a metyrapone test. **If the ACTH stimulation test is already markedly blunted, then the metyrapone test may not be necessary**.

Several conditions require specific consideration because they may alter the interpretation of cortisol levels. These include critical illness, congenital low CBG in which reduced CBG levels, thus total cortisol is low, and pregnancy in which CBG levels are elevated. In this case, measurement of free serum or salivary cortisol is indicated.

d. Diagnosing hypoadrenalism in the critically ill patient. Partial impairment of the HPA axis is frequently considered in critically ill patients, especially in association with conditions such as hypotension, hyponatremia, hyperkalemia, or a history of head trauma. Because random serum cortisol levels in the critically ill often reach levels as high as 30 to 60 μg/dL, it is clear that the diagnostic "pass" values of the aforementioned ACTH tests are entirely improper for such patients. Very high cortisol levels should not come as a surprise because ACTH and cortisol secretion can be turned on, in the critically ill, by acute response circulating factors ("circulating CRH-like factors," e.g., tumor necrosis factor α) other than ACTH. Based on the serum cortisol response to Cortrosyn, relative hypoadrenalism is reportedly fairly common in the intensive care unit setting. On the other hand, serum free cortisol response to ACTH test is much less frequently impaired, thus indicating that some critical illnesses modify cortisol binding in the serum because of hypoproteinemia or reduced CBG/CBG-binding capacity. Because no factually substantiated consensus on the diagnostic criteria in this setting exists at the present time, the following principles are applied to the diagnosis and management of

hypoadrenalism in the critically ill.

i. Hypoadrenalism cannot be diagnosed using any of the criteria for normalcy used in the noncritically ill.
ii. In the interpretation of random serum cortisol, serum protein levels should be considered.
iii. When clinical suspicion is reasonably strong, and unless random cortisol level is clearly elevated (e.g., ≥30 to 35 μg/dL), high-dose glucocorticoid replacement therapy should be seriously considered, regardless of the outcome of dynamic testing and if no contraindication to such treatment exists, because it has been shown to benefit some patients under these circumstances.

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F. Treatment of adrenal insufficiency

1. Chronic adrenal insufficiency

a. **Primary adrenal insufficiency** requires replacement with both glucocorticoids and mineralocorticoids.

i. Glucocorticoid: hydrocortisone (15 to 25 mg) or cortisone acetate (20 to 35 mg) in two or three divided oral doses per day; higher dose should be given in the morning at awakening, the next either in the early afternoon (2 hours after lunch; two-dose regimen), or at lunch and afternoon (three-dose regimen) is recommended. Because **cortisol levels fall markedly at night**, some believe that a once-daily dose is sufficient. Many patients receiving chronic glucocorticoid replacement therapy are candidates for attempted individual dose refinement because of common confounders such as osteoporosis, diabetes, or complaints of easy bruising, subtle puffiness, or increasing waist circumference. The use of hydrocortisone, rather than dexamethasone or prednisone, allows close dose titration based on serial serum cortisol measurements in the course of 8 to 12 hours following oral intake of hydrocortisone. In the less compliant patient, prednisolone (3 to 5 mg/day), administered PO once or twice daily, may comprise a reasonable alternative. Dose requirements may be higher in extremely obese or very active persons because cortisol secretion correlates with body surface area, and cortisol

turnover is increased in obesity. Increased doses are also required if drugs known to enhance the metabolism of glucocorticoids are used concomitantly (e.g., barbiturates, phenytoin, and rifampin). Lower doses are indicated in significant liver disease (slow metabolism of glucocorticoids), in geriatric patients, and in those with diabetes mellitus, peptic ulcer, or hypertension.

Several delayed-release hydrocortisone preparations have been studied and are presently reserved for difficult cases, for example, the modified-release hydrocortisone formulation (Plenadren) allowing once-daily dosing which is available in Europe. Reliable indices in assessment of glucocorticoid replacement doses include attaining appropriate weight; regression of pigmentation and postural hypotension; and resumption of adequate energy levels in the absence of signs of glucocorticoid excess such as weight gain, particularly at the central compartment, insomnia, or peripheral edema.

Mineralocorticoid replacement is necessary in primary adrenal insufficiency in patients with confirmed aldosterone deficiency, but dose requirements are variable. The synthetic mineralocorticoid fludrocortisone (Florinef) is given in the morning as a single daily dose, starting at 0.05 to 0.1 mg after initial volume and sodium repletion have been achieved. A daily dose of 0.05 to 0.2 mg is usually sufficient in adults. Patients can be started on a liberal sodium intake. Persistent hypotension, orthostatic hypotension, hyperkalemia, or increased PRA indicates that increased doses are needed, whereas hypertension, hypokalemia, or edema would require down titration of Florinef. Hypertension not responsive to dose lowering or the return of hypokalemia/orthostatic hypotension with the reduction in dose would require the addition of antihypertensive treatment.

ii. **Adrenal androgen replacement** may improve overall sense of well-being in both sexes and restore impaired libido in women. **DHEA** at doses of 25 to 50 mg/day are reportedly well tolerated but is occasionally associated with slight hyperandrogenic phenomena in women. Long-term

effects and safety remain untested. After an initial trial period of 6 months of DHEA replacement, benefits and side effects should be weighed. Serum morning DHEA-S levels at the mid-normal range comprise a reasonable target during follow-up, but attention should be given to age because serum DHEA-S declines with aging as of early adulthood on.

iii. **Patient education** includes instruction to adjust glucocorticoid dosage for mild illnesses and stressful events; in addition, patients should always carry a card or wear a bracelet (Medic-Alert Foundation) indicating their

p. 205p. 206steroid dependency. A traveling kit that provides cortisone acetate–deoxycorticosterone acetate for intramuscular self-injection, and hydrocortisone (100-mg) or dexamethasone (4-mg/mL; Decadron) vials for emergency intravenous administration, is recommended.

iv. **Intercurrent illness** or **stress** requires an adjustment of glucocorticoid therapy, but not of mineralocorticoid therapy. For minor illnesses (e.g., respiratory tract infection, dental extraction, and unusual physical challenge), glucocorticoid dosage is doubled until the condition has resolved. Vomiting and diarrhea require hospitalization because they preclude oral intake of replacement therapy and result in rapid dehydration. During major stress, the maximum daily glucocorticoid requirement is equivalent to 300 mg of hydrocortisone.

Although the need for any increase in the replacement dose of glucocorticoids during routine surgical procedures has been challenged in a controlled trial, the safety of maintaining the regular dose during elective major surgery has not been sufficiently tested. **Traditionally, 100 mg of hydrocortisone is administered intravenously before anesthesia, followed by 100 mg q8h** until the patient has stabilized postoperatively. Lower doses (10 mg of hydrocortisone per hour via continuous intravenous drip) have also been successfully applied in practice, and are perhaps suitable for lesser procedures. Medication is tapered rapidly (3 to 5 days) to the previous dosage. Acute

situations do not require higher doses of mineralocorticoids because hydrocortisone at high doses has sufficient mineralocorticoid activity. Major catastrophes or emergencies (e.g., trauma, major emergency surgery, sepsis, and myocardial infarction) require treatment, as in acute adrenal crisis.

b. **Secondary adrenal insufficiency.** Secondary adrenal insufficiency does not require mineralocorticoid replacement. Sex hormone replacement may be needed because of the associated gonadotropin deficiency.

2. **Acute adrenal (Addisonian) crisis**
   a. Intravenous hydrocortisone (100 mg) as a bolus.
   b. Intravenous saline and glucose.
   c. Hydrocortisone, 100 mg q8h as a continuous infusion for the first 24 hours.
   d. Hydrocortisone is then tapered during recovery by decreasing one third of the daily dose every day, until a maintenance dosage is reached, preferably within 5 to 6 days. Once the dose of hydrocortisone is <100 mg/day, fludrocortisone (0.1 mg/day) is added.
3. **HPA suppression**
   a. **Alternate-day glucocorticoid therapy.** During treatment with pharmacologic doses of glucocorticoids, the total daily dose of steroid is best given as a single morning dose to prevent complications, using short-acting glucocorticoids (hydrocortisone and prednisone) but not long-acting agents (dexamethasone and beclomethasone). Short-acting agents given once daily allow time for some HPA recovery between doses, minimizing HPA suppression. When possible, patients are switched from daily to alternate-day regimens. The total daily dose is doubled and given every other morning, such as 50 to 100 mg of prednisone every other day. One method is to shift prednisone from the day off to the day on at daily increments of 5 mg. When the day-off dosage reaches 5 mg, tapering is at 1 mg every other day.
   b. **Tapering glucocorticoids.** Once prednisone is reduced to 5 mg/day, switch to 20 to 25 mg of hydrocortisone every morning. The short half-life of hydrocortisone allows time for recovery of the suppressed HPA system. The 8 A.M. plasma

cortisol is measured monthly; a value of <10 μg/dL indicates continued HPA suppression. Once 8 A.M. plasma cortisol exceeds 10 μg/dL, hydrocortisone can be withdrawn.

c. **A normal ACTH test** (1 μg cosyntropin) demonstrating peak serum cortisol >20 μg/dL indicates recovery of the HPA axis, and all replacement can be stopped. If 8 A.M. serum cortisol is >10 μg/dL but the response to ACTH is p. 206p. 207still blunted, steroid coverage for major illnesses will be necessary as long as the ACTH test yields a subnormal response.

4. **Adrenal insufficiency during pregnancy**

The glucocorticoid of choice for the pregnant hypoadrenal women is hydrocortisone, which affords some monitoring. **Dexamethasone should be avoided** altogether because it crosses the placenta and may adversely affect embryonic bone. Because free cortisol levels also increase significantly, from week 22 of gestation, it is customary to increase hydrocortisone by 20% to 40% as of the 24th week on. Still, individualization of treatment is needed, and women should be closely watched for clinical signs of over- and under-replacement. Hydrocortisone stress dosing is needed during active phase of delivery, similar to that used in major surgical stress. The oral dose should be doubled for 24 to 48 hours postpartum. The diagnosis of new-onset adrenal insufficiency in pregnancy is challenging because symptoms are nonspecific and increased levels of total cortisol because of increase in CBG. Higher post-ACTH diagnostic cortisol cutoff levels of 700 nmol/L (25 μg/dL), 800 nmol/L (29 μg/dL), and 900 nmol/L (32 μg/dL) have been proposed for the first, second, and third trimesters, respectively.

III. PRIMARY HYPERALDOSTERONISM

A. General principles

The human adrenal cortex secretes several steroids with predominantly mineralocorticoid properties, the most important being **aldosterone.** DOC is the most potent mineralocorticoid of the nonaldosterone steroids, demonstrating about one thirtieth of the potency of aldosterone. Although the major adrenal glucocorticoid, cortisol, binds

effectively to the mineralocorticoid receptor, it has minimum mineralocorticoid potency under normal conditions because of its rapid conversion to cortisone by 11-hydroxysteroid dehydrogenase (type 2) at the receptor site. However, excessive amounts of cortisol can saturate this enzyme capacity to neutralize cortisol and lead to enhanced mineralocorticoid activity.

Under most physiologic conditions, the renin–angiotensin system is the main regulator of aldosterone secretion. Through generation of angiotensin II, this system responds to alterations in sodium and volume status. **Volume depletion** induces the release of renin and the formation of angiotensin II, with subsequent angiotensin II stimulation of aldosterone secretion, leading to retention of sodium and water to restore blood volume. **Volume expansion** leads to reductions in renin, angiotensin II, and aldosterone to facilitate sodium and water excretion. Additionally, potassium and ACTH stimulate aldosterone secretion directly, independent of volume changes. Even small increments in plasma potassium lead to significant stimulation of aldosterone secretion, which, in turn, facilitates renal potassium excretion. Potassium depletion has the opposite effect, lowering aldosterone to minimize potassium excretion.

B. Etiology

Primary hyperaldosteronism (primary aldosteronism [PA]) implies autonomous hypersecretion of aldosterone, whereas in various forms of secondary hyperaldosteronism the stimulus is extra-adrenal. There are at least **five distinct forms**:

1. Adrenal aldosterone-producing adenoma (APA) (~30% to 40% of all cases). Somatic mutations account for more than 50% of APA: The largest number reside in the potassium channel KCNJ5, but mutations at the sodium and calcium ATPases (ATP1A1 and ATP2B3); calcium channels (CACNA1D and CACNA1H); *β*-catenin (CTNNB1); and ARMC5 also underlie the development of APA.
2. Idiopathic hyperaldosteronism (IHA) with bilateral (micronodular) hyperplasia of the adrenals (BAH) (60% to 70%).
3. Unilateral micronodular adrenal hyperplasia (1% to 2%).
4. **Familial hyperaldosteronism** (FH): (a) **type I, glucocorticoid-remediable hyperaldosteronism (GRA)**, a rare familial entity characterized by BAH with reversal of clinical and biochemical abnormalities following glucocorticoid

administration; (b) **type II**: familial occurrence of APA or bilateral IHA or both); (c) **type III: bilateral hyperplasia caused by germline mutations in the *KCNJ5*** encoding for G-protein–activated inward rectifier potassium channel 4; p. 207p. 208(d) **type IV**: a few cases with germline mutations in the calcium channel CACNA1D or CACNA1H; and (e) finally, and not yet entitled with a distinct FH serial number, there are the rare cases of MEN1 with APA.

5. Aldosterone-producing adrenal carcinoma (rare).

C. Prevalence

Until the past decade, the prevalence of primary hyperaldosteronism in the hypertensive population had been estimated at 0.01% to 2.2%, but the prevailing belief now is that the rate may vary between 2% and 15%, depending on the population in question. The rate increases with severity of hypertension, such that it may be approximately 2% in subjects with mild-to-moderate hypertension, increasing to as high as 13% or even higher in severe (>180/110 mmHg) or resistant hypertension.

D. Clinical findings

Most of the pathophysiologic findings in primary hyperaldosteronism can be explained by the effects of excessive aldosterone on sodium and potassium transport. Thus, one observes increased renal tubular reabsorption of sodium and water, leading to volume expansion and hypertension, and enhanced renal excretion of potassium and hydrogen ions, leading to hypokalemia and mild metabolic alkalosis.

1. **Hypertension** is the most prominent and almost universal finding in the disorder and, contrary to previous beliefs, can be mild, moderate, or severe.
2. **Hypokalemia** is far less common than previously believed, and is present in only half of patients with APA and 17% of those with IHA. If **hypokalemia** is significant (<3.5 mEq/L), patients can have symptoms related to potassium depletion, including muscle weakness, fatigue, cramping, and, in severe cases, muscle paralysis. Potassium depletion can produce a renal concentrating defect, leading to **polyuria** and **polydipsia,** which are resistant to vasopressin. Potassium repletion, however, can completely reverse

these symptoms.

Chronic hypokalemia also alters the electrical potential of myocardial cells, leading to the electrocardiographic findings of the widened QT interval and U waves in this disease.

3. Hypokalemia impairs insulin secretion from pancreatic β cells, whereas aldosterone per se increases oxidative stress, which and may jointly cause the **diminished glucose tolerance** seen in approximately 50% of patients with PA. The metabolic syndrome is commonly seen in PA, reportedly afflicting >40% of patients, although this has been recently challenged.
4. Aldosterone excess results in a **mild metabolic alkalosis,** which is not due to a direct aldosterone effect but seems best correlated with the degree of hypokalemia in these patients.
5. Mild **hypomagnesemia** may be present and appears to result from decreased tubular reabsorption of magnesium. Magnesium deficiency may contribute to insulin resistance in PA.
6. **Increased risk for adverse cardiovascular** effects: increased rate of stroke in younger subjects (<40 years), especially in GRA; a twofold greater prevalence of left ventricular hypertrophy (after adjustment for hypertension duration); higher prevalence rates for coronary artery disease, nonfatal myocardial infarction, heart failure, cardiac fibrosis, and atrial fibrillation.

Physical examination of patients with primary hyperaldosteronism reveals few findings. Most typically, edema is almost always absent. When it is present, prolonged hypokalemia may blunt some circulatory reflex responses; consequently, postural hypotension and bradycardia can occur. Nevertheless these are *not* common findings.

E. Effect of somatic mutations or genotype on phenotype in PA

1. Somatic mutations

a. KCNJ5 somatic mutations are present in approximately 40% of APAs. A point mutations in and near the selectivity filter of the potassium channel KCNJ5 produce increased sodium conductance and cell depolarization, triggering calcium entry into glomerulosa cells, the signal for aldosterone production, and cell proliferation. Two somatic mutations in KCNJ5 (G151R and L168R) were identified. Patients with KCNJ5

mutations are younger on presentation, p. 208p. 209more often female than male, nodule size is larger than those without (27 mm vs. 17 mm), and associated with higher preoperative aldosterone levels but not with therapeutic outcome after surgery.

b. Somatic mutations in ATP1A1 (encoding an Na^+/K^+ ATPase α subunit), ATP2B3 (encoding a Ca^{2+} ATPase) showed male dominance, increased plasma aldosterone concentrations, and lower potassium concentrations compared with mutation-negative cases.

c. CACNA1D (encoding a voltage-gated calcium) mutations, possibly comprising 11% of APAs, have been linked to smaller tumors and older age than those with KCNJ5 mutations.

2. Germline mutations

a. GRA (FH type 1) is a rare condition (<1% of PA) which should be considered when PA is diagnosed at a young age (e.g., <20 years) and/or in the context of a strong family history of hypertension, stroke at a young age, or familial PA. The disease results from a chimeric 11β-hydroxylase/aldosterone synthase gene in which the coding sequence of the aldosterone synthase is controlled by the 11β-hydroxylase promoter, thus making aldosterone synthesis sensitive to ACTH rather than to angiotensin II. Dexamethasone therapy reverses both high blood pressure and the associated biochemical abnormalities (i.e., hypokalemia, hyperaldosteronism, and hyporeninemia), usually within the first 21 to 28 days of therapy. Genetic testing is now available. For long-term treatment, the lowest dose of dexamethasone effective in controlling blood pressure, and correcting the biochemical and hormonal abnormalities should be selected.

b. Early-onset hyperaldosteronism in childhood has been seen in some families carrying the KCNJ5 mutations.

F. Diagnosis

The classic triad of biochemical criteria for the diagnosis of primary hyperaldosteronism includes (a) hypokalemia with inappropriate kaliuresis; (b) suppressed PRA; and (c) elevated aldosterone levels that

do not fall appropriately in response to volume expansion or sodium load. **Active case detection** is now recommended because of the presumed high prevalence of PA under the following circumstances:

1. **Spontaneous or diuretic-induced hypokalemia.** Spontaneous or unprovoked hypokalemia of 2.7 mEq/L or less in hypertensive patients is usually due to PA, especially APA. In a patient who does not receive diuretics, urinary potassium excretion >30 mEq in 24h in the presence of a serum K^+ concentration <3.5 mEq/L is inappropriately high and is thus indicative of mineralocorticoid excess.
2. **Moderate or severe hypertension, *particularly in the nonelderly***
3. **Resistant hypertension**
4. **Adrenal incidentaloma and hypertension**
5. **Hypertension and sleep apnea**
6. **Family history of hypertension of early onset or cerebrovascular accident at a young age (<40 years).**
7. **Hypertension in first-degree relatives of patients with PA.**

G. Screening tests

Current guidelines call for use of the **plasma aldosterone/renin ratio (ARR) as the screening test to detect PA in these patient groups**. Although blood pressure–lowering drugs have multiple effects on PRA, in many cases, withdrawal of treatment for the purpose of testing is neither feasible, because blood pressure may rise unacceptably, nor necessary, because interpretation can be usually made taking into consideration the known effects of the specific drugs used. Spironolactone and eplerenone as well as high-dose amiloride comprise exceptions to this practice and must be discontinued for at least 6 weeks prior to testing. Additionally, in patients with mild hypertension, drug withdrawal (2 to 4 weeks) prior to testing still appears to be preferable.

1. **PRA.** The **chronic hypervolemia of primary hyperaldosteronism accounts for the suppressed renin levels** characteristically seen in this disease. However, low renin is actually seen in only **60% to 80%** of patients, perhaps because many hypertensive patients are initially treated with diuretics and

vasodilators p. 209p. 210that stimulate renin activity. Additionally, **25% of the essential hypertension population displays low levels of renin activity** of uncertain etiology, and low PRA is observed in the elderly. Among the various assays available, PRA rather than plasma renin concentration (PRC) is the preferred method. Because ARR is heavily dependent on PRA and dependence is highest at the low end of the assay range (e.g., lowering measured PRA from 0.2 to 0.1 ng/mL will **double** the calculated ARR), care must be taken not only to collect samples properly but also to use a reliable laboratory with documented performance and sufficient assay sensitivity at the low range as low as 0.2 to 0.3 ng/mL/hour.

2. **Aldosterone measurements.** Aldosterone secretion is suppressed by increased dietary sodium, hypervolemia, and hypokalemia. Plasma and urinary aldosterone concentrations also decrease with advancing age to 30% to 50% of the values seen in young subjects, making age corrections necessary, especially in evaluating hypertensive patients over 60 years of age. A significant number of patients with primary hyperaldosteronism (~30%) have basal aldosterone levels that are within the normal range. In patients with serum potassium <3 mEq/L, potassium repletion (200-mEq potassium diet for 5 days or potassium chloride elixir, 60 to 120 mEq daily PO) should be initiated with repeat measurements of aldosterone after repletion. Potassium depletion can actually reduce and “normalize” adrenal aldosterone secretion in some patients.
   a. For the basal measurement of PRA and aldosterone, patients can be on a regular diet. Sampling should be done in the morning hours, after the patient has been awake for at least 2 hours and in the sitting position for 15 minutes. Ideally, patients should have unrestricted dietary salt intake before testing and should be potassium replete. Blood is collected for PRA in tubes containing ethylenediaminetetraacetic acid and centrifuged at room temperature to avoid cryoactivation of prorenin to renin.
   b. **Interpretation of the ARR.** Although the ARR is generally recommended as the best screening test, there are no universally accepted trough values that define abnormal ratio levels. ARR cutoff values depend on the assay and on whether plasma

aldosterone, PRA, and direct renin concentration are measured in conventional or system international units.

c. Attention should be paid to the following:

i. Units. Most published cutoff values refer to aldosterone expressed as ng/dL, and PRA expressed in ng/mL/hour. With this presently most popular unit system, most groups use ratios exceeding 20 to 40 as the cutoff level requiring further diagnostic workup for PA. Less often, PRC (mU/L) rather than PRA is measured, and aldosterone levels are provided in SI units (pmol/L), and suggested critical ratios, under these circumstances, range from 70 to 130.

ii. Effect of drugs. *β*-Blockers, clonidine, *α*-methyldopa, and nonsteroidal anti-inflammatory drugs (NSAIDs) suppress PRA and aldosterone and may lead to a false-positive ARR; all diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and dihydropyridine calcium channel blockers **increase PRA** and may lead to a false-negative ARR. Blood pressure–lowering drugs with minimal effects on ARR include *α*-blockers, hydralazine, and slow-release verapamil. Contraceptives increase PRA but decrease PRC.

iii. Effect of age. PRA declines with age more than aldosterone, leading to higher ARR.

iv. Chronic renal failure is linked to low PRA and high ARR.

v. Aldosterone levels. In the absence of hypokalemia, low aldosterone levels (<9 ng/dL) are inconsistent with PA. On the other hand, strict requirement for high plasma aldosterone results in a significant rate of false-negative cases. Even if aldosterone levels ≥15 ng/dL are set as a requirement for the diagnosis in the context of increased ARR, some patients may be unduly excluded. Although not explicitly stated by the manufacturers or expert reviews, some popular commercial aldosterone kits yield higher p. 210p. 211than previously reported aldosterone levels. Therefore, LC–MS-MS–based assays are preferable.

vi. **Definitive and confirmatory tests.** When spontaneous hypokalemia, plasma renin below detection levels plasma aldosterone >20 ng/dL coexist, there may be no need for further confirmatory testing. This is particularly true for young (e.g., <40), recently diagnosed, nonobese, and nonsmoking subjects not receiving blood pressure–lowering drugs. However, given the variability of basal aldosterone and renin levels in this disorder, particularly in the context of antihypertensive drugs and age-related decline in renin, the nonsuppressibility of aldosterone in response to volume expansion maneuvers is a very useful indicator of primary hyperaldosteronism. Volume expansion via saline infusion, high-salt intake, or mineralocorticoid administration in any condition other than primary hyperaldosteronism suppresses aldosterone levels by >50%. In primary hyperaldosteronism, an additional volume load has only a minimal effect on aldosterone concentration. Spuriously increased ARR may be corrected by the use of one or more of the following tests.

H. Confirmatory tests

1. **Aldosterone suppression tests: salt-volume loading tests.** These tests should be deferred until hypokalemia is corrected and are not recommended in individuals with severe hypertension, renal or congestive heart failure, or cardiac arrhythmia.

a. Saline infusion test

i. Patients should be on a regular diet. Obtain serum K^+ and proceed only if concentration is ≥4 mmol/L.
ii. Obtain baseline aldosterone levels.
iii. Infuse 0.9% sodium chloride solution for 4 hours (500 mL/hour, a total of 2 L).
iv. Obtain repeat samples for aldosterone and potassium. Following the infusion, plasma aldosterone will normally drop by at least **50%** or below 5 ng/dL, whereas patients with primary hyperaldosteronism will display postinfusion levels >10 ng/dL.

b. Oral salt loading test

i. Increase sodium intake to >200 mmol/L and add slow-release potassium chloride tablets to keep serum potassium

in the normal range.

ii. Obtain 24h urine collection to verify that the intended intake has been attained.

iii. Obtain 24h urine collection starting on the morning of day 3 for the measurement of urinary aldosterone. Urinary aldosterone excretion >12 to 14 μg in 24h is highly suggestive of PA, whereas excretion <10 μg in 24h practically excludes this diagnosis.

iv. LC–MS is the preferred method for measurements because radioimmunoassays for urinary aldosterone perform poorly in this setting.

c. Fludrocortisone administration with oral sodium loading

i. Patients should be treated for 4 days with fludrocortisone 0.1 mg q6h together with slow-release potassium (levels of k measured qid, close to 4.0 mmol/L), slow-release NaCl supplements (30 mmol three times daily with meals), and sufficient dietary salt to maintain a urinary sodium excretion rate of at least 3 mmol/kg body weight.

ii. Upright plasma aldosterone levels measured at 10 A.M. basally and on day 4, plasma aldosterone and PRA are measured at 10 A.M. with the patient in the seated posture, and plasma cortisol is measured at 7 and 10 A.M.

d. Captopril challenge test

Under normal conditions, inhibition of angiotensin II–converting enzyme leads to acute increase in PRA, because of acute disinhibition of renin release, whereas plasma aldosterone declines because of the reduction in angiotensin II generation. In PA, PRA remains suppressed because of hypervolemia, and plasma aldosterone does not change appreciably because it is secreted autonomously.

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i. After 1 hour in the sitting position, obtain blood for PRA, aldosterone, and cortisol.

ii. Administer 25 to 50 mg of captopril as a single oral dose and keep the patient in the sitting position for 1 to 2 hours.

Draw a second blood sample for PRA, aldosterone, and cortisol.

iii. **Interpretation.** Plasma aldosterone declines by at least 30% in normal subjects, but it is hardly affected in PA. The test is not suitable for patients receiving ACE inhibitors or ARBs. Plasma aldosterone may be decreased in this test in some patients with IHA. Equivocal or false-negative results are not uncommon.

2. **Tests to differentiate APA and BAH (IHA)**

Patients with **APA respond favorably to surgery, whereas BAH patients do not** and require prolonged medical therapy. Thus, a preoperative distinction between APA and BAH as the cause of hyperaldosteronism must be made.

a. **Adrenal CT and MR scans.** Once the biochemical diagnosis of primary hyperaldosteronism has been firmly established, CT scans are effective in identifying various adrenal tumors, particularly adenomas with a diameter of 1 cm or more. **MRI offers no advantage over CT scan.** The results with BAH are variable, ranging from an apparently normal gland to bilateral diffuse enlargement. However, the identification of an adrenal lesion should not be automatically assumed to represent APA, even when the diagnosis of PA has been firmly established. First, **adrenal incidentalomas can be seen in as many as 10% of the general population**. Second, unilateral adenoma might represent one large nodule in an essentially bilateral disease (BAH). Third, unilateral adrenal hyperplasia may not be identified by these methods. Forth, bilateral nodularity may represent either true bilateral disease or a composite condition with true APA on one side and a nonfunctioning adrenal nodule on the other gland. Finally, small adenomas can be missed by either CT or MRI, leading to erroneous diagnosis of BAH. This is why the concordance rate between CT and the more difficult, but accurate adrenal venous sampling for aldosterone does not usually exceed 50% to 60%. CT is still helpful in identifying the malignant potential of larger lesions (>2.5 cm) through their radiologic features (density in HU units, regularity, etc.) and in identifying the correct adrenal vein to aid in subsequent catheterization during adrenal venous sampling.

b. **Adrenal vein sampling for aldosterone concentration**

i. In skilled hands and experienced centers, catheterization of

the adrenal veins with collection of adrenal vein effluent is the most accurate and definitive means of correct identification of hyperaldosteronism induced by unilateral disease, that is, APA or unilateral hyperplasia. Sampling can be done through simultaneous catheterization of both adrenals or as a sequential procedure, either unstimulated or stimulated by Cortrosyn injection, and while several protocols exist most experts favor continuous Cortrosyn infusion to minimize variability.

ii. **Interpretation.** Interpretation is highly dependent on the actual protocol used. False lateralization could result from episodic secretion of aldosterone or from dilution effects.

a) **Episodic secretion** of aldosterone can be avoided by simultaneous sampling from both adrenals and is also minimized if samples are collected following injection of ACTH.

Samples obtained from either side may consist of a variable mixture of adrenal and extra-adrenal venous blood (e.g., **"pure"** adrenal blood compared to a "contralateral" **diluted sample**). **Simultaneous measurement of aldosterone and cortisol** in both adrenal veins and the inferior vena cava (IVC) provides an excellent indicator of sampling-site dilution, using an aldosterone to cortisol ratio to correct for errors induced by the location of the catheter. With continuous Cortrosyn infusion (50 μg of cosyntropin per hour, initiated 30 minutes before catheterization and p. 212p. 213continued throughout the procedure), a high side to low side ratio of "cortisol-corrected" aldosterone >4 is indicative of unilateral disease (in most cases, APA). A ratio <3 suggests bilateral disease. In unstimulated testing, a ratio >2 suggests lateralization. One might also expect that the aldosterone to cortisol ratio should be markedly suppressed on the contralateral side compared with levels from the IVC.

c. **Adrenal radioisotope scanning** with iodocholesterol or

NP-59 is often helpful in the differential diagnosis of primary hyperaldosteronism. With 7 days of dexamethasone suppression (0.5 mg, two times a day), asymmetric uptake is compatible with APA, whereas bilateral uptake favors the diagnosis of BAH. This is not a useful procedure for small APA, but is very useful when the suspected adenoma on CT ≥1.5 cm, especially when access to high-quality adrenal venous sampling is limited, as it is in many parts of the world.

3. **Ancillary tests for equivocal cases**
   a. **Posture test.** APA appears to be quite responsive to ACTH, but not to angiotensin II. The opposite pertains to BAH, in which angiotensin II is the major regulator.
      i. **Procedure for posture test**
         a) Samples for PRA and plasma aldosterone are obtained between 8 and 9 A.M., after the patient has been in the supine position for 30 minutes.
         b) The patient assumes upright posture and ambulates moderately for 4 hours, at which time samples are collected again.
      ii. **Interpretation.** Normal subjects assuming upright posture always increase PRA and, therefore, plasma aldosterone levels, and this is further enhanced with ambulation. Because PRA is suppressed in APA, plasma aldosterone does not respond to posture and declines in association with the diurnal reduction in ACTH (8 A.M. to noon). Patients with BAH show a normal increase (>25% of the baseline value) in aldosterone levels with upright posture, accounted for by a partially intact renin response, and enhanced adrenal gland sensitivity to angiotensin II. However, up to 50% of patients with APA demonstrate posture increases in plasma aldosterone. In fact, the reliability of the test in distinguishing APA and BAH has been questioned in light of recent information that the magnitude of posture response depends on baseline levels of aldosterone, independent of adrenal pathology. This should, therefore, be seen as an ancillary procedure and interpreted only in the context of additional functional and imaging procedures.
   b. **Plasma 18-hydroxycorticosterone (18-OHB).** The immediate precursor to aldosterone biosynthesis is 18-OHB,

which, like aldosterone, originates primarily from the adrenal cortical zona glomerulosa. The levels of 18-OHB are particularly high in APA, and plasma 18-OHB concentrations >100 ng/dL indicate that PA is the result of APA; anything less than this value, especially <50 ng/dL, is more likely a result of BAH.

I. TREATMENT

1. **APA.** Surgical removal of the gland containing the tumor is the treatment of choice. Most adenomas are small, often <1 cm in diameter, and twice as many occur on the left side as on the right. Potassium repletion, either by oral potassium supplementation or by preoperative treatment with the mineralocorticoid antagonist spironolactone (50 to 200 mg/day over 2 to 3 weeks), must be achieved before surgery. Although surgical outcome is imperfect in terms of hypertension control, with cure achieved in <50% of correctly diagnosed subjects, at least partial improvement is the rule in most. Older age, severe preoperative systolic pressure, and the use of multiple blood pressure–lowering drugs are negative predictors of cure. Hypokalemia, on the other hand, resolves within days after surgery. Late recurrence of hypertension, but not hypokalemia, has been reported. Aggressive medical treatment is suggested for patients who do not undergo surgery (see BAH), with attempted treatment to target hypertension as well as all associated risk factors.
2. **BAH.** Because the surgical cure rate of BAH (normalization of blood pressure) is only **19%**, these patients should be treated medically. Although **spironolactone** p. 213p. 214(12.5 to 200 mg daily) is the obvious choice, results in BAH have been quite variable, and long-term spironolactone treatment is frequently accompanied by impotence and gynecomastia in males and by menstrual disorders in females. **Eplerenone**, an alternative mineralocorticoid receptor antagonist that does not interact with the androgen or progesterone receptor, is now available and can be attempted when side effects of spironolactone are intolerable. **Amiloride** (40 mg/day), a potassium-sparing diuretic that acts on renal tubular cells

independently of aldosterone activity, has been shown to be a successful therapeutic agent in the treatment of primary hyperaldosteronism. Additionally, dihydropyridine calcium channel blockers, ACE inhibitors, and ARBs are often effective in PA.

J. DIFFERENTIAL DIAGNOSIS

Hypertension and hypokalemia as the presenting symptoms are common in other syndromes.

1. **CS.** Hypertension and hypokalemia may be the presenting symptoms in CS. In Cushing disease, PRA is normal to high, and plasma aldosterone is normal (PRA, no increase or decrease; aldosterone, no increase or decrease). In CS secondary to ectopic ACTH secretion, plasma DOC reaches high levels in response to excessive circulating ACTH. This weaker mineralocorticoid, originating mainly in zona fasciculata cells, commonly induces a **mineralocorticoid excess syndrome** that precedes the manifestations of excessive glucocorticoids. The "hypervolemic" state induced by DOC results in suppression of PRA and aldosterone secretion (DOC ↑; PRA ↓; aldosterone ↓).
2. **Malignant hypertension.** In accelerated or malignant hypertension, **excessive hyperreninism** secondary to renal damage leads to high levels of aldosterone, frequently **accompanied by hypokalemia** (PRA ↑↑; aldosterone ↑).
3. **11β-Hydroxysteroid dehydrogenase (type 2) deficiency.** Because cortisol's affinity for the renal mineralocorticoid receptor is as high as that of aldosterone, and circulating cortisol levels are 1 000-fold higher than those of aldosterone, 11β-hydroxysteroid dehydrogenase type 2, which converts cortisol to cortisone (a molecule incapable of interaction with the mineralocorticoid receptor), is needed to protect the mineralocorticoid receptor from excess activation by cortisol. 11β-Hydroxysteroid deficiency results in an apparent mineralocorticoid excess syndrome secondary to undisturbed access of cortisol to the relatively nonspecific renal mineralocorticoid receptor. This inherited condition, which results in hypertension and hypokalemia, has been described initially in children and more recently in adults. Diagnosis is confirmed by establishing an increased ratio of urinary tetrahydrocortisol (a metabolite of cortisol) and tetrahydrocortisone (a metabolite of cortisone). The glycyrrhizic

acid contained in licorice, which induces an acquired form of apparent mineralocorticoid excess syndrome, exerts its effect via inhibition of 11β-hydroxysteroid dehydrogenase.

4. **Congenital adrenal hyperplasia due to either 11α-hydroxylase deficiency or 17α-hydroxylase deficiency.** In both conditions, defective cortisol production leads to a compensatory rise in ACTH, which stimulates, in turn, the biosynthesis of the weaker mineralocorticoids produced in the zona fasciculata by cells independent of angiotensin II but sensitive to ACTH (corticosterone ↑; DOC ↑; PRA ↓; aldosterone ↓). Both hypertension and hypokalemia are accompanied by virilization in 11α-hydroxylase deficiency and by primary amenorrhea (females) or eunuchoid features or pseudohermaphroditism (males) because of the sex hormone deficiency in 17α-hydroxylase deficiency.

   Low doses of dexamethasone appear to be the treatment of choice for both 11α-hydroxylase and 17α-hydroxylase deficiencies. Androgens or estrogens are also added in 17α-hydroxylase deficiency.

5. **Liddle syndrome** is a rare familial disorder characterized by hypertension and hypokalemic alkalosis in the absence of the excessive secretion of any of the known mineralocorticoids. The primary defect resides in increased reabsorption of sodium chloride and enhanced secretion of potassium in the distal tubule, secondary to various "activating" mutations in the β or γ subunit of the sodium epithelial p. 214p. 215channel. Hypertension and hypokalemia are relieved by either **amiloride** (10 to 40 mg daily) or **triamterene** (100 to 300 mg qid in divided doses), but **not by spironolactone**. Both PRA and aldosterone are classically low.

6. **Low-renin hypertension.** Approximately one fourth of patients with essential hypertension demonstrate low levels of PRA. It appears that this traditionally defined subset of patients with "essential hypertension" overlaps, at least to some extent, with BAH patients who do not have clearly increased circulating aldosterone but are detected through increased ARR.

7. **Renovascular hypertension.** Hyperaldosteronism and hypokalemia secondary to excessive renin stimulation in renovascular hypertension are uncommon, because most of these

patients have normal to high-normal peripheral PRA. In severe cases with excessive peripheral PRA, hyperaldosteronism with hypokalemia may be encountered (PRA ↑ or N; aldosterone ↑ or N).

8. **Ingestion of exogenous mineralocorticoids.** Overdose of fludrocortisone (occasionally prescribed for orthostatic hypotension) or the chronic use of nasal sprays containing α-fluprednisolone (for chronic rhinitis) may result in hypertension and hypokalemia, accompanied by suppressed PRA and aldosterone levels (PRA ↓; aldosterone ↓).

IV. SECONDARY HYPERALDOSTERONISM

A. Pathophysiology and etiology

Hyperaldosteronism secondary to excessive stimulation of the renin–angiotensin axis is encountered in a variety of clinical instances, all of which are associated with **enhanced production and release of renin** from the kidney. The most common stimuli for such hyperreninemia are sodium loss or salt deficiency (e.g., sodium restriction, diuretics, diarrhea, and salt-losing nephropathy), volume depletion (e.g., hemorrhage and dehydration), or volume redistribution with reduced "central" or "effective" blood volume (i.e., edematous states such as nephrotic syndrome, cirrhosis with ascites, and some stages of congestive heart failure). Very high levels of PRA and aldosterone are normally observed in pregnancy, particularly during the last two trimesters. Excessive intake of potassium can directly increase aldosterone secretion. On rare occasions, the hypersecretion of renin is unprovoked, as in Bartter syndrome or renin-secreting tumors. Two unique conditions in which primary defects underlie secondary hyperaldosteronism, Barttter syndrome and Gietleman syndrome, are discussed.

B. Bartter syndrome

1. **Pathogenesis.** Bartter syndrome includes a number of genetically transmitted abnormalities in the transport of sodium chloride in the loop of Henle, leading to hypokalemia, metabolic alkalosis, hyperreninemia, hyperaldosteronism, and hyperplasia of the juxtaglomerular apparatus. Normally, active sodium chloride transport in the thick ascending loop of Henle occurs via the loop diuretic–sensitive Na–K–2Cl cotransporter at the luminal membrane, which facilitates the entry of sodium chloride to tubular

cells; potassium channels which allow back leakage from the cell to the lumen of reabsorbed potassium, so that the Na–K–2Cl cotransport system can be reloaded for continued shuttling of NaCl into the cell; and chloride channels located at the basolateral membrane to allow diffusion of the chloride anions entering the cell via the Na–K–2Cl cotransporter to the interstitial fluid and then further into systemic circulation. Malfunction of any of the components of this system (Bartter syndrome type 1-5) will induce volume contraction secondary to tubular salt loss, which resembles the effect of thiazide diuretics. Hypovolemia comprises a powerful and chronic stimulus for the release of renin, and hence, increased secretion of aldosterone. Further, the resultant enhanced delivery of sodium to the distal tubule elicits, through electroneutral exchange mechanisms, increased excretion of potassium and hydrogen, and hence, hypokalemia and metabolic alkalosis. The latter two are further enhanced by high aldosterone concentrations. **Hypertension does not evolve** because of the continued "diuretic" effect and because of compensatory formation of vasodilator prostaglandins prostaglandin E_2 (PGE_2) and prostacyclin, which nevertheless are powerful stimulators of renin secretion. Bartter syndrome, then, can be caused p. 215p. 216by autosomal recessive mutations in the Na–K–2Cl cotransporter, the luminal potassium channel, and the basolateral chloride channel, which are referred to as Bartter syndrome types I, II, and III, respectively. An **acquired form** of Bartter syndrome can result from **gentamycin treatment**.

2. **Clinical features.** Kaliuresis, hypokalemic alkalosis, hyperreninemia, secondary hyperaldosteronism, and normotension in a nonedematous patient, in whom gastrointestinal potassium and chloride loss and the abuse of laxatives or diuretics have been excluded, establish the diagnosis. Infrequently, hypomagnesemia further complicates these abnormalities.

C. Gitelman syndrome results from mutations in the gene encoding the thiazide-sensitive Na–Cl cotransporter in the distal tubule and likewise leads to renal sodium wasting, hyperreninemia, secondary hyperaldosteronism, hypokalemia, metabolic alkalosis,

hypomagnesemia, and hypocalcemia.

1. **Treatment principles** are similar as in Bartter syndrome and Gitelman syndrome.
   a. **Correction of hypokalemia** is accomplished by the administration of **spironolactone**, 100 to 300 mg daily, or **amiloride** (or both). Persistent hypokalemia, despite these measures, may require a low-sodium diet.
   b. **Correction of hyperreninemia and hyperaldosteronism.** Indomethacin (1 to 2 mg/kg/day), **ibuprofen** (400 to 1 200 mg/day), and aspirin (0.6 to 3.0 g/day) are all effective cyclo-oxygenase inhibitors that will decrease prostaglandins PGI_2 and PGE_2 production, thereby reducing renin and aldosterone secretion.
   c. When present, hypomagnesemia should be corrected (10 to 20 mEq magnesium daily). Correction of hypomagnesemia also facilitates the normalization of serum potassium levels.

V. HYPOALDOSTERONISM

A. Hyporeninemic hypoaldosteronism

Hyporeninemic hypoaldosteronism is most often associated with mild-to-moderate renal insufficiency, especially in older individuals with varying degrees of hyperkalemia. The most consistent underlying renal disorder has been diabetic nephropathy, although hyporeninemic hypoaldosteronism has also been found in certain interstitial nephropathies. Hyperkalemia in this entity fails to raise aldosterone secretion because this response apparently requires activation of intra-adrenal renin, which may be impaired as well. ACE inhibitors, ARBs, direct renin inhibitors, and NSAIDs, which impair angiotensin II formation or renin secretion, respectively, tend to aggravate this entity or "induce" it in borderline subjects.

1. **Diagnosis.** The diagnosis is made by demonstrating the failure of PRA and plasma aldosterone to increase in response to a combined postural (i.e., 2-hour ambulation) and diuretic test (60 mg furosemide PO, given after baseline levels of PRA and aldosterone have been obtained).
2. **Treatment.** When hyperkalemia is significant and warrants therapy, the treatment choice depends on the patient's blood pressure. If hypertension coexists, furosemide therapy will not only reverse the hyperkalemia but can also restore normal renin and

aldosterone secretion after months of therapy. If the patient is hypotensive or presents with orthostatic hypotension, low doses of fludrocortisone should be tried (starting with 0.05 mg daily). It should be noted, however, that the dosage needed is often higher than that used in Addison disease (i.e., 0.2 mg/day).

B. Unique cases of drug-induced hypoaldosteronism

1. **Heparin:**
   Heparin treatment, especially when given for a prolonged period, can suppress aldosterone secretion and result in hyperkalemia, presumably by a direct effect on the zona glomerulosa.
2. **Calcineurin inhibitors**
   Treatment with immunosuppressive drugs, such as cyclosporine and tacrolimus, may lead to hyperkalemia, due to diminished secretion of, as well as lesser responsiveness to aldosterone.

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C. Addison disease

Hypoaldosteronism may be the earliest manifestation in Addison disease.

D. Transient hypoaldosteronism following unilateral adrenalectomy for an APA

The occurrence of transient hypoaldosteronism following unilateral adrenalectomy for an APA can be minimized by preoperative administration of spironolactone (400 to 600 mg/day), which partially restores the responsiveness of the chronically suppressed renin–angiotensin–aldosterone axis.

E. Congenital hypoaldosteronism

Congenital hypoaldosteronism results from enzymatic defects in aldosterone synthase (an autosomal recessive trait), which is the last enzyme involved in the biosynthetic chain of aldosterone in the zona glomerulosa. This enzyme actually catalyzes three steps, two of which are conversion of corticosterone into 18-OHB (18-hydroxylation step), followed by conversion of the 18-OH group to aldehyde. Mutation in the aldosterone synthase gene impairs the ability of the aldosterone synthase protein to catalyze these steps, **resulting in type I and type II** aldosterone synthase deficiencies, respectively. Aldosterone biosynthesis is impaired in both aldosterone synthase deficiency types, whereas **corticosterone** of zona glomerulosa origin is **excessively produced**. The two defects differ, however, in that 18-OHB is

deficient in type I but overproduced in type II.

1. **Clinical features.** The features of this syndrome vary, appearing as volume and sodium depletion, hyperkalemia, and shock in some, and as asymptomatic hyperkalemia in others. It has been described in isolated nomadic tribes with a high rate of consanguinity. The levels of PRA are high in response to volume deficiency.
2. **Diagnosis.** Specific diagnosis is made by measurements of the ratio of the urinary metabolites of 18-OHB and aldosterone, a procedure limited to special centers.

F. Hyperreninemic hypoaldosteronism

The syndrome of hyperreninemic hypoaldosteronism is encountered in critically ill patients. This condition can follow prolonged hypotensive episodes and is manifested by low-grade, unexplained hyperkalemia. The production of cortisol remains intact, whereas both plasma aldosterone and 18-OHB are decreased, suggesting a selective impairment of the zona glomerulosa cells.

VI. PSEUDOHYPOALDOSTERONISM

A. Pseudohypoaldosteronism type I

Pseudohypoaldosteronism type I is a group of rare salt-losing conditions with hyperkalemia, detected in infancy, some of which tend to resolve spontaneously with time. Pseudohypoaldosteronism type 1 is caused by mutations in the α, β, or γ subunit of the sodium epithelial channel (autosomal recessive transmission; severe dehydration, respiratory tract infections; affects all aldosterone epithelial target tissues, i.e., kidney, lung, colon, and salivary glands) or by loss of function mutations in the mineralocorticoid receptor (autosomal dominant or sporadic form; generally milder and may improve with time). Acquired forms are encountered in obstructive uropathy and following renal transplantation. Treatment consists of **salt and fluid replacement**.

B. Pseudohypoaldosteronism type II

Pseudohypoaldosteronism type II, also termed **Gordon syndrome** or **familial hyperkalemic hypertension**, is a monogenic form of hypertension with hyperkalemia that results from mutations in With No lysine (WNK) kinases 1 and 4, and proteins affecting the thiazide-sensitive Na–Cl cotransporter that mediates NaCl reabsorption in the distal nephron. Malfunction of these mutated proteins results in

enhanced sodium chloride reabsorption in the distal tubule, volume expansion, hypertension, suppression of renin secretion, and reduced availability of tubular sodium and water for exchange with potassium and hydrogen in the cortical-collecting tubular cells. Generally, these patients respond well to treatment with **thiazide diuretics**.

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18 Pheochromocytoma and Paraganglioma

George T. Georges, Ankur Jindal, L. Romayne Kurukulasuriya, and James R. Sowers

Pheochromocytomas (also known as adrenal paragangliomas) and paragangliomas (also known as extra-adrenal pheochromocytomas) are **neuroendocrine tumors** originating from the embryonic neural crest tissue that can produce one or more catecholamines. Pheochromocytomas arise from adrenomedullary chromaffin cells and account for 80% to 85% of chromaffin cell tumors. About 15% to 20% of tumors are paragangliomas. They are extra-adrenal, arise from the neuroendocrine tissues along the paravertebral axis and can present **anywhere from the base of the skull to the pelvis**.

I. EPIDEMIOLOGY

A. Prior reports from the Mayo Clinic between 1950 and 1979 point toward an annual incidence of 0.95 per 100 000 person-years. Because nearly half of all cases are identified at autopsy, it suggests that pheochromocytoma is often under diagnosed. Data from northern Europe yield a lower incidence, approximately 2.1 per million per year, with 40% of diagnosis made at autopsy. Newer detection techniques, including mass spectrometric analysis, have improved detection in affected patients.

B. Pheochromocytomas and paraganglioma (PPGL) display similar frequency in male and female adults. In children, they are often hereditary and are associated with multiple and extra-adrenal tumors, approximately 60% of cases occurring in boys. It has been shown that about 25% of the apparently sporadic cases may be hereditary. Due to this, it is recommended that all PPGL patients have genetic testing done. Familial disorders associated with PPGL have an autosomal dominant inheritance. Type 1 neurofibromatosis (NF-1; Von Recklinghausen disease) is associated with inactivating mutations of the neurofibromin 1 tumor-suppressor gene. Von Hippel-Lindau (VHL) disease is associated with mutations of the VHL tumor-

suppressor gene, resulting in pheochromocytoma in 25% of the affected patients. Multiple endocrine neoplasia (MEN) type 2A is due to mutations in the RET proto-oncogene and can present with pheochromocytoma in up to 50% of the affected patients. It is also seen with MEN type 2B. Mutations in succinate dehydrogenase (SDH) subunit genes (*SDHB*, *SDHD*, *SDHC*, *SDHF2*, and *SDHA*) are responsible for most cases of familial paraganglioma. *SDHB* gene is associated with the highest incidence of malignant paraganglioma (37.5%) compared to other *SDH* genes.

II. ANATOMY/BIOCHEMISTRY

A. PPGL generally present as benign, vascularized, encapsulated lesions, with an average diameter of 5 cm and a weight of <70 g (Fig. 18-1). It is estimated that **approximately 10% of pheochromocytomas are malignant**. Approximately 20% of extra-adrenal mediastinal and abdominal secretory paragangliomas are malignant. Malignancy is defined as metastasis to nonchromaffin tissue. Pheochromocytoma occurs more frequently after 60 years of age. Paraganglioma tends to affect young adults and arises from the sympathetic paravertebral ganglia or the parasympathetic ganglia. These can be part of a familial syndrome. Sympathetic extra-adrenal paragangliomas are usually secretory and are located in the lower mediastinum, abdomen, or pelvis, whereas approximately 95% of the parasympathetic paragangliomas are nonsecretory and are located in the head, neck, and upper mediastinum.

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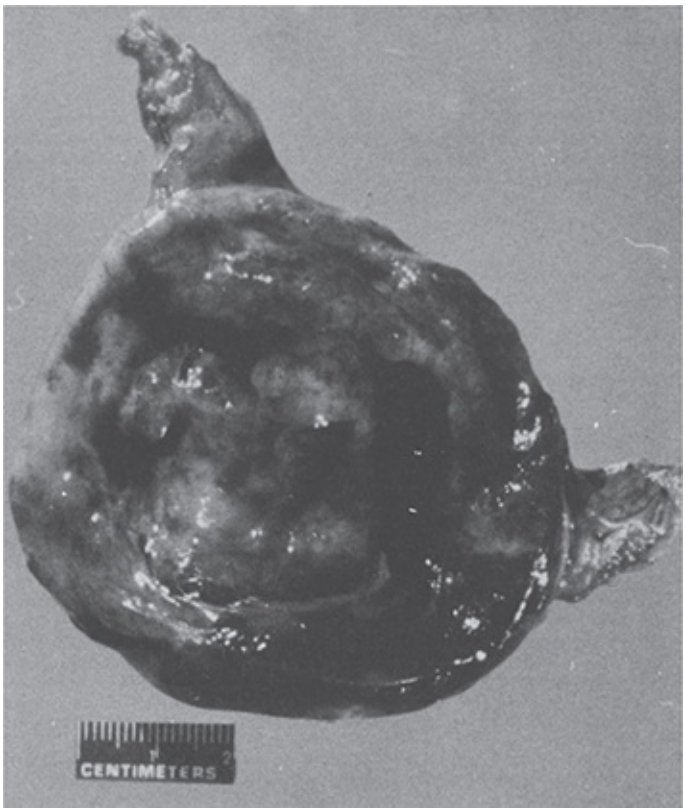

Figure 18-1. Pheochromocytoma of the adrenal gland. Tumor is well encapsulated and exhibits hemorrhagic dark mottling.

B. Although most pheochromocytomas secrete both epinephrine and norepinephrine, there is usually a predominance of norepinephrine. However, some tumors produce only norepinephrine and, in rare cases, only epinephrine or dopamine. Other substances produced by pheochromocytoma include adrenomedullin (a potent vasodilating peptide), chromogranin A, and neuropeptide Y.

III. CLINICAL PRESENTATION (Table 18-1)

Symptoms can be due to mass effect or catecholamine excess.

A. The clinical presentation of PPGL is variable; there is no correlation among tumor size, circulating levels of catecholamines, the severity of symptoms, and/or hypertension (HTN).

B. Most patients present with paroxysmal or sustained HTN, episodic headaches, palpitations, and diaphoresis. The frequency of these paroxysms/spells is variable, but in up to 74% of patients, these symptoms occur on a weekly basis. The duration of these spells is usually <1 hour, but spells lasting a few hours have been reported. Adrenergic α-receptor mediated vasoconstriction results in HTN, facial

pallor, and cool moist extremities. Some patients can be normotensive if the amount of catecholamines secreted to the circulation is small. Peripheral vasoconstriction and increased catecholamine-induced basal metabolism are responsible for increased temperature and sweating. Flushing is not typical of PPGL. In severe cases, patients can develop nausea, vomiting, epigastric and/or chest pain, and seizures. Orthostatic hypotension can occur as a result of volume depletion and predominance of epinephrine/dopamine production by the tumor. Untreated PPGLs are associated with left ventricular hypertrophy, cardiac ischemia, and excess cardiovascular morbidity and mortality.

C. Clinical manifestations may differ based on the location of the tumor. For example, tumors present along the base of the skull and neck may present with p. 220p. 221p. 221p. 222dysphagia, hoarseness, tinnitus, and so on, because of the mass effect. Changes in body position, intra-abdominal pressure, and some medications and exercise may precipitate some of the paroxysmal manifestations of pheochromocytoma.

TABLE 18-1 Clinical Manifestations of Pheochromocytoma

Symptoms

- Common
  - Headache (72%–92%)
  - Sweating (60%–70%)
  - Palpitations with or without tachycardia (51%–73%)
  - Nervousness (35%–40%)
  - Weight loss (40%–70%)
  - Chest or abdominal pain (22%–48%)
  - Nausea with or without vomiting (26%–43%)
  - Weakness or fatigue (15%–38%)
- Less common
  - Visual disturbances, constipation, warmth, dyspnea, paresthesias, flushing, polyuria, polydipsia, dizziness, grand mal seizures, bradycardia (noted by patients), tightness in throat, tinnitus, dysphagia, hoarseness, dysarthria, gagging, painless hematuria

Signs

- Blood pressure changes (seen in 98% of patients)
  - Sustained hypertension
  - Paroxysmal hypertension (which may alternate with hypotension)
  - Orthostatic hypotension

- Hypertension induced by a physical maneuver
- Paradoxical blood pressure response to some antihypertensive drugs
- Marked pressor response to anesthesia

- Other signs of catecholamine excess
  - Hyperhidrosis
  - Tachycardia, arrhythmia, reflex bradycardia, forceful heartbeat
  - Pallor of the face and upper part of the body
  - Anxious, frightened, troubled appearance
  - Hypertensive retinopathy
  - Dilated pupils; very rarely, lacrimation scleral pallor or injection, and the pupils may not react to light
  - Leanness or underweight
  - Tremor
  - Raynaud phenomenon or livedo reticularis; occasionally, puffy, red cyanotic hands in children; skin of extremities wet, cold, clammy, and pale; gooseflesh, cyanotic nail beds
  - Mass lesion in the abdomen or the neck
  - Signs caused by encroachment on adjacent structures or by invasions and pressure effects of metastases

Manifestations Related to Complications of Coexisting Diseases or Syndromes

- Myocardial infarction
- Congestive heart failure ± cardiomyopathy
- Arrhythmias, tachycardia, unexplained hypotension, or cardiac arrest following induction of general anesthesia
- Shock
- Cerebrovascular accident
- Azotemia
- Hypertensive encephalopathy
- Ischemic enterocolitis ± megacolon
- Dissecting aneurysm
- Severe preeclampsia during pregnancy; fever, shock, or sudden death prepartum or postpartum
- Cholelithiasis
- Mucocutaneous neuromas
- Thickened corneal nerves (seen only with slit lamp)
- Marfanoid habitus
- Alimentary tract ganglioneuromatosis
- Neurofibromatosis
- Cushing syndrome

D. There are asymptomatic patients who are diagnosed with pheochromocytoma as a result of functional testing done for adrenal incidentalomas. Some asymptomatic PPGLs are also detected during family screening in patients who have a family history of hereditary PPGL. Some PPGLs are found only at autopsy.

IV. SCREENING/DIAGNOSIS

A. A diagnosis of pheochromocytoma is suggested when there is biochemical evidence of excessive catecholamine production in addition to clinical manifestations. Patients with pheochromocytoma and overt signs and symptoms usually have very **high levels of plasma catecholamines** (>2 000 pg/mL). On the other hand, because of the heterogeneous nature of the disease, normal levels of catecholamines in asymptomatic patients do not necessarily rule out the diagnosis.

B. Screening for pheochromocytoma is indicated in patients with severe sustained or paroxysmal HTN, particularly if they are refractory to reasonable antihypertensive therapy. Patients with episodic symptoms of headaches, tachycardia, and diaphoresis, even in the absence of HTN, should be screened, in addition to patients with hypertensive episodes during parturition, micturition, a family history of pheochromocytoma, MEN syndromes, VHL disease, or NF-1.

C. Pheochromocytomas secrete varying catecholamines and their metabolites in different concentrations. Available assays in the clinical setting to identify patients with pheochromocytoma include a 24-hour urine collection for fractionated metanephrines (normetanephrine and metanephrine), free catecholamines (epinephrine and norepinephrine), and vanilmandelic acid, in addition to plasma levels of catecholamines and metanephrines. None of these tests are 100% accurate because of limited sensitivity and specificity, but their combination in the appropriate clinical setting will allow the best possible diagnostic yield.

D. Measurements of 24-hour urine metanephrines and catecholamines have been suggested for use as an initial screening test. Urine-unfractionated metanephrines and urine vanillylmandelic acid (VMA) have lower sensitivities (~77% and 64%, respectively) and, for this reason, are less suitable for screening. “Fractionated” metanephrines is one of the most commonly used screening tests that has a sensitivity and specificity of 97% and 69%, respectively, and, according to other studies, may be even higher with use of liquid chromatography with mass spectrometry. The sensitivity of urine catecholamines is 86% and specificity is 88%.

E. The emergence of fractionated plasma metanephrines levels by means of high-performance liquid chromatography has significantly contributed to improving accuracy in the diagnosis of

pheochromocytoma. Reported sensitivity of this test is up to 99%, with a specificity of 89%, making **plasma-fractionated metanephrines a superior test** for excluding the presence of pheochromocytoma, because of the very high sensitivity and low rate of false-negative values compared to other available options. Furthermore, when combined with other diagnostic measures, plasma-fractionated metanephrine determination has been demonstrated to be an efficient as well as cost-effective diagnostic approach to pheochromocytoma. Plasma metanephrines should be collected with the patient supine, and reference intervals should be established in the same position because posture can affect the values.

F. Clinicians should be aware of factors that can produce false-positive results. This includes stress and ingestion of various substances, including caffeine, acetaminophen, tricyclic antidepressants, phenoxybenzamine, and levodopa, which should be avoided for 2 weeks prior to testing. Renal insufficiency will influence urine catecholamines, leading to elevation in plasma norepinephrine and dopamine, but plasma epinephrine measurements are still reliable for diagnosis.

G. When the values are equivocal but the clinical suspicion is strong, for example, with plasma catecholamine levels between 1 000 and 2 000 pg/mL, a clonidine suppression test can be performed if the patient is hypertensive. Alternatively, in normotensive patients, a glucagon provocative test can be useful to establish the diagnosis.

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H. Finally, measurement of **chromogranin A in plasma** (elevated in patients with pheochromocytoma) may be useful because it is not affected by medications used to treat HTN. However, there are limitations to its interpretation, which include elevated levels seen when used concomitantly with proton-pump inhibitors, in addition to compromised renal function that greatly influences the specificity of the test. A combination with other diagnostic modalities, such as plasma catecholamines measurements, would be required to improve its diagnostic yield.

V. LOCALIZATION/IMAGING

A. Following the biochemical diagnosis of pheochromocytoma, the next step is to localize the lesion, which can be challenging. Computed

tomography (CT) (Fig. 18-2A) and magnetic resonance imaging (MRI) are the current methods of choice for localization of these tumors. They have sensitivities of 98% and 100% and specificities of 70% and 67%, respectively. PPGLs have characteristic imaging. Nonenhanced CT attenuation is usually over 20 HU. Contrast washout is less than 50% at 10 minutes after p. 223p. 224administration, suggestive of a delayed contrast washout. (Adenomas have a contrast washout of more than 50% after 10 minutes. Delayed contrast washout is seen in pheochromocytomas, carcinomas, and metastases.) Tumors may show increased vascularity, cystic, and hemorrhagic changes. MRI appearance of pheochromocytomas is characterized by distinctive bright signal on T2-weighted images. MRI is preferred over CT in patients with metastatic disease, familial pheochromocytoma for detection of skull base and neck paragangliomas, patients allergic to contrast, and in patients where radiation exposure should be reduced, such as pregnant women, children, and patients who have been exposed to radiation recently.

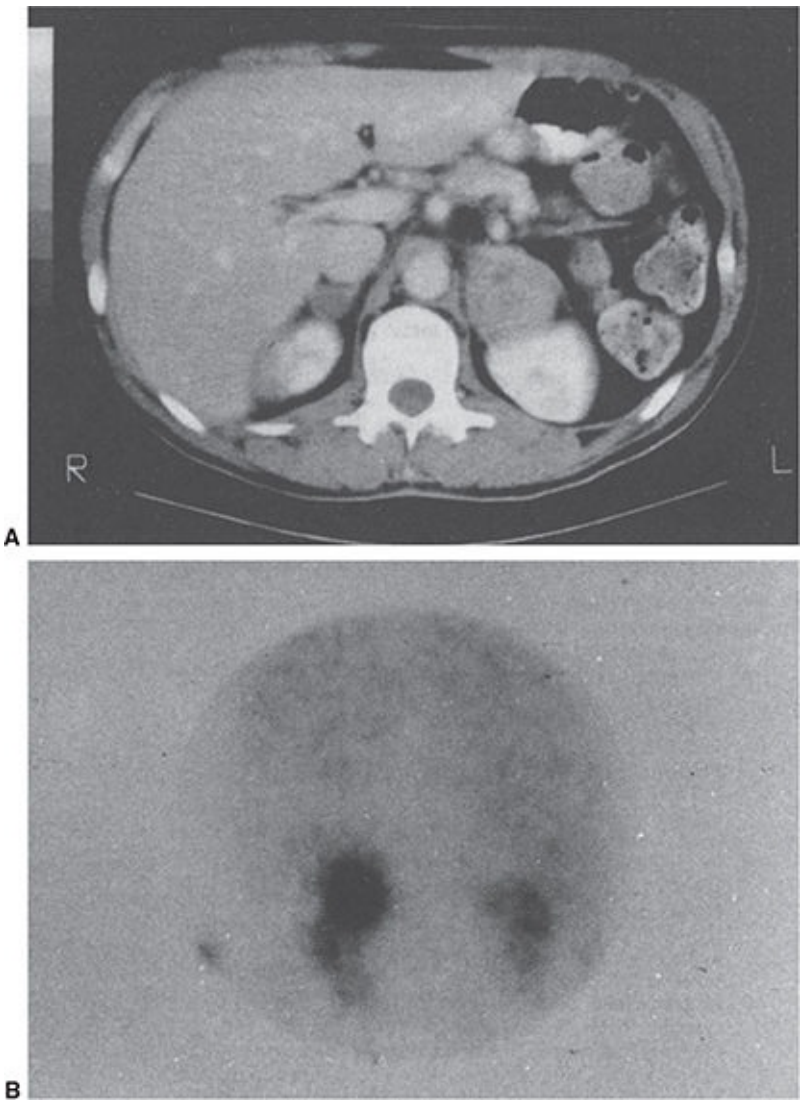

Figure 18-2. **A.** Computed tomographic demonstration of pheochromocytoma in the left adrenal. **B.** MIBG scan, posterior view, localizing the pheochromocytoma to the left adrenal; this location was confirmed by renal scan. MIBG, ^{131}I-*meta*-iodobenzylguanidine.

B. When biochemical findings are suggestive, imaging with CT or MRI is found to be equivocal, *meta*-iodobenzylguanidine (MIBG) scintigraphy using radioactive iodine (^{123}I) may be used for localization (Fig. 18-2B). This imaging modality has higher specificity (virtually 100%) and positive predictive value, despite poor sensitivity (78%). It may also be useful for identifying metastatic disease.

C. Positron emission tomography (PET) scanning using radioactive isotopes, including 18F-fluorodeoxyglucose [^{18}F-FDG], can also be performed as an alternative when other diagnostic studies are equivocal. Additionally, as compared with MIBG, it was suggested

that ^{18}F-FDG/CT can provide better localization of metastatic disease.

D. Octreotide scintigraphy may be useful in some MIBG-negative tumors.

E. A study of nonpheochromocytoma individuals has shown that epinephrine and norepinephrine concentrations are higher in the right adrenal vein compared to the left adrenal vein. Therefore, adrenal vein sampling) should not be used in the investigation of an adrenal pheochromocytoma. If used, it may result in unnecessary adrenalectomy.

VI. TREATMENT

A. Surgical resection is the definitive treatment for PPGL. Appropriate preoperative management with attention to blood pressure, heart rate control, and volume repletion is essential for favorable perioperative outcome. Preoperative management should be started 7 to 14 days before surgery.

B. Selective α-adrenergic blockers are the preferred initial treatment, and once adequate α-adrenergic blockade has been achieved, β-adrenergic blockers can be added to control tachycardia and/or blood pressure. Other agents like calcium channel blockers may be added if needed. Preoperative preparation should include liberal salt and fluid intake, for volume repletion.

C. Nonspecific α-adrenergic blockers, particularly phenoxybenzamine, have been advocated for preoperative management and prevention of hypertensive crisis during surgery. Prazosin, terazosin, or doxazosin can be used to control the episodic HTN, while adequate α-blockade is achieved. Calcium channel blockers, either as monotherapy or in combination with other antihypertensive agents listed above, can be considered.

D. Preoperative salt and fluid intake is important to correct catecholamine-induced volume contraction. This will help prevent postoperative hypotension. Preoperative blood pressure less than 130/90 mmHg while seated, and systolic blood pressure greater than 90 mmHg while standing, with heart rate 70 to 80 bpm, should be targeted. Surgery should be planned after these targets, and α-blockade is achieved. Careful hemodynamic monitoring and aggressive fluid management is important during surgery. Blood pressure, heart rate, and blood glucose should be monitored for 24 to 48 hours postoperatively. Minimally invasive surgical procedures have largely

replaced open adrenalectomy. Laparoscopic adrenalectomy is relatively safe, with less surgical complications, shorter hospital stay, and better cosmetic results, compared to open adrenalectomy. Open adrenalectomy is indicated in patients who have tumors larger than 6 cm and for invasive tumors. Open resection is preferred for paragangliomas unless they are small and not invasive.

E. Pregnancy complicating pheochromocytoma is considered high risk. If the tumor is diagnosed in the first 24 weeks of pregnancy, it should be removed after proper preoperative management. If the tumor is diagnosed in the third trimester, the patient should be managed medically until delivery because a cesarean section and tumor removal may be performed at the same time. Vaginal delivery is not recommended.

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VII. MALIGNANT PPGL

A. Malignant PPGL, by definition, has metastasized to a nonchromaffin site at the time of diagnosis. The 5-year survival rate for patients with malignant PPGL is <50%. About 50% of patients have indolent disease, with survival up to 20 years, and the other 50% have more aggressive disease with a life expectancy of 1 to 3 years. Management is primarily palliative and is directed at controlling cardiovascular complications and tumor-related compressive symptoms. Adequate control of blood pressure should be achieved using α_1-adrenergic blockers. (These are agents like parazosin as opposed to phentolamine.) Other agents should be added if indicated. Severe cases, with extremely high levels of catecholamines, can be treated with α-methyl-paratyrosine, which inhibits catecholamine synthesis.

B. Metastatic lesions should be resected if possible. Hepatic resection can be done for localized liver metastasis, whereas painful skeletal metastatic lesions can be treated with external radiation therapy or cryoablation therapy. Local tumor irradiation with repeated doses of ^{131}I-MIBG has proven therapeutic value. Radio-frequency ablation of hepatic and bony metastases is effective in selected patients. Transcatheter arterial embolization could be used for widespread liver metastases.

C. For aggressive tumors, combination chemotherapy may be considered.

A chemotherapy regimen consisting of cyclophosphamide (Cytoxan and Neosar), vincristine (Oncovin and Vincasar), and dacarbazine (DTIC-Dome) given cyclically every 21 to 28 days is beneficial but not curative.

VIII. GENETIC TESTING

A. Approximately 25% of sporadic PPGLs can be hereditary. Therefore, it is recommended that **all patients undergo genetic testing**. Because there are approximately 14 PPGL susceptible genes, clinical features should determine which genes should be tested.

B. Because of the high incidence of paragangliomas associated with the *SDH* gene mutation and the high incidence of malignancy associated with SDHB mutation, it is recommended that all patients with paragangliomas test for the *SDH* gene and patients with metastatic disease test for SDHB mutation.

IX. LONG-TERM MANAGEMENT

A. Surgical resection does not guarantee long-term cure. Familial and malignant pheochromocytomas have a higher change of recurrence, but benign small tumors can also recur. Due to this recurrence, PPGL patients need long-term follow-up with biochemical testing and/or imaging.

B. Because of specific phenotype and genotype presentations of PPGL, the Endocrine Society Guidelines recommend personalized management of these patients (including biochemical analysis, imaging, surgery, and follow-up). Examples are (a) *RET* and *NF-1* gene mutation-associated tumors that produce normetapherines and metanephrines. Tumors caused by mutations of VHL and SDH do not produce much metanephrines. (b) In patients with mutations of *SDH* genes, localization should be done to detect extra-adrenal tumors. (c) Surgical approach and extent will depend on the size of the tumor and potential for malignancy. (d) Follow-up may just be biochemical surveillance in most PPGLs or imaging in addition to biochemical surveillance in patients with SDHB mutation. Owing to the complexity and rarity of the disease, PPGL should be best managed by a multidisciplinary team, including an endocrinologist, surgeon, radiologist, genetic counselor, and primary care provider.

X. SUMMARY

PPGLs are rare neuroendocrine tumors that may occur in 25% to 30% of patients as a part of a familial syndrome. The **classic triads** of symptoms are **headaches, palpitations, and sweating**. Patients can have paroxysmal or sustained HTN or resistant HTN. Twenty-four hour urinary-fractionated catecholamines and metanephrines, and plasma-fractionated metanephrines are the required initial biochemical testing. Once biochemical testing confirms the presence of PPGL, imaging with CT or MRI should be done. MIBG scanning can be done if CT and MRI are negative, if the patient has multiple tumors, or when metastatic disease is suspected. ^{18}F-FDG/PET is the most sensitive for detecting metastatic disease. Surgical removal of PPGL is the mode of treatment. p. 225p. 226Preoperative preparation with heart rate, blood pressure monitoring, and fluid management should be started 7 to 14 days before surgery. Malignant PPGLs are tumors that have metastasized to nonchromafin tissue and have a 5-year survival rate <50%. All patients with PPGL need long-term follow-up. Owing to complexity of the condition, personalized management of these patients by a multidisciplinary team is recommended.

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19 Hormonal Hypertension

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I. GENERAL PRINCIPLES

Hypertension is a condition of multifactorial causality that contributes heavily to the risk of coronary artery and cerebrovascular disease, the leading causes of mortality in developed countries. Hypertension is defined as average systolic or diastolic blood pressure above the 95th percentile for age, sex, and height (in children) on at least three occasions, and prehypertension is defined as blood pressures between the 90th and 95th percentiles. In adults, prehypertension is defined as systolic blood pressure from 120 to 139 mmHg or a diastolic pressure from 80 to 89 mmHg. Studies have shown that blood pressure tracking is increased with repetitive measurement. Children with higher body mass index are more likely to continue to have higher blood pressure. In the recent National Health and Nutrition Examination Survey 2011 to 2012, the overall prevalence of hypertension among US adults aged 18 years and older was 29.1% and is similar in both men and women. The prevalence is highest among non-Hispanic black adults (42.1%) compared with non-Hispanic white (29%) and non-Hispanic Asian (24.7%). The prevalence of hypertension increases with age.

II. CHARACTERISTICS OF HORMONAL HYPERTENSION

This chapter deals primarily with hypertension caused by dysfunction of the renin-angiotensin-aldosterone system (Figure 19-1). Other endocrine disorders such as tumors that secrete norepinephrine and/or epinephrine (i.e., pheochromocytoma) and thyroid disorders are covered in separate chapters. To begin suspecting endocrine hypertension, one must be alert to clues that would suggest secondary hypertension, including severe or resistant hypertension, an acute rise in blood pressure, age less than 30 years in nonobese, nonblack patients with a negative family history of hypertension and no other risk factors for hypertension, malignant or accelerated hypertension, and proven age of onset before puberty. For heuristic purposes, hypertension has been categorized by Laragh and colleagues as low-renin hypertension, high-renin hypertension, or normal-

renin hypertension. Only the first category is associated with hypertension caused by disorders of the renin-angiotensin-aldosterone axis (Table 19-1). Low-renin hypertension may comprise a substantial portion of treatment-resistant hypertension, but the prevalence and incidence is not clear.

In this chapter, the following steroid-dependent forms of hypertension are examined. These are summarized in Table 19-1.

A. Low-renin hypertension

1. 11β-Hydroxylase deficiency
2. 17α-Hydroxylase/17,20-lyase deficiency
3. Primary aldosteronism (adrenal tumors or hypertrophy)
4. Familial hyperaldosteronism type 1, e.g., Glucocorticoid-remediable aldosteronism (GRA)/dexamethasone-suppressible hyperaldosteronism
5. Apparent mineralocorticoid excess (AME)/11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) deficiency
6. Liddle syndrome
7. Cushing syndrome

B. High-renin hypertension

1. Renovascular abnormalities
2. Juxtaglomerular cell tumors
3. Bilateral endocrine dysfunction of the kidney

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TABLE 19-1 Forms of Endocrine Hypertension with Suppressed Renin (PRA)

Signs and Symptoms	Hormonal Findings	Source	Geneti
A. Steroidogenic enzyme defects			
Steroid 11β-hydroxylase deficiency (hypertensive virilizing congenital adrenal hyperplasia): ambiguous external genitalia in newborn females; precocious isosexual development/virilization	Low aldosterone, elevated serum androgens/urine 17-ketosteroids; elevated serum DOC (mineralocorticoid) and 11-deoxycortisol (S)	Glandular: ZF of adrenal cortex	Mutatio *CYP1*

and rapid growth in both sexes			
Steroid 17*α*-hydroxylase/17,20-lyase deficiency (congenital adrenal hyperplasia). 46,XY patients have ambiguous or undervirilized external genital appearance, internal blind vagina, no Müllerian derivatives. 46,XX patients have lack of secondary sexual development at puberty and primary amenorrhea	Low aldosterone, low serum/urinary 17-hydroxysteroids; decreased cortisol, increase corticosterone (B) and DOC in plasma: serum androgens and estrogens low, serum gonadotropins elevated	Glandular: ZF of adrenal cortex and interstitial cells of gonads (Leydig cells in testes—ovarian thecal cells)	Mutatio gene
B. Hyperaldosteronism			
Primary aldosteronism associated with aldosterone-producing adenoma (Conn syndrome): muscular weakness; hypokalemia in sodium-replete state	Elevated plasma aldosterone, 18-OHF and 18-oxocortisol (18-OHF and 18-oxoF): normal 18-OHF/aldo ratio	Adenoma (“clear cell” tumor; suppression of ipsilateral 2G)	Somati ion c ~50% childr 2.5:1 fema
Adrenocortical hyperplasia (as above)	Plasma findings as above; hormonal source established by radiologic scan studies	Focal (micronodular/macronodular) or diffuse adrenal cortical hyperplasia (may be unior bilateral)	Possibl aldo- aden
Idiopathic primary aldosteronism (as above); deoxycorticosterone-producing tumor (as above)	High plasma aldosterone elevated 18-OHF/aldo ratio; high plasma DOC	Hyperactivity of ZF of adrenal cortex; adenoma/carcinoma	Somati chan ATPa
C. Glucocorticoid-remediable aldosteronism: hypokalemia in sodium-replete state, familial hyperaldosteronism, Type 1	Elevated plasma (and urinary) aldosterone responsive to ACTH and suppressible by dexamethasone within 48 hr; steroids 18-hydroxy-11-deoxycortisol (18-	Abnormal presence of *CYP11B2* enzymatic activity in adrenal ZF allowing completion of synthesis of aldosterone from 17-deoxysteroids	Hybrid chim *CYP1* gene expre level (regu *CYP1* and (oxida (func

	OHS), 18-OHF, and 18-oxoF elevated in plasma		*CYP1*
D. Apparent mineralocorticoid excess; failure to thrive; cardiac conduction changes; + left ventricular hypertrophy and vessel remodeling; some Ca^{+} ion abnormalities: nephrocalcinosis, rickets	Low plasma ACTH and secretory rates of all corticosteroids; serum F normal because of delayed plasma clearance; extreme hypokalemia and severe early-onset hypertension aggravated by any sodium intake—or by hydrocortisone or ACTH—and responding to spironolactone	High F bioactivity in periphery caused by (a) defective oxidase function (F → E) 11*β*-HSD2 or (b) slow clearance of 5*a/β* reduction to (allo)dihydro-F	Mutatio *HSD1* (plac isofo

ACTH, adrenocorticortropic hormone; DOC, deoxycorticosterone; E, Cortisone; F, cortisol; HSD, hydroxysteroid dehydrogenase; OHF, hydroxycortisol; OHS, hydroxydeoxycortisal; PRA, plasma ZF, zone fasciculata.

III. LOW-RENIN HYPERTENSION

A. Congenital adrenal hyperplasia with steroid 11*β*-hydroxylase deficiency (see Chapter 22). Congenital adrenal hyperplasia (CAH) is a group of autosomally inherited disorder caused by mutation in the genes encoding for steroidogenic enzymes that involve cortisol synthesis. 11*β*-Hydroxylase deficiency CAH is caused by defect in the gene responsible for adrenal cortical 11*β*-hydroxylation, *CYP11B1*, which is responsible for the conversion of 11-deoxycortisol to cortisol and 11-deoxycorticosterone (DOC) to corticosterone in the zona fasiculata (ZF) of the adrenal cortex. DOC, a precursor steroid hormone for aldosterone, is a moderately potent mineralocorticoid that causes sodium retention and volume expansion, resulting in hypertension with suppressed plasma renin activity (PRA). The excess production of adrenal androgens leads to virilization, prenatally in the genetic female and postnatally in both sexes.

The prevalence of steroid 11β-hydroxylase deficiency is approximately 1 in 100 000 births in the general population. It accounts for **5% to 8% of CAH** cases and may be differentiated from the more prevalent form, steroid 21-hydroxylase deficiency by the variable presence of hypertension and absence of salt wasting. The incidence is much higher in Israel (1 in 5 000 to 7 000 births) because of a clustering of cases traced to Jewish families of North African origin, particularly from Morocco and Tunisia, who tend to carry one particular mutation.

1. **Clinical features.** Virilization is the most prominent clinical feature of classic 11β-hydroxylase deficiency. In this condition, inefficient cortisol synthesis provokes adrenocorticotropic hormone (ACTH) hypersecretion. Accumulation of steroids proximal to the blocked 11β-hydroxylase provides substrate for excessive ACTH-stimulated adrenal androgen secretion. An affected female fetus exposed in utero to excess adrenal androgens can develop ambiguous or frankly masculinized external genitalia. The internal female genital structures, including ovaries and uterus, are intact. Postnatally, continued excessive adrenal androgen production can result in progressive penile/clitoral enlargement; premature appearance of axillary, pubic, and facial hair; acne; deepening of voice; and rapid skeletal growth. If adrenal androgens are not suppressed by adequate treatment, early epiphysial fusion results in short stature. Late-onset or nonclassic variants of 11β-hydroxylase deficiency have also been identified with attenuated severity of the features of the classic disorder.
2. **Laboratory findings.** In 11β-hydroxylase deficiency, 11-deoxycortisol (compound S) cannot be hydroxylated to cortisol, and DOC cannot be hydroxylated to corticosterone (Fig. 19-2). Cortisol deficiency leads to endogenous ACTH overstimulation of adrenal androgens that do not require 11-hydroxylation for their synthesis. Dehydroepiandrosterone (DHEA) and androstenedione, themselves weak androgens, are converted mainly in the periphery to testosterone and other sex hormones. Stimulation with exogenous ACTH produces a brisk rise in serum DOC and 11-deoxycortisol to about five times their normal levels, along with elevated levels of DHEA and androstenedione. DOC and its metabolites cause sodium retention, kaliuresis thereby hypokalemia, volume expansion, and hypertension. PRA and,

secondarily, aldosterone are suppressed (Fig. 19-1). A 24-hour collection of urine will demonstrate elevated levels of tetrahydro-11-deoxycortisol and tetrahydrodeoxycorticosterone, the principal metabolites of compound S and DOC. Urinary 17-ketosteroids are also elevated, reflecting the raised serum levels of adrenal androgens.

3. **Treatment.** Glucocorticoid administration corrects oversecretion of ACTH, DOC (largely a product of the ACTH-responsive ZF), and adrenal-derived androgens. The preferred mode of administration in young children is hydrocortisone in a dosage of 10 to 15 mg/m^2/day; postpubertal patients can receive more potent and long-acting steroids, such as prednisone or dexamethasone. Reduction of DOC levels produces natriuresis, diuresis, volume contraction, and a rise in renin, which stimulates aldosterone production. Long-standing hypertension that is unresponsive to glucocorticoid administration might require therapy with other antihypertensive drugs, such as calcium channel blockers. Dietary sodium restriction also helps reduce hypertension in mineralocorticoid-driven p. 230p. 231p. 231p. 232hypertension. Mineralocorticoid supplements should not be administered to hypertensive patients. Females with severe forms of virilizing CAH may undergo surgical reconstruction of the external genitalia.

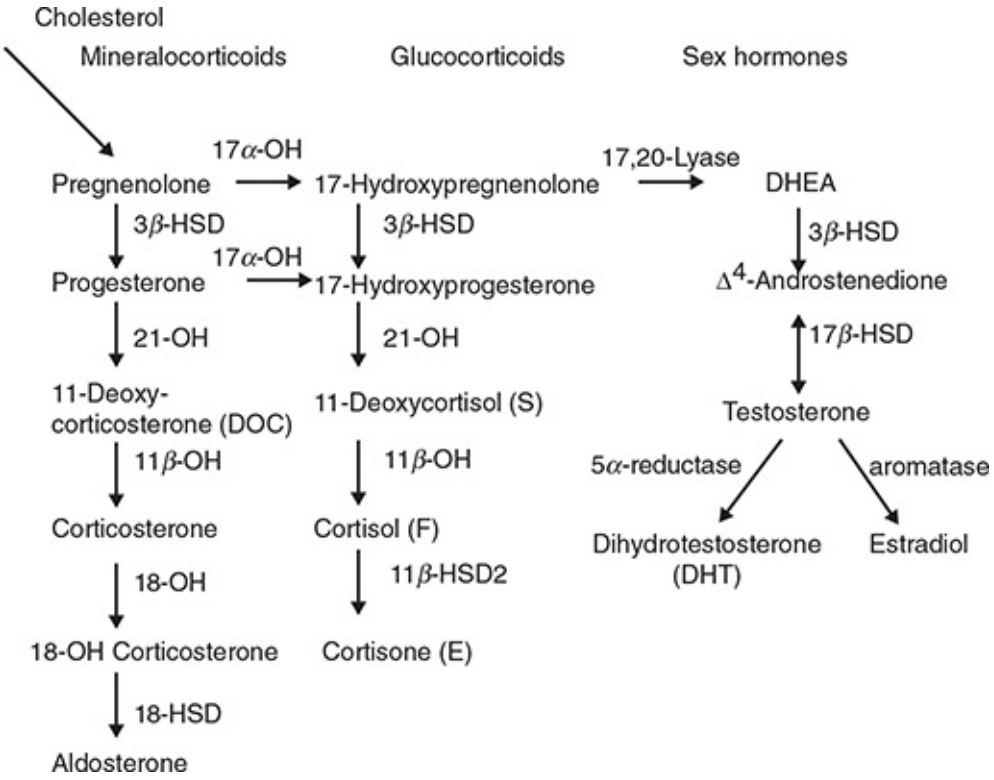

Figure 19-1. Pathways of steroid biosynthesis. ACTH, adrenocorticotropic hormone; DOC, deoxycorticosterone.

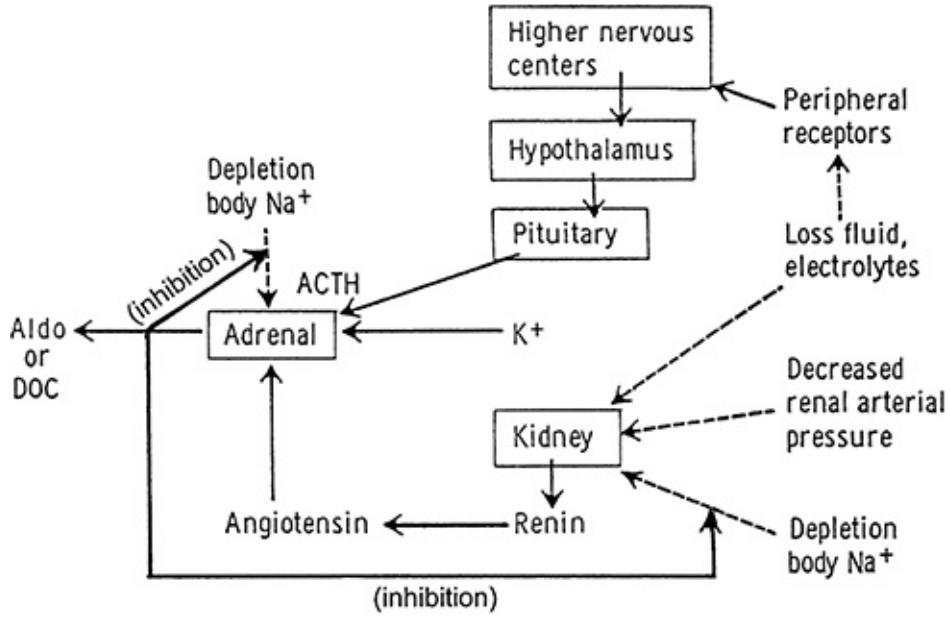

Figure 19-2. Regulation of the renin-angiotensin-aldosterone pathway. DHEA, dehydroepiandrosterone; HSD, hydroxysteroid dehydrogenase; OH, hydroxylase.

4. Genetics. There are two genes (*CYP11B1* and *CYP11B2*)

encoding two isozymes, 11β-hydroxylase and aldosterone synthase. The enzyme 11β-hydroxylase, encoded by *CYP11B1*, is responsible for the conversion of DOC to corticosterone and 11-deoxycortisol to cortisol; this gene is defective in 11β-hydroxylase deficiency CAH. Numerous mutations in *CYP11B1* causing 11β-hydroxylase deficiency have been characterized. The type of mutation and the degree of elevation of DOC does not always correlate directly with the presence or degree of hypertension, even when patients carry identical *CYP11B1* mutations. Mutations in *CYP11B1* tend to cluster in exons 6 through 8, but they have been detected throughout the gene in this autosomal recessive condition. Allelic variants consisting of mild mutations account for the nonclassic forms of this disease. In contrast, aldosterone synthase is encoded by *CYP11B2*, which is responsible for converting corticosterone to aldosterone. A separate set of mutations in *CYP11B2* causes a rare autosomal recessive form of hypoaldosteronism known as *CMO II deficiency* that is characterized by sodium wasting, *hypo*tension, and failure to thrive in infancy. The latter gene and enzyme are intact in CAH due to 11β-hydroxylase deficiency.

B. CAH with steroid 17α-hydroxylase deficiency. Homozygous defects in another adrenal cortical gene, *CYP17A1*, which encodes cytochrome P450c17 enzyme that catalyzes both the 17α-hydroxylase reaction and the 17,20-lyase reaction, cause a different form of hypertensive CAH. This disorder accounts for perhaps 1% of CAH cases.

1. **Clinical features.** Combined deficiencies of steroid 17α-hydroxylase/17,20-lyase enzyme result in diminished production of cortisol and of sex steroids, whereas isolated defects in the 17,20-lyase function impair the production of androgens and estrogens only. **Isolated deficiency of 17,20-lyase activity, therefore, is not a form of hypertensive CAH** but is a potential cause of abnormal sexual development.

   Because the combined defect is shared by the adrenals and the gonads, the production of all androgens and estrogens is reduced. The phenotype of genetic females is unambiguously female. The external genitalia of genetic males are either ambiguous or female, and a number of these patients have been reared as girls. Males have defective development of internal reproductive organs

because blocked androgen production precludes any embryonic Wolffian duct development, whereas intact testicular Sertoli cell production of anti-Müllerian hormone inhibits formation of female structures.

In both sexes, puberty fails to progress normally because of lack of sex steroid secretion. This is in direct contrast to 11β-hydroxylase deficiency that is associated with precocious pubertal development. This diagnosis is often made in young females or apparent females presenting at pubertal age with primary amenorrhea or lack of development of secondary sex characteristics. The disorder can be revealed earlier in 46,XY individuals presenting in infancy or childhood with genital ambiguity, micropenis, hypospadias, and/or cryptorchidism depending on the severity of the mutation. Patients of both genders can also present with hypokalemia and hypertension due to mineralocorticoid excess, that is, DOC and/or aldosterone in this form of CAH.

Massive overproduction of corticosterone at serum concentrations 30 times normal and higher appears to provide for adequate physiologic response to infection or other stress; as a result, these patients do not experience shock and "adrenal crisis."

2. **Laboratory findings.** The 17-deoxysteroids, DOC more so than corticosterone, are increased in serum and urine. As in 11β-hydroxylase deficiency, aldosterone production, although not enzymatically blocked, is very low secondary to the suppressed renin attributable to excess DOC. Plasma ACTH levels are less elevated than in other conditions of impaired cortisol production, perhaps as a result of limited feedback response to the presence of this marginal glucocorticoid activity. Exogenous administration of ACTH results in a 5- to 10-fold rise in serum 17-deoxysteroids, including progesterone and DOC, and a blunted cortisol response.

p. 232p. 233Basal levels of C_{19} steroids, precursors of the sex hormones, are generally low in blood and urine. Gonadotropin production is extremely elevated in both sexes because of the absence of any sex steroid feedback.

3. **Treatment.** Glucocorticoid replacement (as in 11β-hydroxylase deficiency) is necessary to suppress DOC production. Sex steroid replacement is initiated at an appropriate pubertal age. In 46,XY

patients with undescended testes, the testes should be brought down to the scrotum. Estrogen replacement induces breast development in genetic females, and menstrual cycles can be established with cyclic estrogen and progesterone. As in CAH due to 11β-hydroxylase deficiency, refractory hypertension may require additional antihypertensive drug treatment(s) and dietary sodium restriction.

4. **Genetics.** The gene encoding the 17α-hydroxylase and 17,20-lyase activities has been characterized (*CYP17*), and numerous-specific defects have been described in association with various disease phenotypes. Mutations selectively reducing lyase activity have also been identified; such mutations produce genital ambiguity in genetic males and sexual infantilism in females, but they do not induce hypertension. **Polymorphisms causing excess 17,20-lyase activity may contribute to features resembling polycystic ovarian syndrome**.

C. Primary aldosteronism. Primary aldosteronism is the most common specifically treatable and potentially curable form of hormonal hypertension accounting for **5% to 15% of hypertension**. This diagnosis should be considered in individuals under 30 years of age with mild-to-moderate hypertension in the absence of obesity.

1. **Clinical features.** Primary aldosteronism is most often due to a **unilateral aldosterone-producing adenoma** (APA) or bilateral idiopathic adrenal cortical hyperplasia. The prevalence of primary aldosteronism varies between studies, but it is noted to be 5% of newly diagnosed hypertensive patients and potentially up to 20% of treatment-refractory hypertension. Adrenal adenomas are mostly solitary, occurring two or three times more frequently in the left gland; multiple adenomas of clinical significance are observed in 10% of cases, and only one fifth of these occur bilaterally. Primary aldosteronism is exceedingly rare **in childhood and more likely to be caused by bilateral adrenal hyperplasia**.
2. **Laboratory findings.** The diagnostic markers used in characterizing primary aldosteronism are **elevated aldosterone with suppressed PRA**; hypokalemia is an inconstant feature. Owing to assay variability, there are differences in opinions regarding the diagnostic criteria, but most agree with The

Endocrine Society Guidelines. A morning ambulatory ratio of plasma aldosterone (ng/dL) to PRA (ng/mL/hour) >30 at baseline. Guidelines state no single confirmatory test has absolute sensitivity and specificity. Oral sodium loading test, saline infusion test, fludrocortisone suppression test, or captopril challenge tests can all be done to confirm primary aldosteronism. Primary aldosteronism is unlikely if urinary aldosterone is <10 mcg/24 hr with oral sodium loading. With captopril challenge aldosterone would remain elevated and PRA remains suppressed. Aldosterone level >10 ng/dL is consistent with probable primary aldosteronism. Fludrocortisone suppression test would confirm primary aldosteronism if upright plasma aldosterone were >6 ng/dL on day 4 at 10 am provided PRA is <1 ng/mL/hr and plasma cortisol concentration is lower than the value obtained at 7 am. Postural testing is seldom used now. Further characterization and localization of the lesion can be accomplished by computed tomography, followed by bilateral adrenal vein sampling with cosyntropin infusion. CT scan is the preferred method compared with magnetic resonance imaging owing to cost and better spatial resolution.

3. **Treatment.** Unilateral adrenalectomy is indicated in cases of isolated APA; this may be done laparoscopically. Blood pressure should be well controlled with medications before surgery. Bilateral adrenal hyperplasia is better managed with sodium restriction (<100 mEq/day) and potassium-sparing mineralocorticoid antagonists, such as **spironolactone** (starting at doses of 12.5 to 50 mg twice daily and increasing to 100 to 200 mg twice daily) or, in refractory cases, **eplerenone**, p. 233p. 234a more selective mineralocorticoid receptor (MR) blocker (starting dose 25 mg twice daily, maximum 50 mg twice daily). **Amiloride** and **hydrochlorothiazide** may be used as ancillary therapy.
4. **Genetics.** Genetics studies of APAs have found recurrent mutations in genes coding for ion channels (KCNJ5 and CACNA1D) and ATPases that regulate intracellular ionic homeostasis and cell membrane potential. The mutations cause

increased sodium conductance and chronic cell membrane depolarization, which, in turn, promote aldosterone production. Three distinct subtypes of nonadenomatous familial hyperaldosteronism (FH) have been identified. **Type I** FH (FH-I) is described as GRA/dexamethasone-suppressible hyperaldosteronism and is associated with a hybrid aldosterone synthase gene (*CYP11B2*) responsive to ACTH stimulation. **Type II** is not linked to *CYP11B2*, and it is not glucocorticoid responsive. FH-II is five times more common than FH-I/GRA and has been linked to chromosome 7p22 in some families, but others have no such linkage. **Type III** FH was first described in 2008 in a family with early-onset severe arterial hypertension refractory to medical treatment and hypokalemia, and has been linked to mutations in KCNJ5. Somatic mutations in KCNJ5 are also found in APAs.

D. GRA or dexamethasone-suppressible hyperaldosteronism.

GRA, also **known as FH-I**, is inherited in autosomal dominant manner. The diagnosis should be considered in patients with a strong family history of early-onset and severe hypertension, often refractory to first-line antihypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors and β-blockers. Although GRA is usually associated with significant morbidity and mortality at a young age from stroke, some families are more mildly affected.

1. **Clinical and laboratory features.** Affected patients typically experience the onset of hypertension in childhood or adolescence. Blood pressure control may be refractory to conventional drug therapy. As in several other forms of low-renin hypertension, the electrolyte profile may not be helpful, because most patients do not have hypokalemia. Basal upright plasma aldosterone to PRA ratios are generally greater than 30. The unique feature of this familial disorder (unlike adenomatous hyperaldosteronism or FH-II) is complete and rapid suppression of aldosterone secretion with glucocorticoid administration. Plasma aldosterone less than 4 ng/dL after suppression with dexamethasone (orally administered, 0.5 mg every 6 hours for at least 48 hours) is **diagnostic of GRA** although there have been cases of false-positive testing. Elevated urinary 18-oxocortisol is an accurate diagnostic tool, but it is not commercially available; thus, genetic studies are important to avoid unnecessary treatment with dexamethasone. There is no abnormality of cortisol secretion.

Aldosterone and PRA responses to sodium manipulations are similar to those in bilateral adrenal hyperplasia or primary hyperaldosteronism due to adenoma. There is also unusual regulation of mineralocorticoid secretion by ACTH in GRA patients; in contrast to the response to ACTH administration in normal subjects, in whom the aldosterone response diminishes after 3 days, serum and urinary aldosterone levels continue to rise during 5 days of ACTH administration in these patients. Thus, chronic stress with consequent activation of the hypothalamic-pituitary-adrenal axis increases blood pressure in GRA patients.

2. **Genetics.** The genetic basis of GRA is a transposition of regulatory elements specific for *CYP11B1* plus exons 1 to 4 (see above discussion about CAH-11 β-hydroxylase deficiency) onto exons 5 to 9 of *CYP11B2* (Fig. 19-3). The net effect of this mutation is *CYP11B2*, the rate-limiting gene for aldosterone synthesis, and is stimulable by ACTH. Screening of families affected with GRA has identified individuals who carry the mutation with only limited penetrance, confirming that other genetic and environmental factors modify the tendency to develop hypertension, even in the case of a monogenic cause of hypertension.

E. Apparent mineralocorticoid excess

1. **Clinical features.** AME is characterized by severe hypertension manifest in early childhood or even infancy, and is associated with low birth weight, failure to thrive, and poor growth. It is a rare autosomal recessive form of low-renin p. 234p. 235hypertension that is attributable to defects in the 11β-HSD2 enzyme (*HSD11B2* gene). The 11β-HSD enzyme consists of two components: 11-reductase (converting inactive cortisone to cortisol, type 1) and 11-oxidase (converting cortisol to inactive cortisone, type 2). **The 11-oxidase component is defective in AME (Fig. 19-4)**. The disorder appears to occur equally in both males and females. Although the disease is found in all racial and ethnic groups, there seems to be an excess of Native Americans with AME. There is a **high mortality of approximately 20%**, attributed to the unusually malignant

hypertension and severe potassium depletion, resulting in cardiac arrhythmias.

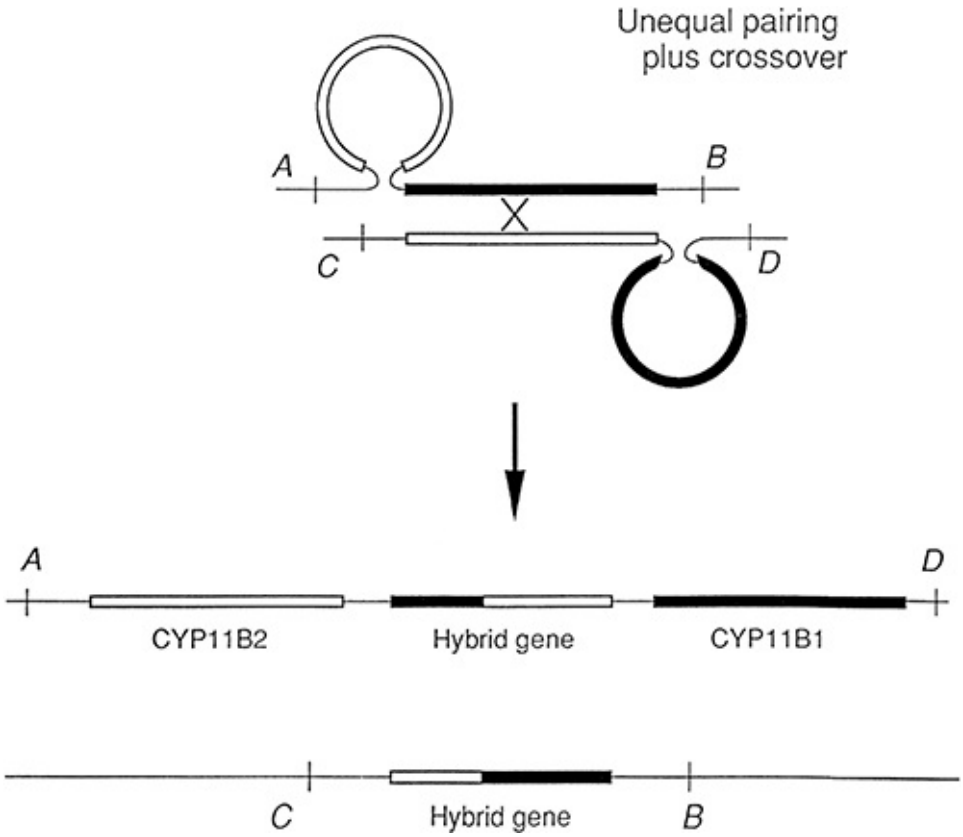

Figure 19-3. Mechanism of misalignment and unequal crossing over in glucocorticoids-remediable aldosteronism (GRA). Note that the gene segment "A–D" contains a third *CYP11* gene with five (regulatory) elements of *CYP11B1* and three (functional) elements of *CYP11B2*. Thus, the hybrid gene is capable of producing aldosterone in response to ACTH stimulation. ACTH, adrenocorticortropic hormone.

Because of the altered enzyme kinetics, the serum half-life of cortisol is prolonged, yet ACTH is suppressed (because of the abnormal cortisol and cortisone ratio at the level of the central glucocorticoid receptors), and patients do not have Cushingoid features. Renal damage may occur due to nephrocalcinosis in some cases. End-organ damage is inevitably observed if hypertension is uncontrolled, which may be reversed by treatment to a limited extent, and some reports of early long-term treatment suggest good response.

2. **Laboratory findings.** The biochemical profile is characterized by low-renin (<1 ng/mL/hour) and profound hypokalemia (<3

mEq/L) with metabolic alkalosis. Diagnosis of the disorder is made on the basis of an **abnormally low serum cortisone and cortisol ratio**; typical patients have abnormal urinary cortisol metabolites (elevation of the THF+5-THF/THE ratio), representing the major metabolites of cortisol (THF, tetrahydrocortisol) and cortisone (THE, p. 235p. 236tetrahydrocortisone). These assays are available in specialized noncommercial laboratories. Aldosterone is suppressed. A diagnostic maneuver used only in research studies is the infusion of cortisol labeled with tritium or deuterium at the 11-carbon position with subsequent measurement of labeled water in the urine. Patients affected with AME cannot oxidize cortisol at the 11-position, and thus they have a markedly reduced capacity to produce labeled water in comparison p. 236p. 237with non-AME hypertensives and controls. Genetic testing is commercially available to confirm the diagnosis.

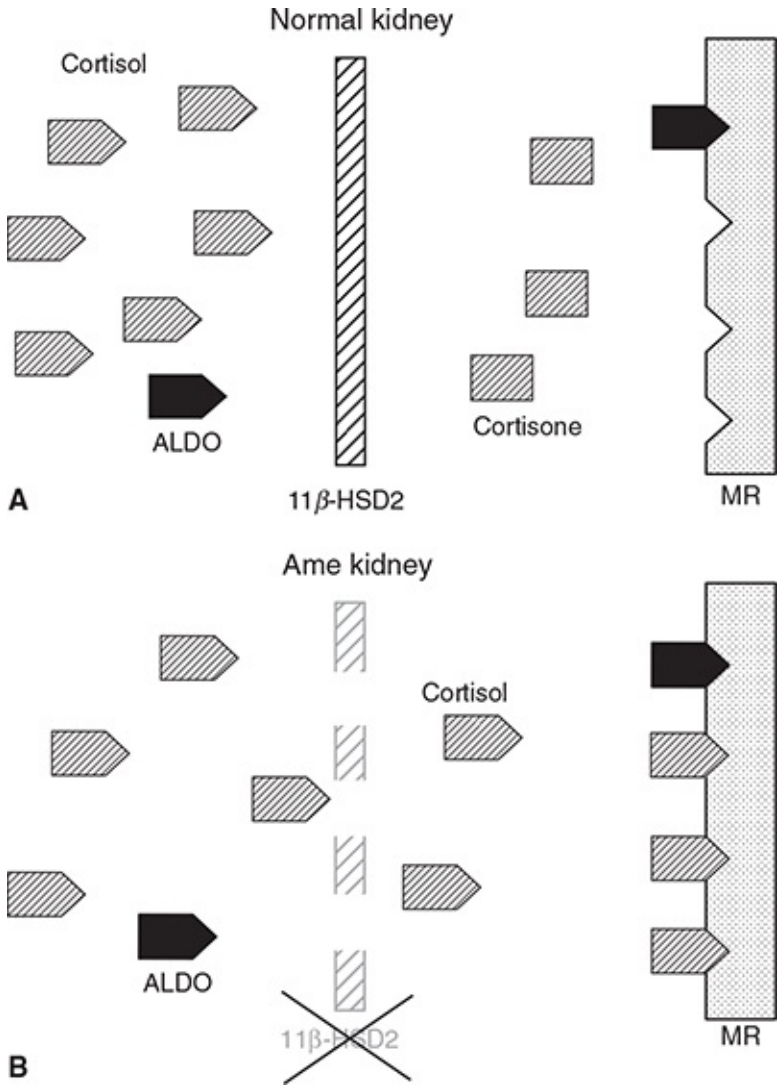

Figure 19-4. The epithelial cell of the cortical collecting duct of the renal distal tubule illustrating the protection mechanism of mineralocorticoid receptors by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). Although aldosterone is a more potent mineralocorticoid than cortisol, the mineralocorticoid receptor binds these hormones with equal affinity. However, cortisol is secreted in milligram amounts daily, whereas aldosterone is secreted in microgram amounts; normal subjects are protected from cortisol overload by the action of 11β-HSD2, because the type 2 isoform of the 11β-HSD enzyme functions unidirectionally to convert cortisol to cortisone **(A)**. Cortisone does not bind to the mineralocorticoid receptor. Aldosterone is not metabolized by the 11β-HSD enzyme because it is a β-lactone and thus has unimpeded access to the mineralocorticoid receptor. However, cortisol saturates the mineralocorticoid receptor in patients with deficient 11β-HSD2 enzyme activity **(B)**. The resulting inappropriate binding of cortisol to the mineralocorticoid receptor causes sodium retention and volume expansion that suppress plasma renin and aldosterone secretion, and causes potassium excretion and hypokalemia.

3. **Treatment.** Mineralocorticoid receptor (MR) blockade with **spironolactone** or **eplerenone**, usually in high doses, results in an initial lowering of blood pressure and an increase in serum

potassium. An addition of **amiloride** or **triamterene** can also blunt mineralocorticoid effects by decreasing sodium channel activity. **Potassium supplementation** is essential to effective management. **Thiazide diuretics** are useful in the event of hypercalciuria and nephrocalcinosis. **Calcium channel antagonists** may also be effective in the adjunctive treatment of mineralocorticoid hypertension. **Kidney transplantation** has now been shown to cause biochemical and clinical cure in a handful of cases.

4. **Genetics.** There is a unique interaction among the two isozymes of 11β-HSD and the MR. The cortisol–cortisone shuttle regulates cortisol availability and binding to the MR. A loss-of-function defect in *HSD11B2* allows cortisol to act as a mineralocorticoid agonist. In brief, the purified MR, or type I receptor, possesses equal affinity for aldosterone and cortisol in vitro. Cortisol is secreted at 1 000 times the rate of aldosterone, yet most people are not hypertensive. The observation that **carbenoxolone** (11β-glycyrrhetinic acid sodium hemisuccinate) and **licorice (glycyrrhetinic acid) produce a hypertensive syndrome** similar to AME through inhibition of 11β-HSD2 suggested that this enzyme was critical to the apparent in vivo specificity of the MR for aldosterone. Enzymatic conversion of cortisol by oxidation at the 11-position to the biologically inert cortisone prevents cortisol access to the MR in the renal cortical collecting ducts; the principal site of expression for *HSD11B2* (Fig. 19-4A). Homozygous defects in *HSD11B2* that result in impaired 11β-HSD2 activity cause the hypertensive syndrome of AME by allowing cortisol to interact ad libitum with the MR (Fig. 19-4B). Numerous mutations in *HSD11B2* have been detected in AME patients and correlated with biochemical phenotype. Interestingly, polymorphisms in or near *HSD11B2* are associated with salt-sensitive essential hypertension. Mild forms of AME have been reported.

F. Liddle syndrome. Liddle syndrome is an autosomal dominant form of low-renin hypertension, distinguished from GRA by **an absence of response to glucocorticoid** treatment and from AME by a **lack of response to mineralocorticoid antagonists** caused by activating mutation in the epithelial sodium channel (*ENaC*, also known as *SCNN1*).

1. **Clinical features and laboratory findings.** These patients often have early-onset **severe hypertension and hypokalemia**. They are not responsive to specific aldosterone antagonists, such as spironolactone. Patients have hypokalemic metabolic alkalosis, **low PRA, and suppressed secretion of aldosterone**. Aldosterone is suppressed even after a low-sodium diet is initiated.
2. **Genetics.** Genetic analysis of the *SCNN1* or *ENaC* gene reveals mutations in the β or γ subunits, which enhances cell-surface ion channel expression or increases channel influx, thereby permitting inappropriate sodium retention and consequent hypertension. Similarly to other genetic forms of genetic hypertension reviewed in this chapter, there is variability in the severity of hypertension even in the same pedigree.
3. **Treatment.** The only effective **treatments are triamterene and amiloride**, which are inhibitors of the distal renal epithelial sodium channel. Blood pressure can be completely normalized; however, the treatment does not affect plasma aldosterone and only partially corrects the low PRA. As in AME, renal transplant has been shown to cause resolution of the symptoms as well as the laboratory abnormalities.

G. Cushing syndrome and disease. Cushing syndrome and disease are additional disorders in which hypertension is associated with adrenocortical hyperfunction. Cushing disease is cortisol excess due to pituitary ACTH-producing adenoma, which is one cause of Cushing syndrome. Cushing syndrome can also be due to iatrogenic causes, adrenal tumors, and, rarely, ectopic ACTH-producing tumors.

1. **Clinical features.** Patients with Cushing syndrome present with moon facies, dorsal fat pad (“buffalo hump”), pigmented striae, hypertension, menstrual p. 237p. 238irregularity, truncal obesity, muscle wasting, impaired glucose tolerance, and low bone mineral density. Children present with growth failure and more often have generalized obesity caused by difference in adipose tissue distribution. Virilization is more common in adrenal carcinomas than in adrenal adenomas. Hypertension is a common finding in Cushing syndrome and occurs in up to 80% of adult cases and about 50% of childhood cases. With iatrogenic Cushing, this is seen in 20% of patients and is dependent on steroid dosage.

The primary cause of elevated blood pressure is probably sodium retention and expansion of extracellular fluid volume secondary to the mineralocorticoid effect of the excess cortisol. Additional factors associated with the hypertension of Cushing syndrome include obesity and insulin resistance. Peripheral vascular resistance is elevated because of a combination of suppression of vasodilators (e.g., prostaglandins and nitric oxide) and stimulation of pressors (e.g., increased plasma renin substrate, angiotensin II receptors, and enhanced sensitivity to norepinephrine). **Aldosterone levels are not usually elevated in Cushing syndrome** and are not likely to be implicated in the hypertension, except in the case of an adrenal tumor co-secreting cortisol and aldosterone. Hypertension can lead to congestive heart failure and cerebrovascular accident in Cushing syndrome. As with many cases of secondary hypertension, the hypertension can persist even after a cure of the primary disorder has been achieved because of chronic renal changes from the long-standing hypertension. Cushing syndrome is rare in children; it is most commonly the result of an adrenal tumor that overproduces glucocorticoid and androgens. In children <**5 years of age, it is also more likely to be malignant**. In adults, pituitary ACTH-dependent Cushing disease is more common.

2. **Laboratory findings**. The diagnosis of Cushing syndrome is suspected based on clinical features. Patients will have elevated midnight salivary cortisol, loss of circadian cortisol variability, high 24-hour levels of urine-free cortisol, and failure to suppress serum cortisol with low-dose dexamethasone. Adrenal Cushing syndrome will have low ACTH with high cortisol and is frequently accompanied by elevated serum and urinary androgens and/or mineralocorticoids. Radiologic studies of the adrenal glands, notably by CT and MRI, are used to document tumors.

   Patients with Cushing disease have elevated serum ACTH levels that suppress with high-dose dexamethasone, whereas ectopic ACTH-producing tumors do not suppress with high-dose dexamethasone. Cushing disease should be confirmed with an MRI with attention to the pituitary and by inferior petrosal sinus sampling to demonstrate laterality of ACTH secretion. Corticotropin-releasing hormone testing, especially when combined with prior dexamethasone suppression, represents

another means of diagnosing this pernicious disease. When ectopic ACTH production is suspected, chest and abdominal imaging should be obtained.

3. **Treatment.** Therapy should be directed at identifying and removing the cause for hypercortisolism. Most often, this entails a **surgical procedure** to remove the primary tumor with or without radiation or chemotherapy. In patients with metastatic ectopic ACTH secretion, bilateral adrenalectomy is recommended. For patients who fail surgical treatment as well as patients who are poor surgical candidates, treatment with drugs that inhibit cortisol synthesis can be effective. **Metyrapone**, which block 11β-hydroxylase, has rapid onset and is effective, but is not commercially available. **Ketoconazole** and **etomidate**, which block several steroidogenic cytochrome P450 enzymes, can be used but require high dosage. **Mifepristone** (RU486), which blocks cortisol action, is also effective.

IV. HIGH-RENIN HYPERTENSION

A. Renovascular abnormalities.

Secondary hyperaldosteronism occurs as a result of oversecretion of renin by the juxtaglomerular apparatus. This occurs in the presence of renovascular abnormalities, most commonly **fibromuscular dysplasia in the pediatric age group**, resulting in renal ischemia. The renovascular abnormality can occur in the main renal artery, in a segmental renal artery, or as a result of coarctation of the aorta. Secondary hyperaldosteronism associated with hypertension can occur p. 238p. 239**after renal transplantation, with genitourinary tract obstruction, or following blunt abdominal trauma**. Intra-abdominal or retroperitoneal **tumors** may cause compression of the renal vasculature with hyperreninemic hypertension. Since the advent of invasive monitoring of premature infants with respiratory distress syndrome, a common **complication of umbilical catheter insertion** has been thrombosis with consequent hypertension. Other medical conditions associated with renal arterial stenosis include **neurofibromatosis and inflammatory arteritides**.

1. **Laboratory findings. PRA** is elevated, accompanied by **high urinary aldosterone** and **low urinary sodium excretion**. Criteria that suggest renal artery stenosis include diastolic blood

pressure greater than 100 mmHg, elevated peripheral vein renin, and an abnormal renal radionuclide scan during ACE inhibitor administration. Although angiography may be used as both a diagnostic and a therapeutic tool, it is an invasive procedure carrying substantial risk of bleeding. Magnetic resonance angiography (MRA) is a noninvasive diagnostic tool, but cannot be used therapeutically. Contrast-enhanced Doppler ultrasound is another useful screening test for patients at risk from renovascular hypertension.

2. **Treatment. Surgical revascularization** has resulted in cure or improvement of hypertension in more than 90% of **pediatric cases with renal artery stenoses**. Percutaneous transluminal renal angioplasty (PCTRA) and renal arterial stent placement have been relatively less efficacious as alternatives to open surgical correction of renovascular lesions. Success rates vary depending on the center and skill of the operator, and potentially carry the risk of vascular perforation. The rate of success with these procedures is also influenced by the extent of disease: patients with bilateral or multiple stenoses are less likely to be cured, and will probably require surgical revascularization. With a single limited stenosis, PCTRA may make the patient amenable to medical management with an ACE inhibitor.

B. Juxtaglomerular cell tumors

1. **Clinical features.** A syndrome consisting of hypertension, hyperreninism, and secondary hyperaldosteronism accompanied by failure to suppress renin with high sodium intake suggests the presence of an autonomous **tumor of the renin-producing juxtaglomerular cells**. Patients with these tumors are often younger than those with essential hypertension and are **usually female**. The diagnosis is made following visualization of a hypovascular mass on an arteriogram or MRA; no arterial stenosis is visible. Other methods of detection include ultrasound, excretory urography, and CT with contrast. In all cases described to date, the blood pressure and plasma renin returned to normal after surgical removal of the tumor.
2. **Laboratory findings. PRA is elevated** and accompanied by **high urinary aldosterone and low urinary sodium excretion; as a result, there is hypokalemia**.
3. **Treatment.** Cure can be achieved with complete tumor resection

by radical or partial nephrectomy, but hypertension may continue if there is established hypertensive angiopathy. The majority of such tumors are benign; recurrences and metastasis are rare.

C. Bilateral endocrine dysfunction of the kidney. In this syndrome, there is severe hypertension, marked hyperreninemia, and hyperaldosteronism. Frequently, there is associated hypertensive encephalopathy and weight loss. The cause of the disorder is unclear. However, hypersecretion of renin occurs equally in both kidneys. The presence of bilateral juxtaglomerular tumors is ruled out by pathologic and arteriographic studies. Treatment should be directed at lowering the blood pressure until remission occurs.

D. Drugs useful in the diagnosis and treatment of high-renin hypertension. Inhibitors of the angiotensin I–converting enzyme are valuable in the diagnosis and treatment of hypertension. In adults with high-renin hypertension, acute **captopril** administration produces a dramatic rise in PRA, a fall in plasma aldosterone, and a fall in blood pressure, reflecting blocked conversion of angiotensin I to angiotensin II. In general, the long-term blood pressure response parallels the acute blood pressure response. In children, the positive predictive value of acute captopril challenge p. 239p. 240with peripheral vein PRA measurement has been estimated at less than 50% for the detection of renovascular disease. Diagnostic accuracy of the ACE inhibitor challenge improves with selective renal vein renin sampling.

Second- and third-generation ACE inhibitors, such as **enalapril and ramipril**, have now been used extensively in **hypertensive children and adolescents**. Diagnosis in such patients has ranged from mild essential hypertension to malignant hypertension of unknown etiology. Although the ACE inhibitors were originally thought to be effective only in high-renin hypertension, they are now favored as first-line agents for various forms of hypertension because of its low incidence of side effects. One important adverse side effect is teratogenicity, and therefore, young women of childbearing potential should be cautioned to use effective birth control. Recent data suggest that cardiovascular morbidity and mortality can be significantly reduced in high-risk older adult patients treated with ACE inhibitors. Salutary effects include improvement in cardiac function in patients with congestive heart failure, reversal of retinopathy, and a decrease in proteinuria in diabetic nephropathy. Patients with diabetic renal disease

show improvement in microalbuminuria and blood pressure when treated with ACE inhibitors. Treatment with an angiotensin II receptor blocker confers similar advantages, including reduced cardiovascular morbidity and mortality.

V. SUMMARY. Although hormonal hypertension accounts for a minority of cases of adult and pediatric hypertension (overall perhaps 1%), making a specific diagnosis can aid in designing an effective therapeutic regimen. Furthermore, understanding the cause of the hypertension can help in identifying other affected family members and in providing anticipatory management and genetic counseling in inherited disorders.

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Use of Salivary Cortisol Assay to Screen for Cushing Syndrome/Disease

Swati Ramteke-Jadhav and Nalini S. Shah

I. INTRODUCTION

The diagnosis of Cushing syndrome (CS) depends on appreciation of a constellation of clinical features and use of appropriate biochemical tests. Although diagnosis in a patient with overt disease is usually easy, appreciating mild CS amid the overwhelming majority of patients with metabolic syndrome and overlapping clinical features of obesity, diabetes, hypertension and menstrual irregularities, is particularly a challenge. There is a need for robust biochemical screening tests to supplement high clinical index of suspicion in such cases. Because abnormality of circadian rhythm is an early indicator of CS, it has been studied as a screening test. Midnight serum cortisol has been shown to have good diagnostic accuracy (subject to the cutoff chosen), but the cost and inconvenience involved in serum sampling have called for easier office-based tests. Late-night salivary cortisol (LNSC) measurement has emerged as simple and reliable biochemical test for screening patients for CS.

II. HISTORY OF SALIVARY STEROID ANALYSIS

Saliva was evaluated as a biological medium for hormonal analysis as early as in 1959 when levels of corticosteroids (mainly 17-hydroxysteroids) were studied in parotid fluid. However, earlier assays were insensitive requiring large volumes of saliva, limiting the acceptance of this technique. The interest in this test was revived in 1978 with description of direct radioimmunoassay (RIA) techniques enabling determination of cortisol in small volumes of saliva. Since then, the assays have advanced with description of automated immunoassays and

mass spectrometric methods.

III. PHYSIOLOGY OF SALIVARY HORMONAL SECRETION

Saliva is a complex fluid produced mainly by three pairs of major salivary glands, (parotid [26%], submandibular [69%], and sublingual [5%]), with a small contribution from gingival crevicular fluid that comes from the tooth gum margin (0.5%). Plasma exudate from minor abrasions or oral wounds contributes variably to the salivary constituents. Specifically, for lipid-soluble hormones like cortisol, the major route of entry into the saliva is the passive diffusion across acinar cell membranes. This process achieves rapid equilibrium between concentration of free cortisol in plasma and that in saliva, thus making it independent of the salivary flow rate. In addition, it is important to consider spurious elevations in the salivary cortisol levels caused by application of some steroid gels/medications and gingival abrasions or infections.

IV. METHODOLOGICAL DETAILS

Several important preanalytical variables need to be considered in evaluation of salivary cortisol levels.

A. Precollection precautions

Precautions to be followed before sample collection include avoiding brushing teeth, smoking or chewing tobacco (because smokers have higher cortisol levels than do nonsmokers), eating or drinking anything except water, and vigorous physical activity for up to 2 hours before collection. Fresh cuts or wounds should be looked for, use of oral medications/gels should be enquired, and patients should be advised to rinse p. 243p. 244the mouth with tap water to avoid potential contamination. Effect of gingivitis, oral sores, or injury on salivary cortisol levels is not known.

B. Collection devices

For most adults, collection of small quantities of saliva is generally not a problem. However, for infants, elderly, or disabled people and those with critical illness, this might sometimes be challenging. Hence, the use of some agents like lemon juice or citric acid has been proposed to stimulate saliva production. However, these agents have been variably shown to interfere in cortisol estimation, and their use should probably be avoided. The collection methods involve direct spitting or drooling into plain plastic containers, suctioning out in infants, and use of the

more aesthetically appealing salivette collection systems. These consist of polyester, polythelene, or a cotton swab that needs to be chewed (30 seconds to 3 minutes, holding 1 to 3 mL of saliva) and collected in tubes. The different methods have some bearing on the cortisol estimation, and consistency in using the same method for repeated estimations is important.

C. Storage conditions

Immediately after collection, the sample can be stored at room temperature and transported to laboratory on the next day. The cortisol levels have been shown to be stable at room temperature for 7 days, at 4°C (i.e. in a regular household refrigerator) for up to 1 month, −20°C for up to 3 months, and at −80°C for a year.

D. Centrifugation, freezing–thawing cycles

At the laboratory, samples are either frozen at −20°C or centrifuged before storing, to be thawed and recentrifuged before analysis, so that the cleanest analytical sample can be obtained. The centrifugation protocols (from 800 to 4 000 g for 2 to 20 minutes) have not been standardized.

E. Assays

Salivary cortisol has been mostly measured by immunoassay methods —first RIA, followed by enzyme-linked immunosorbent assay, then automated electrochemiluminescent assays, and, more recently, by liquid chromatographic methods coupled with mass spectrometry (LC–MS). Although each method has its unique advantages and disadvantages, the overall performance of LNSC in diagnosis of CS by any of the methods is comparable (Table 20-1). The simplicity, greater availability (clearance by the US Food and Drug Administration), less expensiveness, small sample volume, and, most importantly, better diagnostic sensitivity (90% to 100%) and specificity (90% to 100%) are the advantages of immunoassays. However, cross-reactivity with endogenous cortisol metabolites and synthetic steroids is sometimes disadvantageous. LC–MS, on the other hand, is technically demanding, involves difficult instrumentation, has limited availability, and cost high. However, its high analytical ability comes at a cost of mildly reduced diagnostic accuracy for CS (sensitivity and specificity 83% to 92%) (Table 20-1). It has an advantage of specifically measuring cortisol alone and the ability to differentiate cortisol from cortisone and other synthetic steroids, which might be helpful in cases of sample contamination or iatrogenic CS.

F. Local reference range

The reference ranges for LNSC provided by different laboratories and study groups vary widely because of heterogeneity in the assay used, the methodology of salivary sample collection (salivettes vs. cotton swabs), the setting (outpatient vs. inpatient), the different categories of controls used (obese vs. pseudo-Cushing), and the statistical methods employed to derive the cutoffs (arbitrary vs. using receiver operating characteristic). In addition, the ethnic/racial differences in the circadian cortisol rhythm are well established. Considering these factors, and the absence of an external proficiency-testing scheme or a certified reference material for cortisol in saliva, it has been emphasized that each center should establish a reference range for an LNSC assay that is specific for its population and the assay.

G. LNSC in the diagnosis of CS

Studies have shown good sensitivity and specificity of LNSC (Table 20-1) as a diagnostic test for CS. Moreover, LNSC has the advantage of stress-free, noninvasive, easy, home-based collection and reflection of free unbound cortisol. The Clinical Guidelines Committee of The Endocrine Society recommended the use of LNSC p. 244p. 245p. 245p. 246as one of the first-line tests for screening and confirmation of CS. It recommended measuring at least two LNSCs for the diagnosis of CS, considering the intraindividual variability of LNSC (11% to 50% in normal subjects as well as in patients with CS). Such variability can be ascribed to assay-related issues or a true biologic variation in tumoral adrenocorticotropic hormone secretion.

TABLE 20-1 **Performance of Late-Night Salivary Cortisol for Diagnosis of CS Various Studies**

First Author	CS (CD, Adrenal Origin, Ectopic)	Controls	Method of Saliva Collection	Assay/ Analytical Sensitivity (nmol/L)	Cutoff (nmol/L)	Method of Deriving Cutoff	Sensitivity (%)/ Specificity (%)
Raff, 1998	39 (30, 5, 4)	39 PCS 73 H	Salivettes	RIA, 0.4	3.6	97.5th percentile of controls	92/–
Castro, 1999	33 (20, 13, 0)	18 obese 30 H	Direct spitting in plastic tubes	RIA, 1.71	4.6 7.72	90th percentile of the normal control 90th percentile of the obese controls	100/87.8 93.3/93.3
Papanicolaou, 2002	122 (98, 12, 12)	34 H, 21 PCS, 23 nonadrenal disorder controls	Expectoration in plastic tubes	RIA, 2.2–5.8	15.17	To optimize specificity to 100%	93/100
Putignano, 2003	41 (33, 7, 1)	27 H 33 PCS, 199 obese	Salivette	RIA, 1.4	9.7	ROC curve	92.7/93.1
Yaneva, 2004	63 (37, 17, 9)	54 obese	Salivettes	RIA, 0.83	5.52	To maximize sensitivity to 100%	100/96
Viardot et al., 2005	12 (5, 3, 4)	16 obese, 20 H, 14 unconfirmed CS, 20 pregnant, 5 treated CS	Salivettes	RIA, 0.8	6.1	ROC to optimize sensitivity (pregnant and treated CS excluded)	100/100
Friedman, 2007	24 (24, 0, 0)	22 PCS	NR	ELISA, NR	4.3	Previously described	45/95
Kidambi, 2007	11 mild CS (9, 2, 0)	NR	Salivettes	ELISA, NR	4.3	Previously described	NR
Baid, 2007		261 obese	Salivettes	RIA, 1.4 LC–MS, 0.11	4.7 2.8	Laboratory provided reference range	–/82 –/86
Restituto, 2008	22 (NR)	89 H, 67 PCS	Chewing cotton wool	ELISA, 0.027	2.21	ROC curve	88/82
Doi, 2008	27 (5, 11, 4) (7 SCS)	11 PCS, 16 H	Salivettes	RIA, 1.38	5.8	ROC curve to optimize specificity	93/100
Cardoso, 2009	21 (11, 9, 1)	60 obese, 61 H	Direct spitting	RIA, 0.5	3.8	ROC curve to optimize sensitivity	100/97.5
Nunes et al., 2009	13 CS, 14 subclinical CSr, 23 SCSA	42 obese 25 NSA	Salivettes	RIA, 0.9	12 (diagnosis of CS) 8 (diagnosis of subclinical CSr) 4.8 (diagnosis of SCSA)	ROC curve	100/100 90/98.1 77/69.1
Carrozza, 2010	21 (15 ACTHD, 6 adrenal)	12 PCS, 25 H	Salivette	ECLIA, 0.6	8.3	ROC curve	100/97.4
Zerikly, 2010	38 (32, 6, 0)	52 PCS, 18 H	Direct spitting in plastic tube	LC–MS, NR	2.95	ROC curve	92.1/92.1
Jeyaraman, 2012	33 (22, 7, 3, 1 occult)	37 PCS, 56 H	Salivette	ECLIA, 0.5	10.87 4.55	97.5th percentile ROC curve	69.23/100 93.9/81.1
Erickson, 2012	47 (37, 2, 8)	202 PCS	Salivettes	LC–MS, 0.11	2.1	ROC curve	83/84.2
Ceccato, 2013	82 (52, 17, 13) 27 CD in remission	73 PCS, 104 H	Salivette	RIA, 1.37	5.24	ROC curve	96.3/97.1
Bukan et al., 2015	28 (28, 0, 0)	30 H, 37 obese	Direct drooling in plastic tubes	RIA, 0.082	2.92 (diagnose CD vs. H) 5.04 (diagnose CD vs. obese)	ROC curve	100/96.7 96.4/100

ACTHD, adrenocorticotropic hormone deficiency; CD, Cushing disease; CS, Cushing syndrome; CSr, Cushing syndrome due to recurrence of Cushing disease; ECLIA, electrochemiluminescence assay; ELISA, enzyme-linked immunosorbent assay; H, healthy volunteers; LC–MS, liquid chromatography–mass spectroscopy; NR, not reported; NSA, nonsecreting adenomas (adrenal adenoma); PCS, pseudo-Cushing syndrome; RIA, radioimmunoassay; ROC, receptor operating characteristics; SCSA, subclinical cortisol-secreting adenomas (adrenal adenoma).

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H. Effect of age and comorbidity

LNSC has been shown to have good sensitivity (95%) and specificity (100%) to diagnose CS in children as well. However, LNSC levels are significantly higher in elderly (>60 years of age) and those with multiple comorbidities, signifying careful selection of age and comorbidity-specific thresholds for diagnosis of CS in this cohort.

I. Pregnancy and patients on oral contraceptive pills

In patients who are pregnant or on oral contraceptive pills, estrogen-

mediated increase in cortisol-binding globulin levels interferes with interpretation of dexamethasone-suppression tests. Because LNSC reflects unbound free cortisol levels, it is especially useful in this setting. LNSC has been shown to have good sensitivity (95%) and specificity (95%) for diagnosing CS in women on oral contraceptive pills. However, because of a higher resetting of the hypothalamic–pituitary axis in late pregnancy, the LNSC levels are significantly higher as compared with nonpregnant subjects. This results in lower specificity (75%) of LNSC in diagnosing CS in pregnant women and the need to exercise caution in this group.

J. Adrenal incidentaloma and subclinical CS

With increasing use of advanced imaging, the prevalence of serendipitously detected adrenal incidentalomas is rising. These adrenal tumors may be associated with mild cortisol secretion with biochemical evidence of cortisol excess, but absence of hard signs of CS, the so-called subclinical CS (SCS). Various studies have uniformly shown a poor performance of LNSC in diagnosing SCS with sensitivity of 22% to 80% and specificity of 30% to 87%. However, it should be noted that the SCS represents the clinical state where cortisol secretion is intermittent and/or of such low quantum as to defy detection with most of the tests of the hypothalamic–pituitary–adrenal axis, which explains the poor performance of LNSC in these patients.

K. Cyclical CS

Cyclical CS is a rare entity characterized by intermittent episodes of cortisol excess interspersed with periods of normal levels lasting for days to years. Given the rarity of this entity, the systematic study of diagnostic accuracy of LNSC in this setting remains to be performed. However, repeated measurements of LNSC over a period of time have been proposed as an efficient way to diagnose cyclical CS.

L. Postoperative follow-up for recurrence of Cushing disease

Few studies have evaluated the performance of LNSC to detect recurrence of Cushing disease on follow-up after surgery. Because reversal of the circadian rhythm is the earliest abnormality, these patients with early recurrence are supposed to have mild CS, and LNSC has been shown to have good sensitivity (80% to 90%) and specificity (90%) in diagnosing subclinical recurrence.

V. CONCLUSION

LNSC serves as a convenient, inexpensive test with good performance in diagnosis of CS under various circumstances. However, consideration needs to be given to methodological details and establishment of an appropriate reference range.

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21 Adrenal Hormones during Acute and Chronic Illness: Evaluation and Treatment

Eva Boonen and Greet Van den Berghe

I. HYPOTHALAMIC–PITUITARY–ADRENAL AXIS ACTIVATION IN ACUTE AND CHRONIC STRESS CONDITIONS

The adrenal gland plays a central role in the normal stress regulation. It consists of both the steroid-producing adrenocortical cells and catecholamine-producing chromaffin cells. Stress stimulates the hypothalamic–pituitary–adrenal (HPA) axis, followed by the release of corticotropin-releasing hormone (CRH) from the hypothalamus (Fig. 21-1A). CRH reaches the anterior pituitary corticotrophs to induce adrenocorticotropic hormone (ACTH) secretion, which stimulates adrenal glucocorticoid production by binding to the melanocortin-2 receptor (MC2R) and activating MC2R–mediated postreceptor effects (Fig. 21-1B). Cortisol itself mediates by negative feedback inhibition homeostasis at the level of CRH and ACTH and turns off this activation of the HPA axis.

The responses of the HPA axis to several stressors have been studied in different contexts including not only major surgery and acute infections, but also chronic infections, autoimmune diseases, metabolic syndrome, and affective and mood disorders. Besides an immediate effect on glucocorticoid production, ACTH also increases the longer term steroidogenic capacity of the adrenal cells by upregulating proteins important for steroidogenesis (Fig. 21-1B). Furthermore, animal studies found structural changes in the adrenal gland during stress, such as hypervascularization of the already highly vascularized adrenal glands.

In conditions of chronic stress, a continued stimulation of the adrenal gland can cause adrenal hypertrophy, which is considered to be an adaptive response essential for the continued provision of cortisol in proportion to the sustained higher requirements of glucocorticoid effects. This was observed in patients who suffer from the metabolic syndrome,

and patients suffering from depression were shown to have hyperplastic adrenal glands.

II. HPA-AXIS RESPONSE DURING CRITICAL ILLNESS

Critical illness is an extreme example of sustained and severe physicial stress; therefore, one would expect that the elevated plasma concentrations of cortisol are also accompanied by high plasma ACTH concentrations stimulating an increased adrenocortical cortisol production. Only few studies report plasma concentrations of ACTH during critical illness. Furthermore, they only reported ACTH measured at one single time point, which holds limited information given the pulsatile secretory pattern and the circadian rhythm of the hormone. Vermes et al. reported daily plasma ACTH and cortisol concentrations measured during the first week of critical illness in patients suffering from trauma or sepsis and documented **acutely elevated plasma ACTH concentrations**, followed by a steep fall in plasma ACTH after 3 days of critical illness. More recently, in a more heterogeneous critically ill patient population, plasma ACTH concentrations were uniformly low, already from the first day of intensive care unit (ICU) stay onward throughout the first week of critical illness. Furthermore, a small study by Polito et al. reported reduced *ACTH mRNA* levels in nine human postmortem pituitary glands from patients who died after septic shock as compared with patients who died suddenly from other diseases, with no compensatory rise in the expression of CRH or vasopressin in the hypothalamus. This was also observed in experimental models of sepsis, with reduced ACTH expression levels in the more chronic phase of critical illness. Nitric oxide or p. 249p. 250p. 250p. 251suppressed orexin was suggested as possible mediators, yet it currently remains unclear what is driving the low ACTH levels in the face of high plasma cortisol. Moreover, if suppressed pituitary ACTH expression was a primary manifestation of organ damage due to shock, this would also cause abnormally low plasma cortisol concentrations, which was not observed in patients.

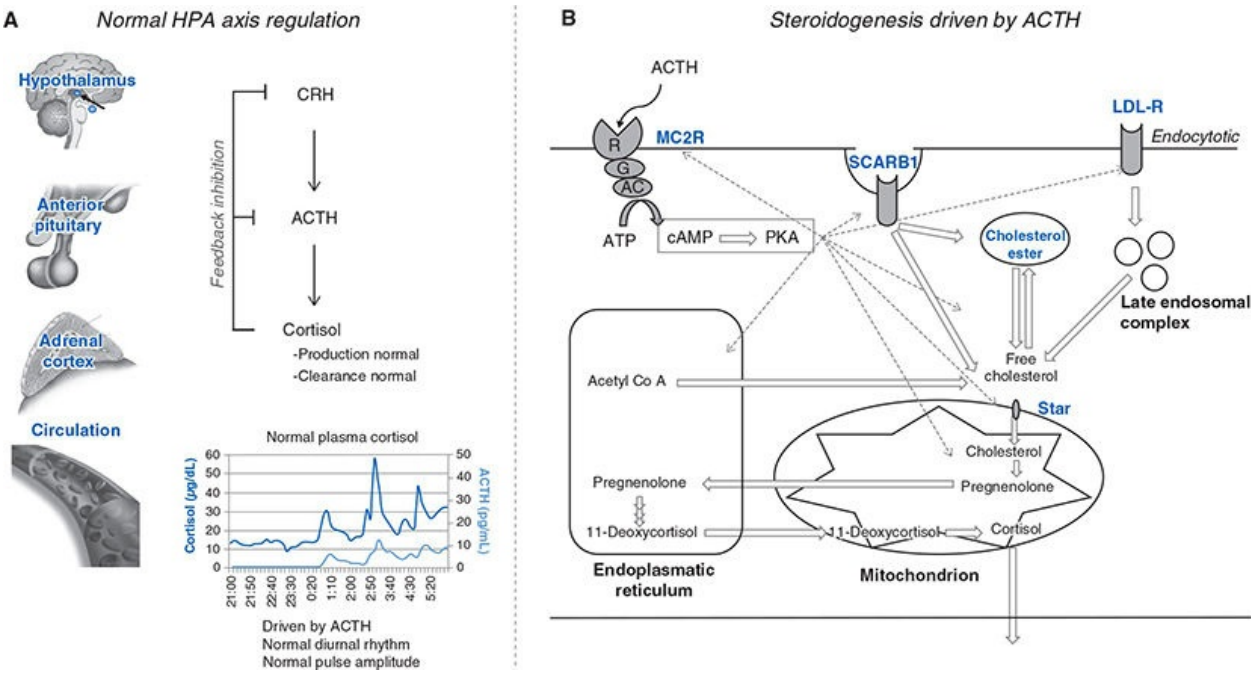

Figure 21-1. **A.** HPA-axis regulation during health. **B.** Steroidogenesis in the adrenal cell with LDL receptor (LDLR), scavenger receptor B1 (SCARB1), hormone-sensitive lipase (HSL), acyl coenzyme A: cholesterol acyltransferase (ACAT), cholesterol esters (CE), HMG coenzyme A reductase (HMGCR), steroid acute regulatory protein (STAR), and cytochrome P450 cholesterol side-chain cleavage enzyme (CYP11A1), with gray dotted arrows indicating ACTH effects. ACTH, adrenocorticotropic hormone; LDL, low-density lipoprotein; HPA, hypothalamic–pituitary–adrenal.

Another possible explanation for the ACTH–cortisol dissociation could be increased adrenocortical sensitivity to ACTH. However, the adrenocortical cortisol secretory response during critical illness in response to exogenous ACTH is often low, as measured by the ACTH stimulation test and unchanged to any given endogenous plasma ACTH level. Furthermore, it was recently shown that ACTH signaling was unaltered during the first week of critical illness in postmortem human adrenal glands, but severely suppressed in the prolonged phase.

A role for non-ACTH stimulators of cortisol production in the adrenal cortex has often been suggested. Cytokines, neuropeptides, and other mediators were studied in animal and cell culture studies. Yet, cortisol production itself was never quantified, until recently, and increased cortisol production was assumed only on the basis of extrapolation from the increased circulating (free) cortisol levels. Recently, however, cortisol production was quantified during critical illness and showed that daytime cortisol production during critical illness was less than double the cortisol production during health. A subsequent study showed that nocturnal cortisol secretion was even lower than in

healthy subjects, suggesting that a 24-hour cortisol production rate in many critically ill patients with high plasma cortisol levels may not be much higher than in healthy controls.

Finally, the observed high plasma cortisol concentrations could also be explained by reduced cortisol metabolism. Indeed, cortisol breakdown was recently shown to be substantially reduced, which resulted in a fivefold longer half-life of cortisol and which explained the high plasma cortisol levels. Furthermore, this reduced cortisol breakdown was accompanied by suppressed expression and activity of A-ring reductases in the liver and by suppressed activity of 11β-hydroxysteroid dehydrogenase type 2 in the kidney.

In this concept, the low plasma ACTH concentrations may well be explained by negative feedback inhibition induced by elevated plasma cortisol caused by reduced cortisol breakdown.

III. ADRENAL FUNCTION DURING CRITICAL ILLNESS

Considering the important function of the adrenal gland in mediating the human response to stress, an adequate adrenal function is indispensable to survive critical illness. As a consequence, impaired function of the adrenal gland has important implications, stressing the importance of detecting and treating this problem. For quite some time now, adrenal insufficiency has been pragmatically dichotomized into two different "disorders": "absolute" adrenal insufficiency and "relative" adrenal insufficiency.

A. Absolute adrenal insufficiency in critical illness

Absolute adrenal insufficiency can be further divided into primary, secondary, and tertiary adrenal failure. Diseases with the abnormality located within the adrenal cortex itself are labeled "primary" adrenal insufficiency, whereas adrenal dysfunction due to pituitary abnormalities is called "secondary" adrenal insufficiency. Insufficient CRH secretion can cause tertiary adrenal insufficiency, with long-term, high-dose glucocorticoid therapy, being the most common cause of such tertiary adrenal insufficiency.

During critical illness, patients with a prior history of adrenal insufficiency are at risk to develop an Addisonian crisis triggered by the stress of the disease. Furthermore, critical illness itself can evoke new-onset absolute adrenal failure. For example, it may be due to adrenal hemorrhage, for which ICU patients may be at higher risk given the coagulation/endothelial disorders present in many types of

severe illnesses or because of several medications frequently used in the ICU that affect cortisol production, such as **etomidate**.

B. Relative adrenal insufficiency in critical illness

In contrast, relative adrenal insufficiency refers to a functional and likely transient, insufficiently activated HPA axis during critical illness, irrespective of the level of p. 251p. 252hypercortisolism that is present. In this condition, the degree of HPA-axis activation is assumed to be not enough to cover the need of cortisol to survive, even when plasma cortisol levels are still higher than during health. Later, the term “critical illness-related corticosteroid insufficiency” (CIRCI) has been introduced as an alternative, indicating that this “relative insufficiency” can occur at any level of the HPA axis and/or may be due to resistance to cortisol in the peripheral target tissues. The possible underlying mechanisms remain highly debated, yet different suggestions were made.

Pro-inflammatory cytokines, impaired blood supply to the anterior pituitary gland or adrenal gland, accumulation of nitric oxide, several neuropeptides, oxidative stress, altered adrenal blood flow, cortisol precursor deficiency caused by low circulating cholesterol levels, or medications that suppress cortisol synthesis have also been suggested to play a role. Target tissue resistance to cortisol, the second part of the definition of CIRCI, could be evoked by decreased glucocorticoid cellular uptake or suppressed expression or activation of the glucocorticoid receptor. Furthermore, low corticosteroid-binding globulin (CBG) levels and decreased CBG affinity may impair cortisol transport.

C. Diagnosis of adrenal insufficiency

Initial diagnosis of suspected adrenal insufficiency starts with the clinical presentation. **Hypotension** refractory to fluid resuscitation and vasopressors may be signs of both absolute and relative adrenal failure, especially when this occurs in a patient who also has hyperpigmentation, hyponatremia, or hyperkalemia. Absolute adrenal failure is further characterized by **low plasma cortisol concentration** with or without a low plasma ACTH concentration and a **suppressed cortisol response to an ACTH stimulation test**.

Diagnostic criteria for CIRCI in critically ill patients remain controversial. A landmark study by Annane et al. suggested a plasma cortisol incremental response <9 μg/dL after the injection of 250 μg ACTH in the face of a high baseline plasma cortisol concentration (>34 μg/dL) as most discriminative for an increased risk of death. However, these findings have not been replicated by other investigators. Furthermore, even the dose of ACTH, used for the ACTH stimulation test, was discussed because **250 μg of ACTH** leads to supraphysiologic ACTH levels and could, therefore, overcome any ACTH resistance. Alternatively, a low dose has been **proposed (1 μg),** but the results of these studies have been conflicting.

The use of a random total plasma cortisol concentration <10 μg/dL during critical illness has also been described. However, total plasma cortisol concentration is the result of adrenal production, secretion, distribution, binding, and elimination of cortisol, and cortisol is secreted in a pulsatile manner. Assessing the adrenal cortisol secretion rate with one single random cortisol measurement thus seems virtually impossible. Finally, a lack of accuracy and a high interassay variation in cortisol assays further limits the use of one cutoff value of cortisol in clinical practice to define CIRCI.

Plasma-free cortisol has also been suggested to be more appropriate because free cortisol is the active form of cortisol. Yet, accurate plasma-free cortisol assays are currently not clinically available, and “normal” levels of free cortisol during critical illness have not been defined.

Measuring **interstitial cortisol** levels with a microdialysis catheter inserted in the subcutaneous adipose tissue in critically ill patients was recently introduced to assess the amount of cortisol availability for target tissues. However, the usefulness of this invasive technique remains unclear because edema is frequently present in the critically ill, regional blood flow is variable, and it is unclear what the subcutaneous adipose tissue tells the clinician about the other target tissues of interest in the critically ill.

D. Treatment of adrenal insufficiency

Patients with an established diagnosis of primary or secondary adrenal failure or patients on chronic treatment with systemic glucocorticoids before critical illness should receive additional coverage with hydrocortisone to cope with the acute stress of the disease.

Furthermore, patients with an acute Addisonian crisis in the ICU are typically treated with high doses of glucocorticoids. This therapeutic strategy is based on the **assumption that cortisol production during critical illness should be increased several fold as compared with the normal production during health, an assumption that was recently invalidated**.

The treatment of CIRCI is even more controversial because two large randomized controlled trials (RCTs) gave conflicting results. The first large trial by Annane et al. investigated treatment on the basis of the results of an ACTH stimulation test in 300 patients with septic shock on vasopressor therapy. All patients were randomly assigned to be treated with placebo or with 200 mg hydrocortisone plus 50 μg fludrocortisone per day for 7 days. The study showed that glucocorticoid treatment reduced the duration of vasopressor therapy and reduced 28-day mortality by an absolute 10% in the subgroup of patients with a low cortisol incremental response to the ACTH stimulation test. However, the relevance of this subgroup analysis has been criticized as well as the widespread use of etomidate during this study. The second large RCT included 499 patients and investigated the impact on 28-day mortality of 200 mg hydrocortisone daily or placebo for 5 days followed by a tapering-down period. This study revealed that hydrocortisone treatment improved survival neither in the nonresponders to an ACTH stimulation test nor in the entire population. In fact, more septic shock relapse was observed in the treatment group. In addition, this study was criticized, mainly for its early stop owing to slow patient recruitment, which reduced the statistical power of the trial.

Smaller nonconclusive studies followed, explaining the ongoing controversy. A systematic review evaluated all high-quality RCTs and concluded that hydrocortisone therapy does not reduce mortality of patients with severe sepsis. Recent guidelines also advise to only treat patients suffering from hypotension that is refractory to vasopressor or fluid resuscitation and then use a hydrocortisone dose of 200 mg/day for a limited period of time.

E. Unraveling adrenal failure

Despite numerous studies investigating diagnosis and treatment of adrenal insufficiency during critical illness, the pathophysiology of this

disease remains incompletely understood, which is the most likely explanation for the ongoing controversy.

Adrenal failure was originally interpreted as a deficient cortisol production, and, as a consequence, treatment strategies were designed to cover this failing cortisol production. However, because it was recently shown that cortisol **production is not or only slightly elevated during critical illness**, the downsides of treating patients with hydrocortisone at a dose that is equivalent to sixfold the daily cortisol production may have outweighed any anticipated benefit. Also, the reduced cortisol breakdown shown to be present in critically ill patients may have substantially increased that risk.

The low ACTH levels uniformly present in sustained critical illness could be explained by negative feedback inhibition evoked by circulating cortisol that is high because it is not being metabolized. Initially, these low levels are likely adaptive and harmless because hypercortisolism is maintained via reduced breakdown. However, if ACTH levels remain suppressed for several weeks, this could have adverse consequences for the integrity of the adrenal cortex, given the importance of ACTH as a trophic factor for the structure and function of the adrenal gland. This impact was recently investigated in adrenal cortex biopsies harvested postmortem from acute and prolonged critically ill patients compared with acute out-of-hospital deaths as controls. This study showed a very pronounced depletion of cholesterol esters and suppressed expression of ACTH-regulated genes in adrenal glands of prolonged, but not acute, critically ill patients, suggestive of adrenal atrophy in the long-stay patients. This phenotype is highly reminiscent of a pro-opiomelanocortin-deficient mouse model that also develops adrenal atrophy.

IV. IMPLICATIONS OF THE NEW DATA

Integrating new study results with previous knowledge may offer a new context for improving diagnosis and treatment of adrenal insufficiency in the ICU. Although these need further validation, we propose here a **model to consider** for future studies.

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TABLE 21-1 **Preliminary Recommendations and Suggestions for Further Research**

Determining Patients at Risk

Acute phase	Little or no evidence to support the presence of "relative adrenal failure" requiring treatment
Chronic phase	• Symptoms consistent with adrenal failure • Progressive decrease of plasma cortisol • Progressive decrease of the cortisol incremental response to repeated ACTH stimulation tests over time

Treatment recommendations

Perhaps 60 mg of hydrocortisone per day suffices?

A tapering down to the lowest effective dose as soon as possible

Preliminary rule of thumb of the ICU of the authors

Critically ill patients. . .

Who are in the ICU for more than **6 d**

With symptoms—unexplained vasoplegia and/or coma for example

With progressively decreasing plasma baseline cortisol concentrations **less than 6 μg/dL**

With an incremental cortisol response to an ACTH stimulation test of **less than 6 μg/dL**

Evidently, these specific threshold levels only apply to the institution's assay (radioimmunoassay [RIA] from Immunotech, Prague, Czech Republic) and cannot be extrapolated to other assays without comparative validation studies.
ACTH, adrenocorticotropic hormone; ICU, intensive care unit.

Because adrenal failure can develop over time, possibly because of sustained ACTH deprivation, the use of repetitive measurements of plasma ACTH and cortisol over time, together with repetitive ACTH stimulation tests, could give information about the risk of an "ACTH-deprived adrenal cortex–type of adrenocortical dysfunction" in critically ill patients. A small study by Briegel et al. indeed already showed that when patients have recovered, the cortisol responsiveness to ACTH is also restored. Another small study showed that repetitive ACTH testing and a progressively decreasing cortisol response were associated with poor prognosis. Currently, large and well-designed prospective clinical studies of repeated measurements of plasma cortisol and ACTH and ACTH stimulation tests over time into the prolonged phase of critical illness and recovery should be performed to further unravel this condition.

Besides accurately determining "whom" to treat, it should also be further investigated "how" these patients should be treated. The currently used dose of **200 mg of hydrocortisone per day is now criticized given that this dose is almost sixfold higher than the cortisol production rate that was recently quantified in critically ill**

patients. Furthermore, given the fivefold longer cortisol half-life in critically ill patients, these doses of 200 mg/day will expectedly result in very high circulating (and, possibly, also tissue) cortisol levels during critical illness, with risks of side effects. Such a treatment expectedly increases cortisol availability in all tissues, explaining the potentially deleterious effects of this treatment. It is clear that more research is needed to further clarify the diagnostic and therapeutic implications of the novel pathophysiologic insights.

V. PRELIMINARY RECOMMENDATIONS

See Table 21-1.

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22 Congenital Adrenal Hyperplasia

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I. PATHOGENESIS

Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders of adrenal steroidogenesis in which there is deficient activity of one of the enzymes necessary for cortisol synthesis. As a result, adrenocorticotropic hormone (ACTH) secretion is stimulated via negative feedback, causing adrenal hyperplasia and overproduction of the adrenal steroids, both those preceding the step that is deficient and those not requiring the disordered enzymatic step. A simplified scheme of adrenal steroidogenesis, showing the series of enzymatic steps required for adrenal steroidogenesis, is depicted in Figure 22-1, and the genes encoding them are presented in Table 22-1.

II. BIOCHEMICAL MARKERS

Heterogeneity in several of these disorders is well recognized, and a range of clinical severity and biochemical abnormality has been documented. The symptoms of each deficiency depend on which steroids are deficient and which are produced in excess. The availability of sensitive and specific radioimmunoassays for the measurement of serum hormone levels has greatly facilitated the diagnosis of these disorders. Serum hormone determinations have largely replaced urinary hormone measurements as the primary method of diagnosis. Urinary hormone measurements can confirm the diagnosis and, with the serum hormone measurements, are useful in monitoring therapeutic response. p. 257p. 258Determination of which hormones are overproduced and which are deficient, and the precursor to product ratio localizes the site of the disordered enzymatic step. Because levels of hormones distal to the enzymatic block (product hormones) may be elevated as a result of

peripheral conversion of the markedly elevated hormones prior to the block (precursor hormones), the precursor to product ratios are important in avoiding misdiagnosis because of misleading elevation of product hormones. In the classic (more severe) disorders, basal hormone levels are usually sufficiently elevated to be diagnostic. In the milder, nonclassic disorders, ACTH stimulation is often necessary to pinpoint the deficiency. ACTH is administered by intravenous bolus or subcutaneously, usually at a dose of 0.25 mg (25 U), although some investigators have employed a dose of 1 mg (100 U). Following ACTH administration, blood levels are generally measured at 60 minutes, although some investigators use 30-minute levels to aid in diagnosis. Administration of glucocorticoid results in suppression of excessive steroid production. A summary of the clinical and biochemical data in the various forms of CAH is presented in Table 22-2.

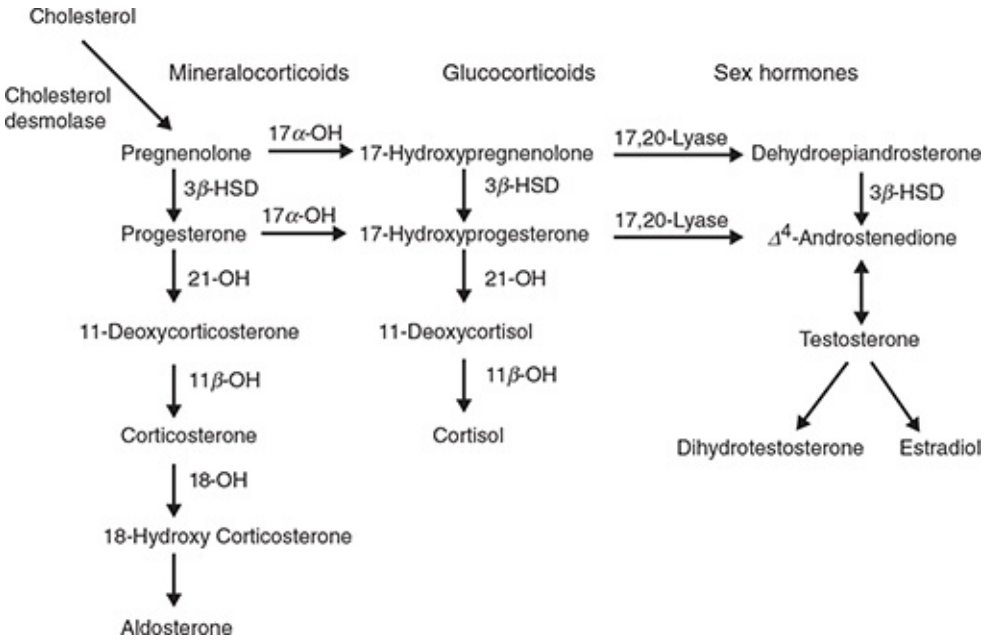

Figure 22-1. Simplified scheme of adrenal steroidogenesis. 17α-OH, 17α-hydroxylase; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 21-OH, 21-hydroxylase; 11β-OH, 11β-hydroxylase.

TABLE 22-1 Enzymes and Genes of Adrenal Steroidogenesis

Enzymatic Activity	Enzyme	Cellular Location	Gene	Chromosomal Location
Cholesterol desmolase (side-chain cleavage)	P450scc (CYP11A1)	Mitochondrion	*CYP11A1*	15q23–24
3β-Hydroxysteroid	3β-HSD (3β-	Endoplasmic	*HSD3B2*	1p13.1

dehydrogenase	HSDII)	reticulum		
17*α*-Hydroxylase/17,20-lyase	P450c17 (CYP17)	Endoplasmic reticulum	*CYP17*	10q24.3
21*α*-Hydroxylase	P450c21 (CYP21A2)	Endoplasmic reticulum	*CYP21A2*	6p21.3
11*β*-hydroxylase	P450c11 (CYP11B1)	Mitochondrion	*CYP11B1*	8q21–22
Aldosterone synthase (corticosterone 18-methylcorticosterone oxidase/lyase)	P450c18 (CYP11B2)	Mitochondrion	*CYP11B2*	8q21–22

Adapted from Levine LS. Congenital adrenal hyperplasia. *Pediatr Rev* 2000;21:159–170.

III. ENZYME DEFICIENCIES IN CAH

A. Congenital lipoid adrenal hyperplasia (steroidogenic acute regulatory protein deficiency)

1. **Pathogenesis.** Lipoid adrenal hyperplasia is a rare form of CAH. In this disorder, there is a failure to convert cholesterol to pregnenolone, leading to a marked accumulation of cholesterol esters in the adrenal gland and gonads—hence the name lipoid adrenal hyperplasia. Conversion of pregnenolone from cholesterol requires the 20-hydroxylation and 22-hydroxylation of cholesterol and the scission of the C-20 to C-22 bond to yield pregnenolone. P450scc, formerly called 20,22-desmolase, is located in the mitochondria. P450scc deficiency affects the mitochondria in the adrenal glands and gonads and results in a **deficiency of all classes of adrenal and gonadal steroids**. There appears to be a single *P450scc* gene, which lies on the long arm of chromosome 15. Mutational analysis of the *P450scc* gene in almost all patients with cholesterol desmolase deficiency has demonstrated normal *P450scc* genes and cDNA sequences. This cDNA sequencing of P450scc should not be ordered routinely and is not currently commercially available. The cause of this disorder is in most cases a mutation in the gene for steroidogenic acute regulatory (StAR) protein, a mitochondrial p. 258p. 259protein that promotes the movement of cholesterol from the outer to the inner mitochondrial membrane. Lipoid adrenal

hyperplasia is the only form of CAH that is not caused by a defective steroidogenic enzyme.

2. **Clinical presentation.** The disorder usually presents in the early neonatal period with adrenal insufficiency with cardiovascular collapse, although later presentation has been reported. Because the defect is also present in the gonad, **genetic males have a female phenotype**, although slight virilization has been reported. A milder, nonclassic form of StAR has been recently reported, in which males had normal genital development. Less severe impairment in ovarian function and spontaneous puberty has been reported in 46,XX patients.
3. **Laboratory findings.** Hormonal evaluation reveals low levels of all adrenal and gonadal steroids and poor response to ACTH and human chorionic gonadotropin (HCG) stimulation (Table 22-2). Imaging studies may demonstrate massive enlargement of the adrenal glands.

B. 3β-Hydroxysteroid dehydrogenase/Δ4,5-isomerase deficiency

1. **Pathogenesis.** The conversion of pregnenolone to progesterone, 17-hydroxypregnenolone to 17-hydroxyprogesterone, and dehydroepiandrosterone (DHEA) to Δ4-androstenedione requires 3β-hydroxysteroid dehydrogenase (3β-HSD)/Δ4,5-isomerase, which is located in the endoplasmic reticulum (Δ4,5 represents a double bond between the fourth and fifth positions of a carbon atom). The 3β-HSD gene mediates both 3β-HSD and isomerase activities and is located on chromosome 1. Deficiency of 3β-HSD/Δ4,5-isomerase results in decreased synthesis of cortisol, aldosterone, and the sex steroids synthesized distally to DHEA (Fig. 22-1). Mutations in the type II 3β-HSD gene have been described in patients with this disorder.
2. **Clinical presentation.** Severe (classic) and mild (nonclassic) forms of this disorder have been reported. The majority of children described with severe 3β-HSD deficiency have manifested salt wasting, although normal aldosterone secretion has been reported.

   The degree of incomplete male differentiation of affected males with the classic form ranges from male phenotype with hypospadias to an almost normal female phenotype, suggesting variable degrees of enzymatic defect in the testes. Normal male secondary sexual development can occur, usually accompanied by

gynecomastia.

Virilization of the external genitalia of an affected female fetus is probably secondary to increased DHEA secretion by the fetal adrenal gland.

The nonclassic form of this disorder has been diagnosed in individuals presenting in later childhood, at puberty, and in adulthood with signs of androgen excess—early onset of pubic hair, growth and bone age acceleration, menstrual abnormalities, acne, hirsutism, and infertility. The degree of bone age advancement is variable and dependent on the extent of androgen exposure and length of exposure during childhood.

3. **Diagnosis.** The hormonal diagnosis of 3β-HSD/Δ4,5-isomerase deficiency is based on elevated serum levels of baseline and ACTH-stimulated Δ5 steroids (pregnenolone, 17-hydroxypregnenolone, DHEA, 16-hydroxypregnenolone, and 16-hydroxy-DHEA) and elevated Δ5/Δ4 steroid ratios. Elevated Δ5 steroids and elevated Δ5/Δ4 steroid ratios are also found in urine. Diagnosis can be confirmed by molecular genetic analysis.

   a. **Stimulated values.** 3β-HSD activity is most often evaluated by measurement of post–ACTH-stimulated levels of 17-hydroxypregnenolone and DHEA, and the ratios of 17-hydroxypregnenolone to 17-hydroxyprogesterone and DHEA to Δ4-androstenedione. Most laboratories have defined 3β-HSD deficiency as the presence of responses to ACTH stimulation more than 2SD above the mean of their control population of 17-hydroxypregnenolone and the ratio of 17-hydroxypregnenolone to 17-hydroxyprogesterone.

      Although each laboratory must establish its own normal age-appropriate control data, normal adult 60-minute ACTH-stimulated levels of 17-hydroxypregnenolone and DHEA have generally been <1 500 and 1 700 ng/dL, p. 259p. 260respectively, whereas normal values for the ratios of stimulated 17-hydroxypregnenolone to 17-hydroxyprogesterone and DHEA to Δ4-androstenedione have been variously reported as <7 to <11 and <5 to <8, respectively. Patients with classic 3β-HSD deficiency have been reported with ACTH-stimulated 17-

hydroxypregnenolone levels of 10 000 to 60 000 ng/dL, DHEA levels of 3 000 to 12 000 ng/dL, and 17-hydroxypregnenolone/17-hydroxyprogesterone and DHEA/androstenedione ratios of 18 to 25 and 18 to 30, respectively. Administration of glucocorticoid results in suppression of the overproduced adrenal steroids (Table 22-2). Mutational analysis of the type II 3β-HSD gene in children with premature pubarche and adult women with hirsutism, diagnosed by previously utilized hormonal criteria, indicated normal 3β-HSD type II genes (gonadal/adrenal specific). Thus, the decreased 3β-HSD activity demonstrated on ACTH stimulation testing was not caused by a mutation in the type II 3β-HSD gene.

b. Testicular deficiency. The steroidogenic function of the testis can be evaluated by HCG stimulation testing. Protocols for HCG testing vary, with dosages ranging from one 500 U dose to five daily doses of 5 000 U. In the presence of testicular 3β-HSD deficiency, testosterone may rise to the normal age-appropriate range, but the markedly increased Δ5/Δ4 ratio is diagnostic of testicular 3β-HSD deficiency.

C. 17α-Hydroxylase/17,20-lyase deficiency

1. **Etiology.** It has been demonstrated that the 17α-hydroxylase activity required for converting pregnenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone, respectively, and the 17,20-lyase activity, by which 17α-hydroxypregnenolone and 17α-hydroxyprogesterone are converted to DHEA and androstenedione, respectively, are mediated by a single enzyme—P450c17. P450c17 is found in the endoplasmic reticulum. A single *P450c17* gene located on chromosome 10 is expressed in both the adrenals and the gonads. Because it is difficult to distinguish 17α-hydroxylase and 17,20-lyase activities in vivo, cases of P450c17 deficiency have traditionally been reported as 17α-hydroxylase deficiency (17-OHD).
2. **Clinical presentation.** 17-OHD produces a concomitant deficiency of glucocorticoids and sex steroids. As a result of the cortisol deficiency, there is increased ACTH secretion, which stimulates excessive 11-deoxycorticosterone (DOC) secretion, resulting in **hypokalemia** and **hypertension**. Females with this disorder present with sexual infantilism, hypertension, and

hypokalemia; males present with incomplete male differentiation (male pseudohermaphroditism), hypertension, and hypokalemia. Undiagnosed affected males have usually been raised as females because of their phenotypically normal female external genitalia with a blind-ending vagina and either undescended or inguinal testes. However, ambiguity of the genitalia in genetic males has been observed, and male sex assignment reported. Both males and females have decreased or absent axillary and pubic hair. Several patients have demonstrated hypertension in infancy.

3. **Diagnosis.** The hormonal diagnosis of 17-OHD is based on the low levels of all 17α-hydroxylated steroids with absent or inadequate response to stimulation with ACTH or HCG. There are also elevated baseline and ACTH-stimulated levels of DOC, corticosterone, 18-hydroxycorticosterone (18-OHB), and 18-OH DOC (Table 22-2). Low basal and ACTH-stimulated levels of cortisol (<5 and <10 μg/dL, respectively) and aldosterone (<4 and <10 ng/dL, respectively) and markedly elevated levels of corticosterone (30 to 100 times), DOC (10 to 40 times), 18-OHB (10 times), and 18-OH DOC (30 to 60 times) have been reported. Absent or low response of serum androgens to HCG, utilizing varying protocols of administration, confirms the presence of the deficiency in the testis. In the untreated state, plasma renin activity (PRA) and aldosterone are usually suppressed secondary to the excessive DOC secretion and consequent hypervolemia. Glucocorticoid administration results in suppression of the overproduced hormones, reversal of the hypervolemia, and gradual rise in PRA and aldosterone (Table 22-2). Diagnosis can be confirmed with molecular genetic analysis.

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4. **Genetics.** The human gene for P450c17 has been cloned and sequenced. Molecular genetic studies of patients with 17-OHD have demonstrated >50 different gene mutations. Base-pair deletions and duplications have been described.

D. 17,20-Lyase deficiency. A number of cases of deficient 17,20-lyase activity with normal 17α-hydroxylase activity have been reported. These patients demonstrate deficiency of sex steroids but normal glucocorticoid and mineralocorticoid secretion. Females with this disorder present with sexual infantilism and males with male

pseudohermaphroditism. Laboratory evaluation reveals elevated levels of 17-hydroxypregnenolone and 17-hydroxyprogesterone, which increase further with ACTH and HCG stimulation. However, sex steroids are decreased and do not increase with ACTH or HCG stimulation. Gonadotropin levels are elevated at puberty. The molecular basis for isolated 17,20-lyase deficiency has been described in a number of patients with mutations in the gene for P450c17.

E. 21-Hydroxylase deficiency

1. **Pathophysiology.** Deficiency of 21-hydroxylase (21-OHD) activity is the most common cause of CAH, accounting for >90% of cases. Failure to adequately convert 21-hydroxylate and 17-hydroxyprogesterone to 11-deoxycortisol results in cortisol deficiency, increased ACTH, adrenal hyperplasia, and increased adrenal androgen secretion. The excessive adrenal androgen production, **most markedly androstenedione, produces the virilization** that is the hallmark of this disorder. Inadequate 21-hydroxylation of progesterone to DOC results in aldosterone deficiency, and **salt wasting occurs in approximately 75% of infants** with classic CAH.
2. **Clinical presentation.** CAH owing to 21-OHD is classified into two forms, the severe or classic form and the milder nonclassic form. The classic form is further subdivided into the salt-wasting form and simple virilizing form. In the classic form, virilization of the affected female begins in utero and ranges in degree from clitoromegaly, with or without partial fusion of the labioscrotal folds, to complete fusion of the labioscrotal folds with the appearance of a penile urethra. If left untreated, there is progression in the signs of androgen excess in males and females: penile and clitoral enlargement, excessive growth, acne, and early onset of pubic hair growth. Bone age advancement leads to early epiphyseal closure, and ultimate stature in untreated or poorly treated children is short. The salt-wasting form is distinguished from the simple virilizing form by aldosterone deficiency. Salt-wasting crisis usually occurs in the first weeks of life, although it may occur in later infancy or childhood, usually precipitated by intercurrent illness. Disordered puberty and infertility in patients with CAH are well recognized; however, normal puberty and fertility with successful treatment have been achieved. Children treated when bone ages are >10 years can undergo true precocious

puberty when adrenal suppressive treatment is instituted.

In the *nonclassic form*, symptoms of androgen excess begin in later childhood, in puberty, postpubertally, or in adulthood and may be intermittent. Early onset of pubic hair development, accelerated growth velocity and bone age advancement, acne, hirsutism, menstrual irregularity, and infertility are common presenting findings. Unilateral testicular enlargement as a result of testicular adrenal rest tumors has been reported. It has been suggested that nonclassic 21-OHD is the most common autosomal recessive genetic disorder in humans, with a prevalence in Ashkenazi Jews of 3.7% (1 in 27) and in a diverse white population of 0.1%.

3. **Diagnosis.** The hormonal diagnosis of 21-OHD is based on elevated baseline and ACTH-stimulated levels of **serum 17-hydroxyprogesterone** and adrenal androgens, particularly **androstenedione**, and their suppression with glucocorticoid treatment. Measurements of the urinary metabolites pregnanetriol and 17-ketosteroids can provide additional confirmation of the diagnosis. In the classic form, (serum) basal 17-hydroxyprogesterone levels are in the range of 10 000 to 100 000 ng/dL; following ACTH stimulation, they rise to levels of 25 000 to >100 000 ng/dL (serum). Androstenedione levels are in the range of 250 ng/dL to as high as 1 000 ng/dL or greater. The aldosterone/PRA ratio has been shown to be decreased in cases of even subtle salt wasting and may aid in determining salt-retaining ability.

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In the *nonclassic form* of 21-OHD, basal circulating levels of 17-OHP are not as high as in the classic form and may be normal, especially if they are not measured early in the morning. However, following ACTH stimulation, there is a diagnostic rise in 17-OHP to levels between approximately 2 000 and 10 000 ng/dL. Glucocorticoid administration results in a prompt decrease in the elevated steroid concentrations (Table 22-2).

Diagnosis of 21-OHD is confirmed by genetic analysis.

4. **Molecular genetics.** Molecular genetic analysis has demonstrated that there are two human P450c21 genes —*CYP21A1P* and *CYP21A2*. The two genes are highly homologous, but only the *CYP21A2* gene is active. The two 21-OH

genes are located in tandem with two highly homologous genes for the fourth component of complement (C4A and C4B). Several other genes are located in this cluster. Before the identification and sequencing of *CYP21A2*, molecular genetic diagnosis was accomplished through genotypic features of human leukocyte antigen markers.

Gene conversions, gene deletions, and point mutations have been reported in patients with 21-OHD. The majority of mutations causing 21-OHD are recombinations between the inactive *CYP21A1P* gene and the active *CYP21A2* gene, resulting in microconversions, accounting for over 90% of mutations.

Gene deletions and large gene conversions also occur. Most patients are compound heterozygotes, having a different mutation on each allele. The severity of the disease is determined by the degree of decrease in enzymatic function caused by the mutation. The salt-wasting form is found in patients with gene deletions or gene conversions or both; however, severe point mutations are also found in these patients.

The **nonclassic disorder** is found in patients with a combination of a severe *CYP21A2* mutation (found in the classic form of the disease) and a mild *CYP21A2* mutation (found in the nonclassic form of the disease), or a combination of two mild mutations. Point mutations, gene conversions, and gene duplications have been reported in these patients. A majority of nonclassic alleles are associated with the exon 7 V281L missense mutation.

Several studies have determined the functional effects of mutations in *CYP21A2*. A single amino acid substitution present in patients with nonclassic 21-OHD results in an enzyme with 20% to 50% of normal activity; mutations in patients with the simple virilizing form of 21-OHD result in an enzyme with 1% to 2% of normal activity; and mutations found in salt-wasting 21-OHD result in <1% enzymatic activity. The phenotypic expression of the most common 21-OHD genotypes has been well established. However, some instances of genotype–phenotype noncorrelation have occurred; patients with two severe mutations predicted to have the classic form of the disease presented with the nonclassic form, and patients with a severe and a mild mutation, expected to cause nonclassic 21-OHD, had the severe form of the disorder.

F. 11α-Hydroxylase deficiency

1. **Incidence.** CAH resulting from 11β-hydroxylase deficiency (11β-OHD) accounts for 5% to 8% of reported cases of CAH. It occurs in approximately 1 in 100 000 births in the general white population. It is more common among Jews of northern African origin and might also be more common in other populations than previously recognized.
2. **Clinical presentation.** An 11β-OHD results in a defect in the conversion of 11-deoxycortisol to cortisol and DOC to corticosterone. Similar to 21-OHD, there is virilization secondary to the excessive secretion of the adrenal androgens, resulting in virilization of the female fetus and postnatal virilization of males and females. Hypertension is commonly observed in this disorder, thought to be secondary to increased DOC secretion, sodium and water retention, and volume expansion. Hypokalemia can also be present. Glucocorticoid administration suppresses the overproduced adrenal steroids (11-deoxycortisol, DOC, and androgens), preventing continued virilization and resulting in remission of the hypertension. The external genitalia of the virilized female can be corrected surgically, as in 21-OHD, and optimal treatment should permit normal growth and pubertal development and fertility.

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TABLE 22-2 Clinical and Hormonal Data

Enzymatic Deficiency	Signs and Symptoms	Laboratory Findings	Therapeutic Measures
Lipoid CAH (cholesterol desmolase deficiency)	Salt-wasting crisis, 46,XY disorder of sexual development (DSD)	Low levels of all steroid hormones, with decreased/absent response to ACTH Decreased/absent response to HCG in male pseudohermaphroditism	Glucocorticoid and mineralocorticoid administration Sodium chloride supplementation Gonadectomy of male pseudohermaphrodite Sex hormone replacemen

		↑ACTH ↑PRA	consonant with sex of rearing
3*β*-Hydroxysteroid dehydrogenase deficiency	Classic form: Salt-wasting crisis, 46,XX and 46,XY DSD, *precocious pubarche*, disordered puberty	↑↑Baseline and ACTH-stimulated *Δ*5 *steroids* (pregnenolone, 17-OH pregnenolone, DHEA, and their urinary metabolites) ↑ACTH ↑PRA Suppression of elevated adrenal steroids after glucocorticoid administration	Glucocorticoid and mineralocorticoid administration Sodium chloride *supplementation* Surgical correction of genitalia and sex hormone replacement as necessary consonant with sex of rearing
3*β*-Hydroxysteroid dehydrogenase deficiency	Nonclassic form: Precocious pubarche, disordered puberty, menstrual irregularity, hirsutism, acne, infertility	↑Baseline and ACTH-stimulated five steroids (pregnenolone, 17-OH pregnenolone, DHEA, and their urinary metabolites) ↑*Δ*5/*Δ*4 serum and urinary steroids Suppression of elevated adrenal steroids after glucocorticoid administration	Glucocorticoid administration
21-Hydroxylase deficiency	Classic form: Salt-wasting crisis, 46,XX DSD, postnatal virilization	↑↑Baseline and ACTH-stimulated 17-OH progesterone and pregnanetriol ↑↑Serum androgens and urinary metabolites ↑ACTH ↑PRA Suppression of elevated adrenal steroids after glucocorticoid administration	Glucocorticoid and *mineralocorticoid replacement* Sodium chloride *supplementation* Vaginoplasty and clitoral recession in female pseudohermaphroditism
21-Hydroxylase deficiency	Nonclassic form: Precocious pubarche, disordered puberty, menstrual irregularity, hirsutism, acne, infertility	↑Baseline and ACTH-stimulated 17-OH progesterone and pregnanetriol ↑Serum androgens and urinary metabolites Suppression of elevated adrenal steroids after glucocorticoid administration	Glucocorticoid administration
11*β*-Hydroxylase deficiency	Classic form: 46,XX DSD,	↑↑Baseline and ACTH-stimulated compound S	Glucocorticoid administration

	postnatal virilization in males and females, hypertension	and DOC and their urinary metabolites ↑↑Serum androgens and their urinary metabolites ↑ACTH ↓PRA Hypokalemia Suppression of elevated steroids after glucocorticoid administration	Vaginoplasty and clitoral recession in female pseudohermaphroditism
11*β*-Hydroxylase deficiency	Nonclassic form: Precocious pubarche, disordered puberty, menstrual irregularity, hirsutism, acne, infertility	↑Baseline and ACTH-stimulated compound and DOC and their urinary metabolites ↑Serum androgens and their urinary metabolites Suppression of elevated steroids after glucocorticoid administration	Glucocorticoid administration
17*α*-OH/17,20 lyase deficiency	46,XY DSD, sexual infantilism, hypertension	↑↑DOC, 18-OH DOC, corticosterone, 18-hydroxycorticosterone Low 17*α*-hydroxylated steroids and poor response to ACTH Poor response to HCG in male pseudohermaphroditism ↓PRA ↑ACTH Hypokalemia Suppression of elevated adrenal steroids after glucocorticoid administration	Glucocorticoid administration Surgical correction of genitalia and sex hormone replacement in male pseudohermaphroditism consonant with sex of rearing Sex hormone replacement in female

ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; DOC, 11-deoxycorticosterone; DHEA, dehydroepiandrosterone; HCG, human chorionic gonadotropin; PRA, plasma renin activity.

Adapted from Miller WL, Levine LS. Molecular and clinical advances in congenital adrenal hyperplasia. *J Pediatr* 1987;111:1.

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al Kandari H, Katsumata N, Alexander S, et al. Homozygous mutation of P450 side-chain cleavage enzyme gene (CYP11A1) in 46,XY patient with adrenal insufficiency, complete sex reversal, and agenesis of corpus callosum. *J Clin Endocr Metab* 2006;91:2821–2826.

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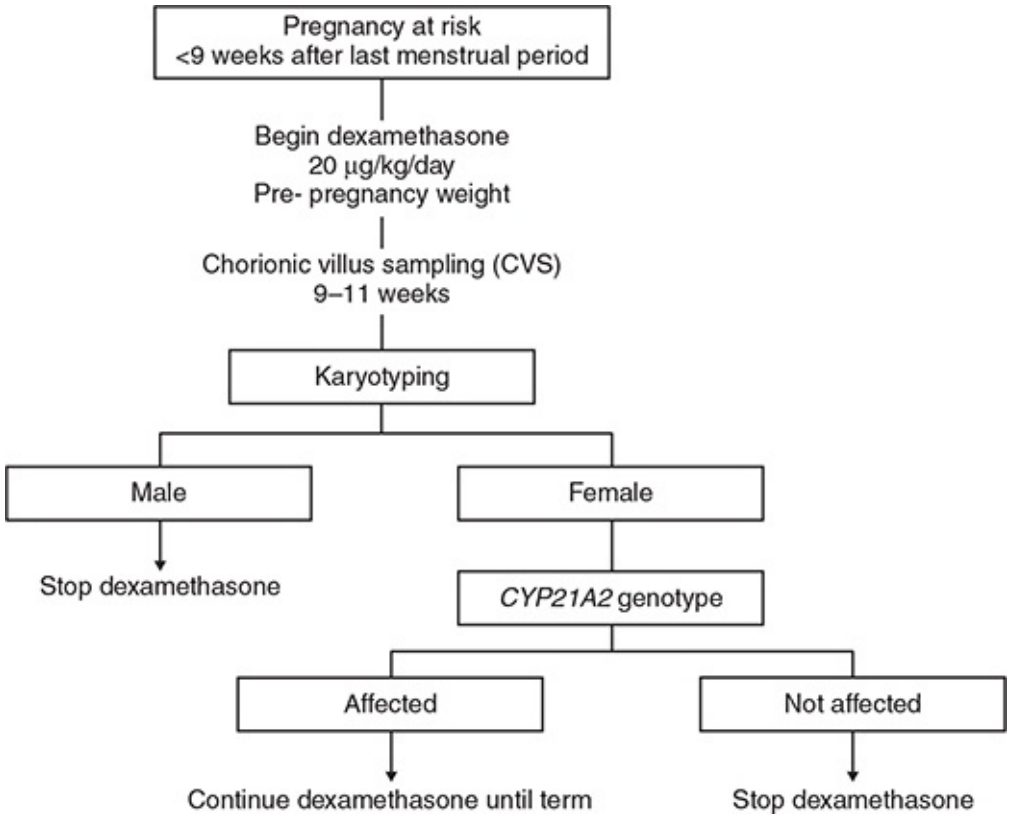

Figure 22-2. Simplified algorithm for prenatal diagnosis and treatment of congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency.

As with 3β-HSD deficiency and 21-OHD, a **nonclassic form** of 11β-OHD has been described, presenting in later childhood, at puberty, and in adult life with signs of androgen excess: (Hypertension is only seen in classic 11β-OHD CAH.) early appearance of pubic and axillary hair, tall stature in childhood,

advanced bone age, acne, hirsutism, temporal hairline recession, amenorrhea, and infertility.

3. **Diagnosis.** 11*β*-OHD is diagnosed on the basis of the presence of elevated baseline and ACTH-stimulated serum levels of 11-deoxycortisol, DOC, and androgens (particularly androstenedione) and their suppression with glucocorticoid therapy. Determination of the urinary metabolites tetrahydro-11-deoxycortisol, tetrahydro-11-deoxycorticosterone, and 17-ketosteroids can confirm the diagnosis. As previously stated, each laboratory must establish its own normal control data. However, normal serum levels of 11-deoxycortisol in the range of 11 to 160 ng/dL and of DOC in the range of 3 to 60 ng/dL have been reported. In patients with classic 11*β*-OHD, 11-deoxycortisol has been reported to be 10 to 40 times elevated (1 400 to 4 300 ng/dL) and DOC 10 to 50 times elevated (183 to 2 050 ng/dL). In the untreated state, PRA and aldosterone are often suppressed secondary to the sodium and water-retaining effect of the excessive DOC (Table 22-2). An interesting observation is the biochemical and clinical variability in this disorder, with dissociation of hypertension, hypokalemia, and virilization, as well as between 11-deoxycortisol and DOC levels. The pattern of hormonal abnormality in the **nonclassic form** is similar to that in the classic form, with less marked hormonal abnormality (Table 22-2).
4. **Molecular genetics.** Two isoenzymes, P450c11*β* and P450c18, are encoded by the *CYP11B1* and *CYP11B2* genes, respectively, lying on chromosome 8q21–q22. P450c11*β* mediates 11*β*-hydroxylation, leading to cortisol synthesis, whereas p. 266p. 267P450c18 mediates 11*β*-hydroxylase, 18-hydroxylase, and 18-oxidase activities, leading to aldosterone synthesis.

   Studies of Moroccan Jewish families with 11*β*-OHD demonstrated a point mutation in codon 448 in *CYP11B1*, resulting in an arginine → histidine substitution in almost all affected alleles. Other mutations of *CYP11B1* in patients with 11*β*-OHD have been reported.

IV. MANAGEMENT OF CAH

A. General principles. The principles of treatment are outlined in Table 22-2. The standard treatment for CAH is glucocorticoid replacement therapy.

B. Glucocorticoids. Hydrocortisone, cortisone acetate, prednisone or prednisolone, dexamethasone, and combinations of these steroids have been used, and various schedules recommended. For adults with 21-OHD, 0.25 mg of dexamethasone at the hour of sleep is the preferred treatment. However, in **children, hydrocortisone is preferred because dexamethasone may lead to shorter height**. The starting dose of hydrocortisone is 8-12 mg/m^2. The lowest dosage of glucocorticoid that produces adequate androgen (or mineralocorticoid) suppression in those disorders with androgen (or mineralocorticoid) excess should be utilized.

C. Mineralocorticoids. Mineralocorticoid therapy, usually in the form of 9α-fludrocortisone (0.1 to 0.3 mg/day), is administered to patients with overt or subtle salt wasting.

D. Salt. Sodium chloride, 1 to 3 g/day, is usually administered to an infant with salt wasting to achieve adequate sodium repletion and normalization of PRA.

E. Sex hormones. Sex hormone replacement at puberty is provided to patients with enzyme disorders that result in gonadal steroid deficiency. Such hormone replacement induces development of secondary sex characteristics.

F. Surgery. Surgical correction of ambiguous genitalia to conform to the sex of assignment has traditionally been performed within the first year of life when the infant is clinically stable. There is active debate about the timing, the decision-making process, and the need for surgery in disorders of sexual differentiation.

G. Experimental treatments. Analogs of the hypothalamic gonadotropin-releasing hormone, in addition to glucocorticoid administration, have been used in the treatment of children with 21-OHD and true precocious puberty. Improvement of final height has been reported. **Growth hormone** has been used in patients with CAH to improve growth velocity and final height. The combination of growth hormone and a luteinizing-releasing hormone analog was also proven to be highly effective in increasing final height. Positive effects of a combination of an antiandrogen (to block androgen effect), an aromatase inhibitor (to block conversion of androgen to estrogen), and a reduced hydrocortisone dose have also been reported.

V. NEWBORN SCREENING.

Screening for CAH resulting from 21-OHD became possible with the development of an assay for 17-hydroxyprogesterone using a heel-stick capillary blood specimen impregnated on filter paper. A number of newborn screening programs have been developed in the United States, Europe, and Japan. Results of screening more than 8 million newborns have been reported. There is a high frequency of CAH resulting from 21-OHD among Yupik Eskimos of southwestern Alaska (1 in 282) and the people of La Reunion, France (1 in 2 141). The worldwide incidence is estimated at approximately 1 in 14 500 live births and approximately 1 in 13 500 among whites. Salt wasting is diagnosed in approximately 77% of newborns. Cost–benefit analysis has indicated that newborn screening for classic 21-OHD is cost-effective.

VI. PRENATAL DIAGNOSIS AND TREATMENT OF CAH RESULTING FROM 21-OHD

A. Prenatal diagnosis.

Prenatal diagnosis of CAH resulting from 21-OHD can be performed in the first trimester of pregnancy by molecular genetic analysis of fetal DNA from chorionic villus sampling (CVS) or amniocentesis. CVS is preferred over amniocentesis because the sample can be obtained at the 10th to 11th week of gestation, rather than the 15th or 16th week-of-gestation time frame for amniocentesis.

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Promisingly, noninvasive prenatal diagnosis using cell-free fetal DNA obtained from maternal plasma could potentially provide the diagnosis of CAH and the chromosomal sex before the ninth week of gestation. In the future, only affected female fetuses will thus be treated.

B. Prenatal treatment.

Prenatal dexamethasone treatment of the female fetus with CAH resulting from 21-OHD has prevented or reduced the degree of virilization of the external genitalia in approximately two thirds of the reported cases. Long-term follow-up into adulthood must be conducted to determine possible long-term complications of this treatment, and studies are currently underway.

1. **Maternal side effects.** In some mothers, the treatment has resulted in significant side effects, including excessive weight gain and edema, gastrointestinal intolerance, hyperglycemia,

hypertension, nervousness or irritability, and striae. These complications resolved after the completion of treatment.

2. **Recommended treatment protocol.** The current recommended scheme when prenatal diagnosis and treatment are requested is depicted in Figure 22-2. Dexamethasone (20 μg/kg of prepregnancy weight per day in two or three divided doses up to a maximum daily dose of 1.5 mg) should be **begun by the ninth week of gestation** in order to reduce virilization in the affected female. First-trimester prenatal diagnosis and fetal sex determination by CVS should be performed, and dexamethasone **continued until term if the fetus is an affected female**. This means that to be effective, treatment must be started blind to the sex and diagnosis of 21-OHD of the fetus. If the fetus is proven to be male or unaffected, treatment is discontinued.

VII. PRENATAL DIAGNOSIS/TREATMENT OF OTHER FORMS OF CAH.

Prenatal diagnosis of 11β-OHD and lipoid adrenal hyperplasia has been reported. DNA analysis of chorionic villus cells and amniotic cells can be used for the prenatal diagnosis of all forms of CAH. Prenatal treatment of 11β-OHD has been reported in several cases and was effective in reducing virilization in one affected female.

VIII. PRENATAL DIAGNOSIS AND TREATMENT: CONCLUSION.

Although the short-term efficacy and safety of prenatal management of CAH has been shown, data are lacking on the long-term effects of prenatal dexamethasone treatment. Studies are currently underway to ascertain the long-term cognitive and medical safety of prenatal treatment.

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23 Adrenal Steroid Excess in Childhood

Kimberly S. Tafuri and Thomas A. Wilson

I. GENERAL PRINCIPLES

A. Divisions of the adrenal cortex. The mature adrenal cortex is divided into three functional and histologic zones.

1. The **zona glomerulosa** secretes aldosterone and is regulated by the renin–angiotensin system, serum potassium concentration, adrenocorticotropic hormone (ACTH), and dopamine.
2. The **zona fasciculata** secretes primarily glucocorticoids and is under the control of ACTH alone.
3. The **zona reticularis** secretes glucocorticoids and adrenal androgens. It is under the regulation of ACTH and possibly a putative factor that stimulates the production of adrenal androgens during puberty.
4. In the human fetus, an inner fetal zone exists that dwarfs the adult adrenal cortex. This **fetal adrenal cortex** secretes primarily dehydroepiandrosterone sulfate and pregnenolone sulfate. The fetal adrenal zone involutes within the first 6 months of age.

B. Embryology of the adrenal gland. Various differentiation factors are involved in the development of the adrenal cortex. The absence of one of these factors, such as Steroidogenic Factor 1 (SF1) or Nuclear Factor Subfamily 0 Group B, previously called DAX1 (NROB1), causes **congenital adrenal hypoplasia** (see Chapter 22).

C. Hormones of the adrenal cortex. Approximately 95% of the plasma cortisol is bound to transcortin, a carrier protein. Only the unbound portion is metabolically active. Cortisol is secreted in a diurnal manner with 8 A.M. concentrations in the plasma usually in the range of 11 ± 2.5 μg/dL; values in the evening are generally 3.5 ± 0.15 μg/dL in the nonstressed child. However, this diurnal rhythm might not be well established until after age 1 year. The adrenal glucocorticoids and their metabolites (including pregnanetriol, the major metabolite of 17-hydroxyprogesterone) can be measured in the urine as **17-**

ketogenic steroids, whereas only the metabolites of cortisol and its immediate precursor, 11-deoxycortisol, are measured as **17-hydroxycorticosteroids**, which are therefore more specific. The urinary free cortisol most closely approximates the unbound plasma cortisol concentration and therefore is preferable for assessing cortisol production. Plasma free cortisol concentrations can also be estimated using salivary cortisol concentrations preferably measured by tandem mass spectrometry. Metabolites of the adrenal androgens are measured in the urine as **17-ketosteroids**. Only about one third of the testosterone secreted is metabolized and excreted as 17-ketosteroids.

D. Hypersecretion of adrenal steroids results from:

1. Excess secretion of ACTH by the pituitary.
2. Ectopic secretion of corticotropin-releasing factor or ACTH from tumors outside the hypothalamic–pituitary axis.
3. Micronodular or macronodular dysplasia of the adrenal.
4. Overproduction of cortisol, aldosterone, adrenal androgens, estrogens, or a combination of these by hyperplastic, adenomatous, or malignant adrenal tissue. The signs, symptoms, and workup depend on which adrenal steroids are secreted excessively. **The most common form of adrenal steroid excess in childhood is congenital adrenal hyperplasia**, which is discussed in Chapter 22 of this book. Adrenocortical tumors occur more frequently in girls and are occasionally associated with hemihypertrophy, urinary tract abnormalities, and tumors in the brain.

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II. GLUCOCORTICOID EXCESS

A. Cushing syndrome is the physical manifestation of excess glucocorticoid action. In children, these manifestations are growth failure, weight gain, muscle weakness, obesity, moon facies, supraclavicular and nuchal fat pads, striae, easy bruising, virilization, hypertension, and glucose intolerance. Rarely, the only manifestation of Cushing syndrome in children is growth failure. **Cushing disease** is Cushing syndrome specifically resulting from excess pituitary ACTH secretion. Ectopic production of ACTH is very rare in children, but is occasionally seen with tumors of the neural crest, thymomas, small cell carcinoma of the lung, carcinoid tumors, Wilms tumors, and

pancreatic tumors.

Exogenous obesity is commonly confused with Cushing syndrome. The differential diagnosis is complicated by the fact that **obese children tend to have mild elevations in 24-hour urinary 17-hydroxycorticosteroid excretion, although urinary free cortisol excretion is normal**. A distinguishing clinical feature is the growth velocity, which is suppressed in children with Cushing syndrome, but normal or even increased in children with obesity. Biochemical studies, as outlined below, will distinguish Cushing syndrome from other forms of obesity. Patients with AIDS who are taking protease inhibitors may develop the metabolic syndrome and a redistribution of body fat that can resemble Cushing syndrome.

The most common cause of Cushing syndrome in children is iatrogenic caused by chronic administration of glucocorticoids and/or ACTH. Endogenous Cushing syndrome in children is rare accounting for only 10% of new cases each year. The etiology of endogenous Cushing syndrome is dependent on the age of the child. In **children <7 years of age**, Cushing syndrome is often secondary to an **adrenal tumor** (adenoma, carcinoma, and bilateral hyperplasia), whereas 75% of cases in **children >7 years** of age are secondary an ACTH-secreting **pituitary microadenoma**. In some adrenal tumors and some cases of bilateral adrenal macronodular adrenal hyperplasia, cortisol secretion is dependent on hormones other than ACTH, such as gastric inhibitory peptide (food-induced hypercortisolism), antidiuretic hormone, gonadotropin-releasing hormone, and thyroid-stimulating hormones in which case ACTH is suppressed. Some adrenal cortical tumors are nonfunctional and therefore endocrinologically silent.

B. Known genetic etiologies: Multiple genetic causes of glucocorticoid excess have been identified: multiple endocrine neoplasia type 1 (MEN-1) in which mutations of the MEN-1 gene present with tumors of the parathyroid glands, pancreatic islet cells, and anterior pituitary gland. The anterior pituitary tumors can be corticotrophinomas; however, prolactinomas are most common. Some patients may also develop adrenocortical tumors, but these are typically nonfunctioning. A MEN-1 like phenotype associated with mutations in cyclic-dependent kinase inhibitor-1B can also present with Cushing disease and is now referred to as **MEN-4**. Familial isolated pituitary adenoma caused by a mutation in the aryl

hydrocarbon receptor interaction protein gene is rarely a cause of Cushing disease.

Bilateral macronodular adrenal hyperplasia secondary to an activating mutation of the α subunit of the Gs protein can occur in **McCune–Albright** syndrome (OMIM # 174800). Primary pigmented bilateral nodular adrenocortical disease (PPNAD) with hypercortisolism is seen in **Carney complex**, a multiple endocrine neoplasia syndrome, resulting from inactivating mutations in the *PRKAR1A* gene characterized by micronodular adrenocortical disease, pigmented lentigines, atrial myxomas, and schwannomas (PRKAR1A) (OMIM # 160980). The Cushing syndrome caused by PPNAD can be periodic, cyclical, or atypical in presentation. Mutations in the tumor-suppressor gene, ARMC5, result in macronodular adrenocortical disease and have been reported in several cases of Cushing syndrome. Other forms of micronodular bilateral adrenocortical hyperplasia may occur as a result of mutations in the phosphodiesterase genes PDE11A and PDE8B.

The majority of cases of adrenocortical carcinoma (ACC) in children are attributable to mutations in TP53, a tumor-suppressor gene causing **Li–Fraumeni** syndrome, an autosomal dominant cancer predisposition syndrome characterized by the presence of four core cancers: sarcoma, ACC, breast cancer, acute leukemia, and brain tumors.

The **diagnosis of hypercortisolism** is made by demonstrating **excess urinary excretion of free cortisol** and by abnormal regulation of the p. 271p. 272p. 272p. 273hypothalamic–pituitary–adrenal axis (Table 23-1). Elevated urinary free cortisol excretion on two to three separate occasions in an unstressed child is highly suggestive of hypercortisolism. Assays and ranges for urinary free cortisol vary among laboratories. Other useful screening tests for hypercortisolism are **loss of normal diurnal rhythm** in plasma cortisol concentrations and **inability of dexamethasone** (0.3 to 0.5 mg/m^2, maximum 1 mg) given at 11 P.M. to **suppress the 8 A.M. plasma cortisol** concentration to <1.8 μg/dL. Medications that enhance the metabolism of dexamethasone, such as many anticonvulsants, rifampin, and aminoglutethimide, may

invalidate the dexamethasone suppression test. Certain medical conditions, such as uncontrolled diabetes, psychiatric conditions, malnutrition, pregnancy, and alcohol dependence, can also result in abnormal dexamethasone suppresibility and elevated urinary free cortisol. A third strategy to screen for abnormal cortisol secretion is to demonstrate loss of diurnal rhythm. Plasma cortisol > 4.4 μg/dL drawn through an indwelling catheter at midnight is suggestive of hypercortisolism. **Salivary cortisol levels** are in equilibrium with plasma free cortisol levels and demonstrate a similar diurnal rhythm. In individuals with a normal sleep–wake cycle, salivary cortisol levels of > 145 ng/dL (4 nmol/L) obtained between 11P.M. and 12 A.M.on two separate occasions are suggestive of hypercortisolism. Tandem mass spectrometry provides fewer false positives than immunoassays. The salivary gland also produces 11β-hydroxysteroid dehydrogenase type 2, the enzyme that deactivates cortisol to cortisone. **Glycyrrhizic acid, present in licorice and tobacco**, can inhibit this enzyme, resulting in elevated salivary cortisol.

TABLE 23-1 Diagnostic Approach to the Child with Evidence of Glucocorticoid Excess

Test	Normal range[a]	Adrenal tumor	Hypothalamic/ pituitary	Ectopic ACTH	Congenital virilizing adrenal hyperplasia
24-hr urinary free cortisol	25–75 μg/m^2/d[b]	↑	↑	↑	↔ or ↓
24-hr urinary 17-OHCS	3 ± 1 mg/m^2/d[b]	↑	↑	↑	↔, ↑, ↓
24-hr urinary 17-KS	[c]	↑↑↑	↔ or ↑	↔ or ↑	↑↑
Diurnal variation	Present	Absent	Absent	Absent	
Cortisol (11 P.M.)	<1.8 μg/mL	>1.8 μg/dL and similar to A.M. cortisol	>1.8 μg/dL and similar to A.M. cortisol	>1.8 μg/dL and similar to A.M. cortisol	
ACTH (11 P.M.)	<7.5 pg/mL	<7.5 pg/mL	>7.5 pg/mL	>7.5 pg/mL	
ACTH (8 A.M.)	<100 pg/mL	<5 pg/mL	>29 pg/mL	>29 pg/mL	
Overnight dexamethasone suppression test: 8 A.M. plasma cortisol	<1.8 μg/dL	>1.8 μg/dL	>1.8 μg/dL	>1.8 μg/dL	
Low-dose dexamethasone suppression test	Suppression of serum cortisol to <1.8 μg/dL	No suppression of serum cortisol	No suppression of serum cortisol	No suppression serum cortisol	Suppression of 17-OH progesterone and cortisol
High-dose dexamethasone suppression test	Suppression of serum cortisol to <1.8 μg/dL	No suppression of cortisol	>50% suppression of serum cortisol	No suppression of serum cortisol	Suppression of 17-OH progesterone and cortisol
CRF stimulation test (1 μg/kg (max 100 μg) IV; Sample at 0, 30, and 45 min.					
Change in ACTH	↑	↔	↑	↔	
Change in cortisol	↑	↔	↑	↔	

ACTH, adrenocorticotropic hormone; OHCS, hydroxycorticosteroids; KS, ketogenic steroids; CRF, corticotropin-releasing factor; IV, intravenous. *Arrows* indicate whether increased, decreased or unchanged.

[a]All normal ranges depend on laboratory.

[b]Data from Migeon C. Physiology and pathology of adrenocortical function in infancy and childhood, In: Collu R, Ducharme JR, Guyda H, eds, *Pediatric endocrinology*. New York: Raven Press, 1981;475.

[c]Normal range for 17-ketosteroids:

Age	24-h 17-KS
<2 wk	<2.0 mg
1 mo–5 yr	<0.5 mg
6–8 yr	<1–2 mg
Puberty and adulthood	<17 mg (males) <13 mg (females)

17-OHCS, 24-h urinary 17-hydroxycorticosteroids; 17-KS, 24-h urinary 17-ketosteroids.

1. **Evaluation of etiology.** Once hypercortisolism is established, clarification of the specific cause is made by a variety of tests, as outlined later and in Table 23-2, none of which is 100% diagnostic by itself. The first step is to demonstrate whether the

hypercortisolism is ACTH dependent or ACTH independent. This requires a sensitive and specific assay and **placing the sample on ice** followed by rapid centrifugation because ACTH is rapidly degraded by plasma proteases. Elevated or normal plasma ACTH concentrations (>29 pg/mL) in the presence of hypercortisolism suggest that the primary pathology is due to excess ACTH secretion of pituitary or nonpituitary origin. Consistently suppressed plasma ACTH (<5 pg/mL) concentrations suggest that the primary disorder lies in the adrenal glands. Suppression of plasma cortisol and urinary free cortisol with high-dose dexamethasone (120 μg/kg/day [maximum = 8 mg/day] in four divided doses) but not low-dose dexamethasone (30 μg/kg/day [maximum = 2 mg/day] in four divided doses) suggests a primary hypothalamic-pituitary disorder. Occasionally, patients with Cushing disease require dosages of dexamethasone >120 μg/kg/day to suppress cortisol production. Lack of suppression to high-dose dexamethasone suggests an adrenal tumor or the ectopic secretion of ACTH (Table 23-3). In the former, ACTH concentrations are suppressed, whereas in the latter situation, ACTH concentrations are elevated. An intact or exaggerated cortisol response to ACTH indicates that the adrenal glands remain under pituitary regulation and suggests a pituitary origin of Cushing syndrome. The ACTH and cortisol responses to corticotropin-releasing hormone (CRH) are generally flat in the ectopic ACTH syndrome and adrenal tumors that secrete cortisol, whereas both responses are intact in Cushing disease. A diagnosis of Cushing disease can be made if the mean baseline cortisol increases by 20% at 30 and 45 minutes and the mean ACTH concentration by 35%, 15 and 30 minutes after CRH administration. A comparison of plasma ACTH concentrations in the inferior petrosal sinus with peripheral and contralateral inferior petrosal sinus concentrations following CRH stimulation may help to lateralize a pituitary microadenoma but may be technically difficult, especially in small children. An inferior petrosal ACTH/peripheral ACTH ratio >2 without CRH and >3 after CRH administration is indicative of pituitary Cushing disease. Demonstration of laterality in ACTH concentrations on bilateral inferior petrosal sampling may give an indication of laterality of a pituitary microadenoma, but is not always reliable.

2. **Imaging studies.** Further confirmation of the diagnosis rests on radiographic and scintigraphic studies aimed at anatomically defining the pathology. If Cushing disease is suspected, magnetic resonance imaging (MRI) of the pituitary with p. 273p. 274p. 274p. 275gadolinium enhancement may define a pituitary adenoma, but still may not locate a small microadenoma in which case inferior petrosal sampling may be helpful. If a primary adrenal cause is suspected, abdominal computed tomography (CT), MRI, ultrasound, or scanning of the adrenal glands with ^{131}I-iodocholesterol may reveal evidence of an adrenal adenoma, carcinoma, or hyperplasia. Adrenal CT is generally considered to provide the best radiographic visualization of the adrenal glands.

TABLE 23-2 Diagnostic Tests for Glucocorticoid Excess

	Test	Normal range	Adrenal tumor	Cushing disease	Ectopic ACTH
Screening test	24-hr urine free cortisol	25–75 μg/d	↑	↑	↑
Screening test	8 A.M. Cortisol postdexamethasone at 11 P.M.	<1.8 μg/dL	>1.8 μg/dL	>1.8 μg/dL	>1.8 μg/dL
Screening test	11 P.M. salivary cortisol	<145 pg/mL	>145 pg/mL	>145 pg/mL	>145 pg/mL
Screening test	Midnight serum cortisol	<4.4 mg/dL	>4.4 μg/dL	>4.4 μg/dL	>4.4 μg/dL
Defining test	Diurnal variation in serum cortisol	Present	Absent	Absent	Absent
Defining test	Cortisol 11 P.M.	<4.4 μg/dL	>4.4 μg/dL and similar to A.M. cortisol	>4.4 μg/dL and similar to A.M. cortisol	>4.4 μg/dL and similar to A.M. cortisol
Defining test	ACTH 11 P.M.	<7.5 pg/mL	<7.5 pg/mL	>7.5 pg/mL	>7.5 pg/mL
Defining test	ACTH 8 A.M.		<5 pg/mL	>29 pg/mL	>29 pg/mL
Defining test	Low dose (30 μg/kg/d [max 2 mg/d]/q 6 hr × 48 hr)	A.M. cortisol < 1.8 μg/dL	No suppression of cortisol	No suppression of cortisol	No suppression of cortisol
Dexamethasone suppression test	High dose (120 μg/kg/d [max 8 mg/d]/q 6 hr × 48 hr)	A.M. cortisol <1.8 μg/dL	No suppression of cortisol	>50% suppression of cortisol	No suppression of cortisol
Defining test: CRF stimulation test	Change in ACTH post-CRF stimulation test 1 μg/kg (max 100 μg) IV	↑	↔	↑	↔

No single test alone is definitive. Multiple defining tests may be required.
ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor; q, every; IV, intravenous. *Arrows* indicate whether increased, decreased or unchanged.

TABLE 23-3 Dexamethasone Suppression Test[a]

Day	Prescription	
1		24-hr urine free cortisol and 8 A.M. serum cortisol
2		” ”
3	Low-dose dexamethasone:	” ”

	(30 μg/kg/d [max = 2 mg/d] in 4 divided doses)	
4	Low-dose dexamethasone: (30 μg/kg/d [max = 2 mg/d] in 4 divided doses)	_____”_____
5	High-dose dexamethasone: (120 μg/kg/d [max = 8 mg/d] in 4 divided doses)	_____”_____
6	High-dose dexamethasone: (120 μg/kg/d [max = 8 mg/d] in 4 divided doses)	_____”_____

[a]Test is interpreted as follows:
Normal response: Suppression of urinary free cortisol to <10 pg/mL and 8 A.M. serum cortisol <1.8 μg/dL during low- and high-dose dexamethasone therapy.
Cushing disease: Greater than 50% reduction in urinary free cortisol and 8 A.M. serum cortisol <1.8 μg/dL during high-dose but not low-dose dexamethasone therapy.
Adrenal adenoma, carcinoma, or ectopic ACTH: No suppression of urinary free cortisol or 8 A.M. serum cortisol during either low- or high-dose dexamethasone therapy.
Adapted from Liddle GW. Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. *J Clin Endocrinol Metab* 1960;20:1539–1560.

^{111}In-octreotide scan may be useful in identifying the source of ectopic ACTH secretion, such as a bronchial or thymic carcinoid tumor.

C. The **treatment** of hypercortisolism depends on the etiology.

1. In **Cushing disease**, a radiographically defined pituitary adenoma should be approached transsphenoidally, if possible, and excised leaving the remainder of the pituitary gland intact. If no radiographic abnormalities are found, a microadenoma can still be discovered and removed under direct visualization of the pituitary at surgery, or if inferior petrosal sinus sampling suggests laterality, a hemihypophysectomy can be performed. If these steps fail to result in cure, the diagnosis should be reevaluated; if still consistent with Cushing disease, pituitary radiation can be used. This should be accompanied by pharmacologic therapy with metyrapone (0.5 to 2.0 g/m^2/day in four to six divided doses orally [PO]) to alleviate the symptoms of hypercortisolism until the response to radiation occurs. Other drugs that reduce cortisol secretion are ketoconazole, aminoglutethimide, mitotane, and etomidate. The former is less toxic and may be used in combination with metyrapone because the two agents work at

different enzyme steps to inhibit cortisol secretion. Etomidate may be infused in subhypnotic doses to obtain rapid control of hypercortisolism. Bilateral adrenalectomy, a therapy of last resort, leaves the patient with adrenal insufficiency and results in a significant occurrence of **Nelson syndrome** (pigmentation of the skin with or without enlargement of the sella turcica secondary to an ACTH-secreting pituitary adenoma).

2. **Adrenal adenomas** and carcinomas should be surgically removed, if possible. Differentiation based on histology alone is difficult. Large tumors or tumors p. 275p. 276that have invaded the adrenal capsule are likely to be malignant. Macronodular or micronodular hyperplasia should be treated with bilateral adrenalectomy.
3. **Glucocorticoid coverage:** Regardless of etiology, all patients with Cushing syndrome must be covered perioperatively with stress doses of glucocorticoids (hydrocortisone 50 to 100 mg/m^2/day in three to four divided doses intravenously or intramuscularly or equivalent) for 2 to 3 days because the remaining pituitary–adrenal axis can be suppressed secondary to the primary process, and adrenal insufficiency frequently occurs following removal of the adrenal tumor, pituitary adenoma, or other tumor producing ACTH or CRH. After the patient is clinically stable, the glucocorticoids should be weaned and maintained at physiologic doses (i.e., 10 to 20 mg/m^2/day) until the hypothalamic–pituitary–adrenal axis has recovered at which time the steroids can be slowly tapered over 1 to 2 months.
4. **Inoperable adrenal tumors** can be treated chronically with metyrapone, aminoglutethimide, mitotane, ketoconazole, or mifepristone in an attempt to alleviate the symptoms of hypercortisolism. Mitotane is cytotoxic to adrenal cells and may be useful in the management of adrenal cortical carcinomas.

III. SEX STEROID EXCESS OF ADRENAL ORIGIN

A. Virilizing and feminizing adrenal tumors become apparent in childhood because of the inappropriate development of secondary sexual characteristics and rapid growth. They are found more commonly in females than males and usually produce androgens or

both androgens and cortisol. Virilizing adrenal tumors or congenital adrenal hyperplasia should be suspected in boys when secondary sexual characteristics occur in the absence of testicular enlargement. In girls, clitoromegaly, body hair, and amenorrhea develop.

Feminizing adrenal tumors produce gynecomastia in males and gonadotropin-independent breast development or vaginal bleeding in girls. Purely feminizing adrenal tumors are exceedingly rare in childhood.

B. The **diagnosis** of an adrenal tumor producing sex steroids is established by demonstrating elevations in plasma sex steroids, dehydroepiandrosterone sulfate, and urinary 17-ketosteroids with suppression of gonadotropins. Adrenal adenocarcinomas tend to produce dramatic elevations in plasma concentrations of dehydroepiandrosterone sulfate and in urinary 17-ketosteroids. Dexamethasone administration (30 μg/kg/day in three divided doses for 7 days) does not suppress the elevations in plasma sex steroids and urinary 17-ketosteroids as it does in normal children and patients with congenital adrenal hyperplasia. Abdominal CT, MRI, or, less commonly, ultrasound may be helpful in localizing the tumor.

C. The **treatment** of choice is surgical removal of the adenoma or adenocarcinoma. The prognosis is best if the tumor is small, well encapsulated, and completely removed. The usefulness of histologic studies in differentiating adrenal cortical carcinomas from adenomas is limited. **Mitotane** (6 to 10 g/m^2/day) may be of some use in reducing steroid production in inoperable tumors, but coverage with glucocorticoids must be provided to prevent symptoms of adrenal insufficiency. Often, thyroxine therapy is required as well because **mitotane lowers serum thyroxine concentrations**. The administration of mitotane is associated with a high incidence of gastrointestinal symptoms, dermatitis, and neurologic side effects, such as lethargy, ataxia, and seizures. **It may also cause gynecomastia.**

IV. ALDOSTERONE EXCESS (Table 23-4)

A. Hyperaldosteronism is rare in childhood. Because aldosterone acts on the distal renal tubule to promote sodium reabsorption and the excretion of potassium and hydrogen ions, hyperaldosteronism results in **hypokalemia, metabolic alkalosis, and hypertension**.

Weakness and polyuria are common manifestations of hypokalemia.

1. **Primary** hyperaldosteronism in children is usually secondary to bilateral hyperplasia of the zona glomerulosa and, rarely, secondary to an adenoma. A rare form of hyperaldosteronism called **glucocorticoid-remediable hyperaldosteronism** has been demonstrated to be due to a fusion gene resulting in an ACTH-responsive promoter for the aldosterone synthetase gene (OMIM # 103900) and can be treated with glucocorticoids.

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TABLE 23-4 Causes of Hyperaldosteronism in Childhood

- Primary hyperaldosteronism
  - Bilateral hyperplasia
  - Adenoma
- Secondary hyperaldosteronism
  - Glucocorticoid-remediable hyperaldosteronism
  - Hyperreninism
    - Renal parenchymal disease
    - Renovascular disease
    - Malignant hypertension
    - Reninoma
    - Bartter syndrome
    - Congestive heart failure
    - Diuretic administration
    - Liver disease with ascites
- Pseudohypoaldosteronism

2. Hyperaldosteronism is also seen **secondary** to a variety of renal and liver disorders, resulting in hyperreninism (Table 23-4).
3. **Bartter syndrome** (OMIM # 607364) is a disorder of renal tubular chloride reabsorption characterized by failure to thrive, **hypokalemia, metabolic alkalosis, and elevations in plasma renin activity**, plasma aldosterone concentrations, and urinary prostaglandin excretion.
4. **Pseudohypoaldosteronism** represents a group of disorders involving renal tubular unresponsiveness to aldosterone, resulting in **hyponatremia and hyperkalemia** despite an elevation in

plasma aldosterone concentration. Neither Bartter syndrome nor pseudohypoaldosteronism is accompanied by hypertension.

B. **Liddle syndrome** is a primary **renal disorder** that can be confused with hyperaldosteronism because patients with Liddle syndrome **have hypertension, hypokalemia, and suppressed plasma renin activity**. However, the plasma **aldosterone concentrations are suppressed** in patients with Liddle syndrome, which has been shown to be due to an activating mutation of the sodium channel in the renal tubule (OMIM # 177200).

C. The **syndrome of apparent mineralocorticoid excess** (OMIM # 218030) also causes symptoms and signs of hypermineralocorticoidism without demonstrable elevations in the serum concentrations of aldosterone or deoxycorticosterone. This condition is due to a **deficiency of 11β-hydroxysteroid dehydrogenase** type 2, resulting in **diminished inactivation of cortisol to cortisone**. The resultant accumulation of cortisol activates mineralocorticoid receptors, leading to volume expansion and hypertension. This form of **hypertension is also improved by dexamethasone**, which suppresses ACTH and cortisol and does not activate the mineralocorticoid receptor as cortisol does.

The **diagnosis** of primary hyperaldosteronism is established by demonstrating hypokalemia and inappropriate hyperkaluria (urinary potassium concentration >20 mEq/L in the presence of hypokalemia) unprovoked by diuretic use, elevated plasma aldosterone concentrations and urinary aldosterone excretion, and suppressed plasma renin activity. Plasma aldosterone concentrations and 24-hour urinary aldosterone concentrations must be interpreted in view of age, posture, and 24-hour urinary sodium intake. If plasma renin activity is not suppressed, one of the disorders listed under hyperreninism in Table 23-3 should be suspected. If CT scans of the adrenal fail to uncover the adenoma, an adrenal scan with ^{131}I-6 β-iodomethylnorcholesterol during the administration of dexamethasone (to suppress ACTH and the uptake of tracer in the zona reticularis and fasciculata) for 7 days before and 5 days after administration of the tracer can help identify an adenoma of the zona glomerulosa.

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D. The **treatment** for an aldosterone-secreting adenoma is removal. The

treatment of choice for bilateral hyperplasia of the zona glomerulosa is spironolactone (1 to 3 mg/kg/day PO in three doses) because adrenalectomy usually does not reverse the hypertension. Glucocorticoid-suppressible hyperaldosteronism should be managed with chronic glucocorticoid therapy in physiologic replacement doses (hydrocortisone 7 to 20 mg/m^2/day or equivalent).

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24 Adrenal Insufficiency in Childhood

Kimberly S. Tafuri and Thomas A. Wilson

I. GENERAL PRINCIPLES.

Adrenal insufficiency can be due either to a primary disorder of the adrenal gland or occur secondary to a deficiency of adrenocorticotropic hormone (ACTH) or corticotropin-releasing hormone (CRH). Secondary adrenal insufficiency is usually associated with deficiencies of other hypothalamic and pituitary hormones. Both conditions may be congenital or acquired.

Presenting complaints of adrenal insufficiency are malaise, weakness, failure to thrive, weight loss, anorexia, hypoglycemia, abdominal pain, vomiting, hypotension, confusion, and coma (Table 24-1). Patients with primary adrenal insufficiency are often pigmented because of the stimulating effect of ACTH on melanocytes, and develop salt craving, hyponatremia, and hyperkalemia secondary to aldosterone deficiency. In contrast, in secondary adrenal insufficiency, serum aldosterone concentrations are maintained by the renin–angiotensin system, and therefore electrolytes are generally normal. The exception to this is the dilutional hyponatremia that can develop in any form of severe cortisol deficiency caused by impaired excretion of free water resulting from unrestrained antidiuretic hormone secretion.

II. ETIOLOGY (Table 24-2)

Adrenal insufficiency in children has a variety of etiologies, which are summarized as follows.

A. Congenital

1. Primary congenital adrenal insufficiency

a. Primary congenital adrenal insufficiency is most commonly caused by deficiency of an enzyme involved in cortisol synthesis, resulting in **congenital adrenal hyperplasia**. There are six such proteins described that cause cortisol deficiency either with or without aldosterone deficiency. Congenital adrenal hyperplasia is discussed

elsewhere (see Chapter 22).

b. **Congenital adrenal hypoplasia** results from absence of a differentiation factor that governs development of the adrenal cortex. Well-described forms of adrenal hypoplasia are a consequence of a deletion or mutation of the gene that codes for steroidogenic factor 1 ("cytomegalic form"; OMIM #. 184757) or a mutation or deletion of an X-linked gene, DAX1 ("miniature form"; OMIM #. 300200). The former condition may also cause XY gonadal dysgenesis. Both forms are associated with hypogonadotropic hypogonadism. Congenital adrenal hypoplasia caused by a defect in DAX1 may be seen as a contiguous gene deletion syndrome with associated developmental delay, glycerol kinase deficiency, ornithine carbamyltransferase deficiency (OTC), and Duchenne muscular dystrophy because the glycerol kinase gene, OTC gene, and the muscle dystrophin gene lie in close proximity to DAX1 on the X chromosome. A third form of adrenal hypoplasia is associated with intrauterine growth retardation, metaphyseal dysplasia, and genital abnormalities (IMAGE syndrome; OMIM #614732). Other genetic forms of primary adrenal insufficiency continue to be described.

2. **Secondary congenital adrenal insufficiency** results from congenital ACTH or CRH deficiency or can be mimicked by adrenal insensitivity to ACTH caused by a defect in the ACTH receptor (melanocortin 2-receptor) itself (OMIM ##. p. 279p. 280202200, 202355), or secondary to a mutation in the *AAAS* gene that encodes a protein believed to be involved in the ACTH receptor mechanism. Mutations in the *AAAS* gene, also known as Triple A syndrome, are associated with alacrima and achalasia (OMIM #. 231550).

TABLE 24-1 Symptoms, Signs, and Laboratory Abnormalities in Adrenal Insufficiency

Symptoms	Signs	Laboratory abnormalities
Nausea	Tender abdomen	Eosinophilia
Vomiting	Dehydration	Hypercalcemia
Diarrhea	Hypotension	Hyponatremia

Abdominal pain	Shock	Hypoglycemia
Anorexia	Orthostatic	↓ Cortisol
Weight loss	Disorientation	↑ Plasma renin activity
Confusion		
Coma		
Dizziness		
Weakness		
Fatigue		
Symptoms unique to patients with **primary** adrenal insufficiency:		
Salt craving	Hyperpigmentation	↑ ACTH
	Generalized	↓ Aldosterone
	Extensor surfaces	Hyperkalemia
	Palmar creases	
	Gingival margins	

TABLE 24-2 Causes of Adrenal Insufficiency in Childhood

Primary adrenal insufficiency (Addison disease)

Acute:

Bilateral adrenal hemorrhage

- With septicemia (Waterhouse–Friderichsen syndrome)
- Without septicemia
  - Due to antiphospholipid antibody or hemorrhagic diathesis

Chronic:

Autoimmune

Congenital adrenal hyperplasia

Congenital adrenal hypoplasia

Infection: Tuberculosis, histoplasmosis, cytomegalovirus, HIV

Medication: Ketoconazole, fluconazole, etomidate

Adrenal leukodystrophy

Wolman disease

Congenital unresponsiveness to ACTH

Secondary adrenal insufficiency

Hypopituitarism

- Congenital
- Acquired
- Tumor
- Trauma
- Radiation

Iatrogenic secondary to chronic steroid therapy or medroxyprogesterone

ACTH, adrenocorticotropic hormone; HIV, human immunodeficiency virus.

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B. Acquired

1. Primary

a. **Primary acquired adrenal insufficiency** results from destruction of the adrenal cortex. Historically, the most common cause was tuberculosis. Other infectious diseases, such as histoplasmosis, coccidioidomycosis, cytomegalovirus, and human immunodeficiency virus, may cause adrenal insufficiency. Currently, in the United States, **Addison disease** more commonly results from autoimmune adrenalitis, resulting in destruction of the adrenal cortex. Serum antibodies often directed against the 21-hydroxylase protein may be present and are useful markers of the autoimmune process.

b. **Autoimmune polyglandular disease type 1** is the association of adrenal insufficiency and a variety of other autoimmune disorders, including hypoparathyroidism, hypogonadism, keratopathy, vitiligo, alopecia, pernicious anemia, dystrophy of the nails and enamel, and chronic active hepatitis. This is an autosomal recessive disorder caused by a defect in the autoimmune regulator gene located on chromosome 21q22.3 (OMIM #240300). Addison disease in conjunction with autoimmune thyroiditis and insulin-dependent diabetes (autoimmune polyglandular disease type 2) is associated with human leukocyte antigen DR3 and DR4. Adrenal insufficiency associated with autoimmune polyglandular syndrome type 2 generally does not appear until adulthood.

c. Lysomal acid lipase deficiency (OMIM #27800) is a lipid storage disease, resulting in hepatosplenomegaly, malabsorption, and adrenal calcification which varies in severity from neonatal presentation (**Wolman disease**) to milder forms presenting later in life known as **cholesterol ester storage disease**. **Adrenoleukodystrophy** (OMIM #300100) is a progressive neurologic disorder with adrenal insufficiency caused by a mutation or deletion of ABCD1, an

X-linked gene which is involved in peroxisomal oxidation of long-chain fatty acids. Both disorders present with progressive adrenal insufficiency.

d. **Acute adrenal insufficiency from bilateral adrenal hemorrhage** may be due to overwhelming septicemia (Waterhouse–Friderichsen syndrome), a hemorrhagic diathesis, anticoagulant therapy, or antiphospholipid antibody.
e. **Medications** such as ketoconazole and related antifungals and the anesthetic, etomidate, may cause adrenal insufficiency by interfering with steroidogenesis. Mitotane, an agent used to treat adrenal carcinoma, results in adrenal insufficiency because of direct toxic effects on the adrenal cortex.

2. **Secondary adrenal insufficiency** results from any process that interferes with the production or release of CRH from the hypothalamus or ACTH from the pituitary. The most common cause is iatrogenic, secondary to chronic suppression of the hypothalamic–pituitary–adrenal axis from long-term (>2 weeks) glucocorticoid therapy and may be seen in children on **inhalable glucocorticoids**, and patients on medroxyprogesterone or long-term opioids. Full recovery of the axis can take up to 12 months.

   Hypopituitarism with adrenal insufficiency also occurs secondary to a sellar or suprasellar mass, an inflammatory or infiltrative process, surgery, or cranial irradiation. This condition is mimicked clinically by congenital unresponsiveness to ACTH because of an absence or alteration of the ACTH receptor (OMIM # 202200); however, serum ACTH concentrations easily distinguish the two.
3. **Relative adrenal insufficiency** without adrenal hemorrhage may be seen in the setting of severe sepsis. Studies suggest that some patients with catecholamine-resistant hypotension have a blunted cortisol response to cosyntropin (i.e., a peak cortisol < 18 μg/dL and/or cortisol increment < 9 μg/dL) and fare better if treated with glucocorticoids. This issue remains controversial in older patients, but is particularly poignant in the setting of low birth weight hypotensive infants who may benefit from modest doses of hydrocortisone but who are also

at risk of developing gastric perforations and adverse long-term developmental consequences from exposure to high-dose glucocorticoids. Data do not show a correlation between cortisol response to ACTH and clinical outcome.

C. Hypoaldosteronism occurs in patients with primary adrenal insufficiency and in some forms of congenital adrenal hyperplasia, but it can also occur as an isolated disorder. Children with enzyme defects in aldosterone synthetase (CYP11B2), which converts corticosterone to aldosterone, present with failure to thrive, salt craving, hyponatremia, hyperkalemia, and hyperreninemia (OMIM #124080). Similar clinical presentations are seen in children with **pseudohypoaldosteronism**, an autosomal recessive or dominant defect in the mineralocorticoid receptor resulting in resistance to aldosterone (OMIM #264350) and by mutations of the epithelial sodium channel that render the renal tubule unresponsive to aldosterone (OMIM #177735). Low serum aldosterone concentrations in hypoaldosteronism and high serum aldosterone concentrations in pseudohypoaldosteronism distinguish these conditions.

III. DIAGNOSIS. A high index of suspicion is crucial because the presenting symptoms of adrenal insufficiency are often subtle, and early diagnosis may be lifesaving. A history of steroid use, the presence of another autoimmune endocrine disorder (especially hypoparathyroidism), a family history of autoimmune endocrinopathies, or unexplained hypotension or hypoglycemia should heighten the suspicion of adrenal insufficiency. Random serum cortisol concentrations must be interpreted in the context of the clinical condition of the patient. If the patient's condition permits, an ACTH stimulation test will establish the diagnosis. Otherwise, the patient must first be stabilized with the administration of dextrose, fluids, electrolytes, and glucocorticoids and the diagnosis established subsequently. **If dexamethasone is used, one can follow with an ACTH stimulation test** within 24 hours to confirm diagnosis of adrenal insufficiency. Infants typically have low baseline serum cortisol concentrations.

A. Tests of the hypothalamic–pituitary–adrenal axis. Tests of adrenal function are divided into those that test the entire hypothalamic–pituitary–adrenal axis (Table 24-3) and those that specifically test the function of the adrenal gland itself (Table 24-4).

An elevated ACTH concentration (>2× the upper normal limit for the assay) in the presence of an inappropriately low serum cortisol concentration (<5 μg/dL) indicates primary adrenal deficiency or adrenal insensitivity to ACTH. However, often, dynamic stimulation tests of adrenal function are required. In the very early stages of primary adrenal insufficiency, mineralocorticoid deficiency may be the only presenting sign. An **elevated plasma renin** activity with a low or low normal aldosterone is indicative of **aldosterone deficiency**.

1. **ACTH stimulation tests** (Table 24-4). A 30- or 60-minute cosyntropin (Cortrosyn) stimulation test is useful as a screening test for adrenal insufficiency. A normal response is a peak serum cortisol >18 μg/dL. In primary adrenal insufficiency, the baseline serum ACTH is elevated, and the cortisol response to cosyntropin is flat. Patients with secondary adrenal insufficiency generally have a blunted cortisol response because of the hypotrophy that occurs in the adrenal in the absence of ACTH stimulation. However, patients with recent acquisition of ACTH or CRH deficiency may still have a normal cortisol response to cortrosyn because the adrenal gland may not yet be hypotrophic.
2. **Insulin-induced hypoglycemia** stimulates CRH and ACTH release, which should result in a serum cortisol concentration >18 μg/dL. Patients undergoing this procedure must be monitored closely, and the hypoglycemia reversed with intravenous (IV) dextrose if unconsciousness or a seizure results from the hypoglycemia. This test is less commonly used in preference for the cosyntropin stimulation test (see above), but has the advantage that it directly evaluates the entire hypothalamic–pituitary–adrenal axis.
3. **Metyrapone** inhibits the 11β-hydroxylase enzyme, which converts 11-deoxycortisol to cortisol. In normal individuals, plasma concentrations of ACTH and compound S (11-deoxycortisol) increase following the administration of metyrapone. Utilizing this property of metyrapone, several different protocols have been designed to test the integrity of the hypothalamic–pituitary–adrenal axis. **The shorter** p. 282p. 283**overnight version of the metyrapone**

stimulation test may be useful in screening patients for adrenal insufficiency. The usual dose of metyrapone is 30 mg/kg (maximum of 1 g) orally (PO) at midnight. Blood is drawn at 8 A.M. the next morning for cortisol, compound S (11-deoxycortisol), and ACTH. An elevated ACTH in the setting of low morning cortisol and suboptimal rise in 11-deoxycortisol is consistent with primary adrenal insufficiency. If ACTH is not elevated, the adrenal insufficiency is most likely central. This test is less commonly used in preference for the cosyntropin stimulation test (see above), but has the advantage that it directly evaluates the entire hypothalamic–pituitary–adrenal axis. It is often difficult to obtain metyrapone, and **this test carries a risk of inducing an adrenal crisis**.

TABLE 24-3 Tests of Hypothalamic–Pituitary–Adrenal Function

Insulin-tolerance test		
Time (min)	**Prescription**	**Laboratory**
0	Regular insulin (0.075–0.1 units/kg IV)	Cortisol, blood sugar
15, 30, 45, 60		Cortisol, blood sugar
Normal response: 50% decrease in blood glucose and plasma cortisol >18 μg/dL on any sample		
Overnight metyrapone stimulation test		
Day	**Prescription**	**Laboratory**
Midnight	Metyrapone (30 mg/kg PO at midnight)	Cortisol, 11-deoxycortisol, ACTH
8 A.M.		Cortisol, 11-deoxycortisol, ACTH
Normal response: serum cortisol concentration <8 μg, 11-deoxycortisol concentration >10 μg/dL, and an elevated ACTH.		
Glucagon stimulation test		
Time (min)	**Prescription**	**Laboratory**
0	Glucagon 30 μg/kg (max of 1 mg) IV, SQ, or IM	Cortisol
60, 80, 120, 150, 180		Cortisol
Normal response: serum cortisol >18 μg/dL on any sample		
Corticotropin-releasing hormone stimulation test		
Time (min)	**Prescription**	**Laboratory**
0	Ovine CRH 1 μg/kg IV	ACTH, cortisol

15, 30, 60	ACTH, cortisol
Normal response: Peak cortisol >18 μg/dL	

ACTH, adrenocorticotropic hormone; IM, intramuscular; IV, intravenous; PO, orally; SQ, subcutaneous.

TABLE 24-4 Tests of Adrenal Function

Cosyntropin (Cortrosyn) stimulation test		
Time (min)	**Prescription**	**Laboratory**
0	Cosyntropin (0.25 mg/m^{2a} (max dose 0.25 mg) IV or IM)	Cortisol
30, 60		Cortisol
Normal response: peak plasma cortisol >18 μg/dL.		

IM, intramuscular; IV, intravenous.
[a]Alternative dose 1 μg for low-dose cosyntropin stimulation test.

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4. **Glucagon** stimulates the adrenal axis and may be used to assess the adrenal axis.
5. **CRH stimulation test** may be used to assess the pituitary–adrenal axis.

A subnormal rise in serum cortisol concentration in response to hypoglycemia, glucagon, or CRH or an inadequate increase in serum 11-deoxycortisol concentration following metyrapone establishes a diagnosis of adrenal insufficiency, but does not define whether the disorder is primary or secondary. Therefore, either plasma ACTH measurement must be obtained or the adrenal response to ACTH must be tested directly by stimulation with exogenous ACTH.

IV. TREATMENT

A. Acute adrenal insufficiency must be managed promptly with IV fluids and glucocorticoids. A solution of 5% dextrose in 0.9% NaCl (450 mL/m^2 in 30 to 60 minutes to correct shock, then 3200 mL/m^2/day) should be infused. Hydrocortisone (2 mg/kg IV) or an equivalent dose of another glucocorticoid should be given every 6 hours until the patient is stable. Greater amounts of dextrose can be

used, if necessary to correct hypoglycemia. If hyponatremia or hyperkalemia is present, higher dosages of hydrocortisone (5 mg/kg every 6 hours) can be used for a mineralocorticoid effect, or the patient can be started on oral fludrocortisone 0.1 mg PO daily (Florinef).

For patients who have not received a diagnosis but who are suspected of having an acute adrenal crisis, the same regimen as outlined above can be used, but dexamethasone (0.5 to 1 mg/m^2) may be substituted for hydrocortisone. This allows an opportunity to promptly carry out a cosyntropin stimulation test while the patient is stabilizing because dexamethasone will not interfere with the measurement of plasma cortisol concentrations.

B. Chronic treatment

1. **Glucocorticoids.** Glucocorticoid replacement is designed to replace the normal cortisol production rate, which is estimated to be 6 to 10 mg/m^2/day. The dosage must be individualized to allow adequate growth but prevent fatigue, malaise, and weakness. Excess glucocorticoid therapy suppresses growth. Equivalent dosages of the various steroids are given in Table 24-5. The more potent steroids are best p. 284p. 285avoided in infants and children because of the difficulty in fine-tuning the dosage to permit adequate growth but prevent symptoms of adrenal insufficiency. The dose of glucocorticoid must be doubled or tripled to cover physically stressful situations (e.g., infections, surgery, and trauma). Patients who have been treated with pharmacologic doses of steroids for more than 2 weeks within the past 6 to 12 months should be given a triple maintenance dose of steroids during times of stress to prevent an adrenal crisis.

TABLE 24-5 Glucocorticoid Replacement Therapy: Average Dose

Glucocorticoid	Parenteral (mg/m^2/d)	Oral (mg/m^2/d)
Cortisone acetate		10–20
Hydrocortisone acetate	8–12 (IM only)	
Hydrocortisone	6–10 (IM or IV)	7–20
Prednisone[a]		2–5
Methylprednisolone[a]	1.0–2.0 (IM or IV)	1.5–4
Dexamethasone[a]	0.15–0.25 (IM or IV)	0.2–0.5

IM, intramuscular; IV, intravenous.
[a]Not recommended for infants and small children.

2. **Mineralocorticoids.** Only patients with primary adrenal insufficiency require mineralocorticoid replacement therapy. The dosage of mineralocorticoid does not vary with body size because aldosterone secretion varies only twofold from infancy to adulthood. Generally, fludrocortisone acetate 0.1 mg/day PO is adequate. Unlike glucocorticoids, the dose of fludrocortisone does not need to be increased to cover stress. Excessive doses of mineralocorticoid result in hypertension and hypokalemia.
3. **Sodium chloride supplementation** is usually necessary in infants with primary adrenal insufficiency caused by underlying mineralocorticoid resistance associated with the immature kidney. The usual dosage is 2 to 4 g/day (4 g = 1 teaspoon). Sodium chloride supplements are generally not necessary in older children who can find access to salt to satisfy their requirement.
4. **Medical alert** bracelet or necklace is advisable for patients with adrenal insufficiency.
5. **Injectable glucocorticoids.** Parents or caretakers should be instructed on how to give injectable glucocorticoids to cover the child's need for cortisol in times of stress or if the child is unable to take medication PO. Generally, hydrocortisone 50 to 100 mg/m^2/day, methylprednisolone 10 to 20 mg/m^2/day, or dexamethasone 1 to 2 mg/m^2/day is sufficient. Hydrocortisone acetate and dexamethasone have the advantage of longer duration of action (12 to 24 hours) than hydrocortisone succinate, which therefore must be repeated every 6 to 8 hours if the child is still unable to take medication PO. Rectal suppositories can also be used emergently if the child is unable to tolerate PO but should be avoided in the setting of diarrhea and may not have predictable absorption.

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SECTION 4

Disorders of the Reproductive System

25

Female Reproductive Endocrinology in Adults

M. Blake Evans, Eric D. Levens, and Alan H. DeCherney

I. OVARIAN INSUFFICIENCY

Ovarian insufficiency refers to disorders of deficient ovarian function **within the ovary (primary)** or to disorders **outside the ovaries**, such as disruptions in the hypothalamic–pituitary axis or extragonadal sites resulting in deranged gonadotropin secretion **(secondary)**. A follicle-stimulating hormone **(FSH)** level may be useful when evaluating patients suspected of ovarian insufficiency, because it may assist in localizing the site of the disruption. Additionally, recent literature reveals that anti-Müllerian hormone (AMH), which is exclusively produced by granulosa cells during the early stages of ovarian follicular development, decreases in concentration with increasing age. Many studies have demonstrated with convincing evidence that **AMH** is the best currently available correlating **measure of primordial follicle reserve**. AMH can improve infertility treatment outcomes, reveal ovarian dysfunction (such as polycystic ovary syndrome [PCOS]), and demonstrate the level of ovarian follicle preservation after ovarian surgery or gonadotoxic cancer drug administration.

A. Primary ovarian insufficiency (Figs. 25-1 and 25-2)

1. **Primary amenorrhea**
   - **a.** The absence of menses within 5 years of initiating pubertal development with breast budding present (if breast development occurs at or before 10 years of age).
   - **b.** No menses by age 13 in addition to the absence of secondary sexual characteristics
   - **c.** No menses by age 15 despite having secondary sexual characteristics
2. **Gonadal dysgenesis.** Gonadal dysgenesis represents a spectrum of pathology culminating in bilateral fibrous streak ovaries lacking primary follicles.
   - **a. Pathophysiology**
     - **i.** Autopsy studies reveal that ovaries of 45,X fetuses are histologically normal until 20 weeks of gestation, but have lost nearly all oocytes at puberty. The absence or paucity of oocytes in the gonadal streak is a result of accelerated germ-cell atresia.
     - **ii.** The oocyte atresia rate is controlled by X-chromosome influences.

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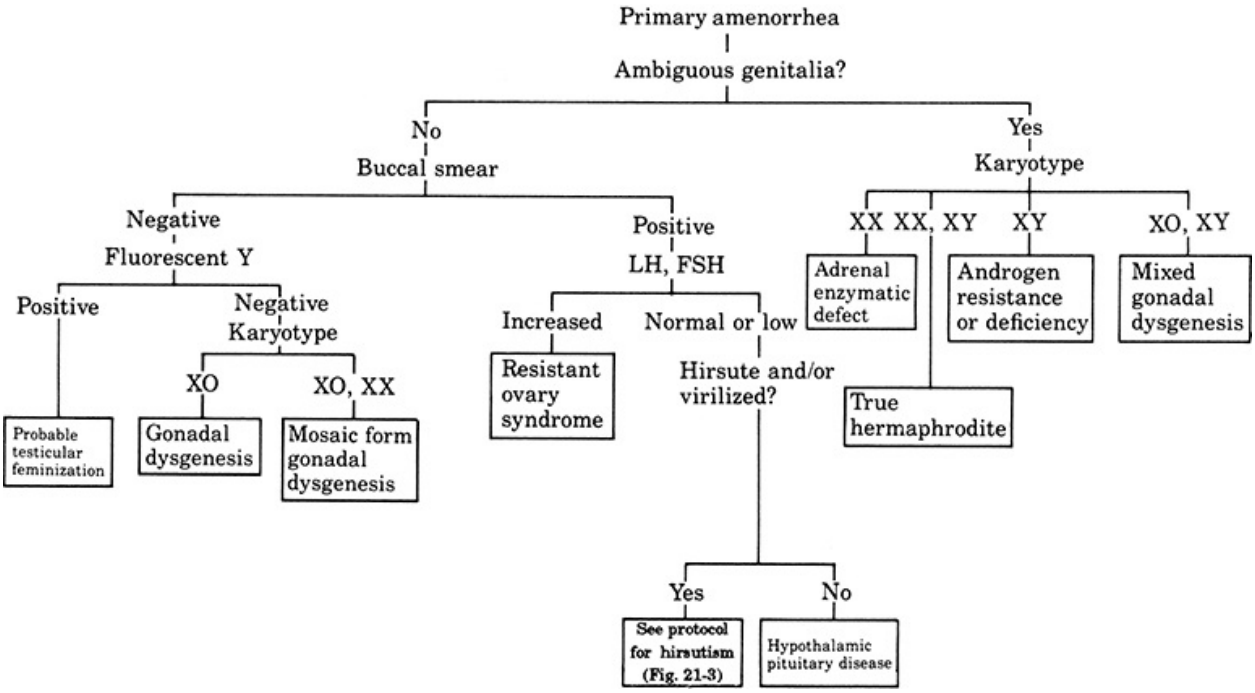

Figure 25-1. Algorithm for the workup of primary amenorrhea. FSH, follicle-stimulating

hormone; LH, luteinizing hormone. (Reprinted with permission from Cave WT Jr, Streck W. Amenorrhea. In: Streck W, Lockwood DH, eds. *Endocrine Diagnosis: Clinical and Laboratory Approach.* Boston: Little, Brown and Company; 1983:191–208.)

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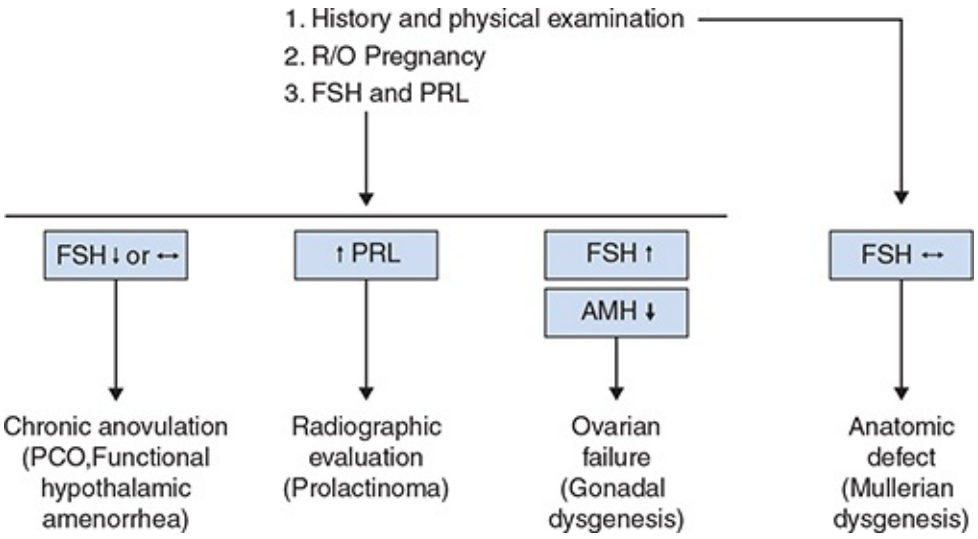

Figure 25-2. Suggested flow diagram aiding in the evaluation of women with amenorrhea. AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; PCO, polycystic ovaries; PRL, prolactin. (Reprinted with permission from Current evaluation of amenorrhea: the practice committee of The American Society for Reproductive Medicine. *Fertil Steril* 2008;90:219–225.)

iii. The gonadal dysgenesis genotype spans from 45,X (sex chromatin–negative) to apparently normal karyotypes 46,XX and 46,XY (sex chromatin–positive). In between are karyotypes with deletions of chromatin material from sex chromosomes, including X-chromosome deletions of the long arm (46,XXq$^-$) or the short arm (46,XXp$^-$). The karyotype may contain more severe deletions, such as a ring X or an X isochromosome.

iv. Genotypic mosaicism consisting of more than one cell population with differing karyotypes may occur as a result of anaphase lag in the first meiotic division or abnormal mitosis after fertilization.

v. The phenotypic spectrum of gonadal dysgenesis is broad, extending from classic 45,X Turner syndrome stigmata (short stature, primary amenorrhea, and sexual infantilism) to those with a normal karyotype and few or no somatic

abnormalities.

vi. Sexual infantilism and short stature are the two most common abnormalities associated with 45,X (Turner syndrome) gonadal dysgenesis and its variants. Short stature may in part be a result of haploinsufficiency of the short stature homeobox-containing gene. Other features include epicanthic folds, low-set ears, a high-arched or cathedral hard palate, micrognathia, short neck, webbing of the neck as a result of congenital formation of a cystic hygroma, ptosis of the eyelids, shield chest, wide carrying angle of the arms, lymphedema of the dorsum of the hands and feet at birth, shortening of the fourth or fifth metacarpals or metatarsals, hypoplastic nails, osteoporosis, horseshoe kidney, coarctation of the aorta, and red-green color blindness.

vii. The term **pure gonadal dysgenesis** has been used to describe patients with streak gonads, female genitalia, and normal Müllerian structures (uterus, cervix, and fallopian tubes) associated with 46,XX or 46,XY (Swyer syndrome) karyotypes. In the presence of a defective SRY gene, the indifferent gonads fail to differentiate in to testes, and thus AMH does not prevent normal Müllerian structures from forming, and the lack of testosterone prevents Wolffian ducts from developing internal male genitalia. These individuals tend to be sexually infantile but of a normal height and lack the typical Turner stigmata.

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viii. Mixed gonadal dysgenesis represents asymmetric gonadal development with a testis present on one side and a gonadal streak on the other side. These patients may develop Wolffian structures, and because the fetal testis is functional during fetal life, ambiguous external genitalia may occur. The typical karyotype in this setting is 45,X/46,XY.

b. Diagnosis

i. The diagnosis of 45,X and X-chromatin–positive variants of gonadal dysgenesis should be considered in any adult female with abnormal menstruation who is shorter than 5 feet, even in the absence of dysmorphic features. The

majority will have primary amenorrhea, although the less severely affected may present with secondary amenorrhea. Pure gonadal dysgenesis should be considered among those with primary amenorrhea and pubertal delay. These patients may be of normal stature. Diagnostic studies should include the following:

a) Plasma FSH and luteinizing hormone (LH) levels (both are elevated).

b) A karyotype of 30 to 50 metaphase preparations should be obtained to assist in establishing the diagnosis. Karyotypes are also helpful to identify those with an XY cell line; however, even among nonmosaic 45,X, standard karyotype may not detect a Y-chromosome–containing cell line; strong consideration should be given to performing molecular studies for a Y-chromosome.

c) Women with mosaic Turner syndrome who do eventually achieve puberty and subsequently ovulate have higher AMH levels than nonmosaic Turner syndrome patients. Therefore, AMH levels can potentially serve as markers of fertility status in mosaic Turner syndrome patients.

ii. An intravenous pyelogram should be obtained to detect renal abnormalities, such as a horseshoe or pelvic kidney or double ureters.

iii. Careful evaluation should be made for cardiovascular abnormalities, including coarctation of the aorta, bicuspid aortic valve, aortic stenosis, and prolongation of the QTc interval. Hypertension should be managed aggressively.

iv. Thyroid function should be evaluated periodically with serum thyroid-stimulating hormone, thyroid hormones, or thyroid peroxidase antibodies, because the incidence of autoimmune thyroiditis (Hashimoto disease) is increased in gonadal dysgenesis and can result in hypothyroidism.

v. Bone age should be ascertained before hormonal treatment with estrogen or human growth hormone (hGH) is begun and monitored carefully during treatment.

vi. Short stature in 45,X gonadal dysgenesis and its variants is usually not the result of growth hormone (GH) deficiency.

However, some sources say that this attenuation in growth is partly due to insufficient GH secretion caused by deficient sex steroid production, and end-organ resistance to insulin-like growth factor-1. Nevertheless, hGH use results in an increase in both short-term and long-term height achievement. The greatest improvements in stature were observed among those patients receiving early hGH treatment with a delay in estrogen replacement therapy until ≥14 years or older. Of note, studies have suggested that hGH use may increase the risk of conductive and sensorineural hearing loss and may induce higher rates of scoliosis and kyphosis.

vii. Carbohydrate intolerance and mild insulin resistance have been noted among many Turner syndrome patients; however, recent evidence suggests that insulin deficiency as a result of pancreatic β-cell dysfunction may be a primary feature of Turner metabolic syndrome. Regardless of the etiology, the risk of diabetes mellitus remains two to four times higher than in weight-matched controls. Therefore, glucose-tolerance testing should be done on a periodic basis.

viii. Conductive and sensorineural hearing loss is also common among these patients and should be evaluated.

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c. Management

i. Estrogen replacement therapy should be initiated slowly (0.3 mg daily of conjugated equine estrogens) at age 14 or 15 and gradually increased to 1.25 or 2.5 mg. After 6 to 12 months of unopposed estrogen use, cyclic medroxyprogesterone or an equivalent progestin to prevent endometrial hyperplasia is added (commonly the first 14 days of each month). The treatment philosophy should be to simulate the normal pubertal process by using a gradually increasing dose of estrogen, which should be individualized for each patient. **Beginning treatment with very low doses permits attainment of the maximal bone growth potential.** The dose should be progressively increased to also induce secondary sexual development. In

young adulthood, patients frequently switch to oral contraceptives or continuous-combined estrogen/progestin preparations: 100 μg ethinyl estradiol patches daily (young adulthood) and 50 μg (by 30 to 35 years of age) with monthly or trimonthly progesterone withdrawal to once again, protect the uterine lining from developing endometrial hyperplasia.

ii. Assessment of progress should be made with frequent office visits for careful documentation of growth velocity and the attainment of pubertal milestones.

iii. Psychological counseling with the goal of improving the individual's sexual self-image is an essential part of the therapeutic program.

iv. Surgical correction of the somatic abnormalities may be indicated (e.g., high-arched palate, webbing of the neck, and ambiguous genitalia).

v. Those with a Y-chromosome or a positive assay for HY antigen should have bilateral gonadectomy because of the high incidence of gonadoblastomas.

vi. Careful follow-up is essential because of the projected long-term administration of estrogens. Any abnormal uterine bleeding pattern should be investigated with endometrial sampling.

vii. Although pregnancy can be achieved in some Turner syndrome patients, **adoption should be suggested owing to the risk of aortic rupture during pregnancy**. An echocardiogram revealing no dilation of the aortic root should not negate the fact that aortic rupture can still subsequently occur. The structure of the aortic wall is abnormal, and dilation can develop after a normal echocardiogram.

3. Menopause

a. Pathophysiology

i. **Menopause** refers to the time around menstruation cessation (mean age of 51 years), with the absence of menses for 12 months. **Perimenopause** refers to the menopausal transition, which has been divided into early and late based on the variability of the menstrual cycle.

ii. Other symptoms and signs of menopause include

vasomotor instability, anxiety, depression, irritability, osteoporosis, and conditions associated with epithelial atrophy, such as dyspareunia, pruritus, and genitourinary (GU) symptoms.

iii. Symptom severity varies among individuals and relates to ovarian estrogen deficiency as well as to personal, familial, and societal attitudes toward aging. Between 25% and 40% of women require medication for menopausal symptom relief.

b. Diagnosis

i. Menopause should be suspected as a cause of amenorrhea in any postpubertal female who has the symptoms listed in Section I.B.1.

ii. Hypoestrogenism (estradiol levels average 15 pg/mL) and elevated FSH levels (30-40 mIU/mL) are consistent with menopause. However, an FSH value >10 mIU/mL should be viewed with suspicion for possible ovarian failure.

iii. Menstruation may cease before age 40 as a result of primary ovarian insufficiency, resulting in hypergonadotropinism and hypoestrogenism; this condition is termed **premature ovarian failure (POF)**. Causes include cytotoxic drugs, irradiation, autoimmune oophoritis, and idiopathic causes. Approximately 20% of women with POF also have autoimmune diseases, such as thyroiditis, hypoparathyroidism, type 1 diabetes mellitus, p. 291p. 292and hypoadrenalism. It seems reasonable to evaluate for these disorders yearly in addition to bone density measurements. Cytosine-guanine-guanine (CGG) trinucleotide repeat disorder, or codon reiteration disorder, is a kind of mutation where the abnormal expansion of DNA triplets (trinucleotides) repeats in certain genes and exceeds the normal, stable threshold. Expansion of CGG trinucleotide repeats within the *fragile X mental retardation-1* (*FMR1*) gene has been associated with fragile X syndrome, whereas premutations in the *FMR1* gene have been linked to idiopathic POF. Any family history of POF,

mental retardation, or ataxia should raise suspicion to evaluate the *FMR1* gene.

iv. An elevated FSH level does not exclude future ovulation because patients have been described who show ovulation and even pregnancy after a transient period of elevated FSH levels. Therefore, it may be more appropriate to refer to these patients as having "primary ovarian insufficiency," "hypergonadotropic hypogonadism," or even "primary hypogonadism" instead of describing the ovaries to have undergone "failure."

c. Management

i. Indications for therapy

a) Disabling hot flashes
b) Severe mucosal atrophy of the GU tract
c) Osteoporosis: baseline bone mineral density should be obtained at the time of diagnosis of POF
d) Certain psychiatric symptoms: low self-esteem, anxiety, and depression.

ii. Absolute contraindications to estrogen therapy

a) Estrogen-dependent tumors, especially of the breast
b) Acute or chronically impaired liver disease
c) Thromboembolic disease
d) Endometrial cancer
e) History of malignant melanoma
f) Undiagnosed abnormal uterine bleeding

iii. Relative contraindications

a) Hypertension
b) Migraine headaches
c) Fibrocystic disease of the breast
d) Chronic thrombophlebitis
e) Gallbladder disease
f) Hyperlipidemia

iv. General principles of therapy

a) Not all women require or need estrogen therapy for menopause.
b) Therapy should be limited to those with severe or disabling symptoms.
c) No data exist on the safest duration of therapy.
d) The lowest effective dose should be used because

complications are related to the dosage and length of therapy. Progesterone should be used in conjunction with estrogen in those with an intact uterus to reduce the risk of endometrial hyperplasia.

e) Despite recent evidence suggesting that hormone therapy may convey some cardioprotective benefits in selected populations of women in early menopause, hormone therapy should not be used for the primary or secondary prevention of disease at the present time.

v. Therapy program

a) Continuous 0.625 to 1.25 mg conjugated equine estrogen (or E2-17β 1 to 2 mg or transdermal E2-17β 100 μg) and medroxyprogesterone, 2.5 to 5.0 mg (or micronized progesterone 100 to 200 mg), may be used to begin therapy. This dose may be adjusted as symptoms abate or persist.

b) Cyclic estrogen therapy consisting of 3 weeks on, 1 week off, with a progestational agent (medroxyprogesterone acetate, 5 to 10 mg per day), can be given for 14 days every 30 to 60 days. However, patients should be instructed to expect menstrual flow. No regimen has been shown to be superior to another.

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c) Estrogen alone may be used for women without an intact uterus who are not at risk for developing endometrial hyperplasia.

d) In addition to regular weight-bearing exercise, daily ingestion of calcium 1 200 to 1 500 mg, in addition to vitamin D 600 to 800 IU, to decrease risk of osteoporosis development is recommended.

vi. Follow-up of therapy

a) Any abnormal uterine bleeding should be thoroughly investigated with endovaginal ultrasound and possibly an endometrial biopsy.

b) Regular periodic examination with careful observation for complications should take place every 6 to 12 months.

vii. Pregnancy

a) Spontaneous pregnancy rates of patients with POF are only 5% to 10%, and the use of donor oocytes with in vitro fertilization should be discussed with the patient.

b) Women with premutations of the FMR1 gene should be counseled extensively regarding possible transmission of the premutation or the full mutation resulting in fragile X syndrome. Preimplantation genetic testing for the FMR1 gene and subsequent in vitro fertilization can be offered to the patient as well.

4. Corpus luteum deficiency

a. Pathophysiology. Deficient corpus luteum function, also termed **luteal phase defect,** remains a controversial diagnosis; nevertheless, it is defined as luteal progesterone production that is inadequate to support the development or to sustain receptive endometrium for implantation. Although they are rarely the cause of primary infertility, luteal phase defects have been implicated as a cause of repeated early miscarriages.

i. Any disturbance of follicular growth and development can produce an inadequate follicle and a deficient corpus luteum.

ii. Specific causes include suppressed gonadotropin-releasing hormone (GnRH) production, inadequate FSH level early in the cycle, a deficient ovulatory surge of LH, an inadequate tonic level of LH, deficiency of LH receptors on the cells of the corpus luteum, or the use of drugs to induce ovulation.

iii. Secondary causes include severe systemic illnesses, medications (i.e., opioids or nonsteroidal anti-inflammatory agents), endocrinopathies (hyperprolactinemia, hyperandrogenism, or thyroid dysfunction), and endometrial defects.

iv. The clinical presentation of the luteal phase defect is recurrent early miscarriages or shortened menstrual cycle length. However, the primary complaints are more likely related directly to the cause, such as galactorrhea or hyperandrogenism.

b. Diagnosis

i. Diagnosis of corpus luteum deficiency depends on documentation of inadequate progesterone production or altered life span of the corpus luteum. Normal basal body

temperatures (BBTs) should be biphasic, with the luteal phase marked by an increased core body temperature of approximately 1°C, occurring at the time of corpus luteal function (~12 to 14 days). Chaotic BBT readings in which there are no apparent mid-cycle temperature shifts preceding the onset of menses strongly suggest anovulation.

ii. Diagnosis can be made by endometrial histology on the 26th day of the cycle to determine whether histologic features are compatible with the menstrual dating. Classically, with inadequate progesterone production, the histologic dating of the endometrium lags behind the menstrual cycle by 2 or more days. There is also disparity in the histologic characteristics of the stroma and glands of the endometrium. However, endometrial biopsy is no longer recommended because histologic endometrial dating is neither accurate nor precise.

iii. A random progesterone level of <3 ng/mL reflects anovulation and is abnormal. Additionally, a midluteal phase P_4 (progesterone) level >10 ng/mL is consistent with adequate P_4 production.

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c. Management

i. Treatment should be directed at correcting the etiologic factor. Hyperprolactinemia can be reversed with bromocriptine or cabergoline (for dosage, see Chapter 10). After physiologic, pharmacologic, or secondary causes (i.e., hypothyroidism) have been ruled out, a magnetic resonance imaging (MRI) can be performed to rule out a prolactinoma. Inadequate follicle stimulation may be improved with clomiphene citrate, letrozole, or FSH. The initial dose of clomiphene (50 mg/day for 5 days) may be increased to 100 mg and then to 150 mg at intervals of two or three cycles. Letrozole can be given as 5 mg/day for 5 days. Certain hyperandrogenic states, particularly those of nontumorous adrenal origin, can be suppressed with a low dose of glucocorticoid, such as dexamethasone (DEX), 0.25 mg at bedtime.

ii. Synthetic progestational agents should not be used because they are teratogenic and luteolytic.

iii. The luteal phase defect can also be managed with progesterone suppositories (vaginal or rectal, 25 to 100 mg twice a day), Crinone 8% every evening, or Prometrium 200 mg twice a day starting 3 days after ovulation to produce a physiologic level of circulating progesterone and lengthen the menstrual cycle by about 3 days. Treatment is continued until menses, or if pregnant, can be continued to approximately 9 weeks estimated gestational age.

5. **The resistant ovary syndrome (aka "Savage syndrome")**
   a. **Pathophysiology**
      i. A term originally described as existing in young women with amenorrhea, elevated peripheral gonadotropins, normal secondary sexual characteristics, 46,XX karyotype, and normal immature ovarian follicles who are unresponsive to exogenous gonadotropin administration. Resistant ovary syndrome previously was distinguished from POF by the presence of ovarian follicles. This diagnosis should no longer be used because there are many different causes that may present identically, in which mutations in both FSH receptors and steps involved in FSH postreceptor action are most common. Other similar familial autosomal disorders include mutations of the phosphomannomutase-2 gene, the galactose-1-phosphate uridyltransferase gene, chromosome 3q containing the Blepharophimosis gene, and the autoimmune regular gene, to name only a few.

B. Secondary ovarian hypofunction (Fig. 25-3)

1. **Hypogonadotropism**
   a. **Pathophysiology**
      i. Ovarian hypofunction secondary to low gonadotropin levels is a common cause of menstrual problems and infertility. FSH has been suggested to be the preferred indicator of hypergonadotropic hypogonadism. LH may be the preferred indicator of hypogonadotropic hypogonadism; plasma LH levels <0.5 mIU/mL indicate hypogonadotropism. Altered gonadotropin secretion can result from disturbances in the pituitary or hypothalamus. Hypogonadism in the setting of

delayed puberty should warrant consideration of MRI of the brain.

ii. Hypothalamic amenorrhea is the most common variety of hypogonadotropic hypogonadism. The disorder may be functional or may result from an organic lesion, such as a tumor.

iii. Patients with hypogonadotropism can be subdivided into those with deficient estrogen production and those with normal or excessive estrogen production. Conditions that produce hypogonadotropism as a result of primary involvement of the hypothalamic–pituitary axis are usually associated with hypoestrogenism. Examples include **Sheehan disease** (hypopituitarism secondary to a pituitary infarction following obstetric shock because of excessive bleeding), isolated gonadotropin deficiency, space-occupying lesions of the sella turcica, empty sella syndrome, congenital defects, and trauma. Increased estrogen secretion from ovarian tumors and functional cysts of the ovary suppress the secretion of LH and FSH, causing anovulation and hypogonadotropism.

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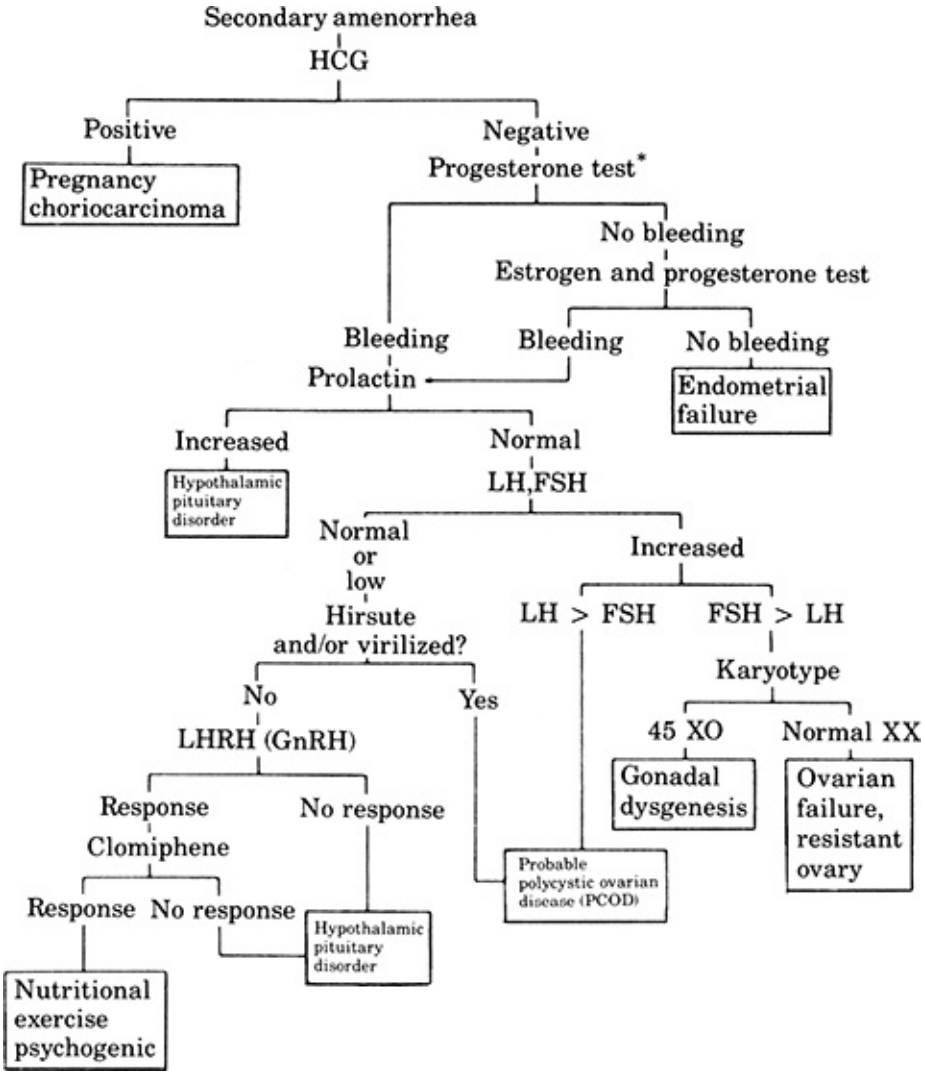

Figure 25-3. Algorithm for workup of secondary amenorrhea. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone. *Obtain LH, FSH. (Reprinted with permission from Cave WT Jr, Streck WF. Amenorrhea. In: Streck WL, Lockwood DH, eds. *Endocrine Diagnosis: Clinical and Laboratory Approach.* Boston: Little, Brown and Company; 1983:191–208.)

b. Diagnosis. Secondary hypogonadism causes include stress, sudden weight loss, emotional disturbances, Kallmann syndrome, and "post-pill" amenorrhea.

i. Kallmann syndrome is a congenital hypogonadotropic state resulting from deficient GnRH secretion by the hypothalamus with associated anosmia secondary to olfactory bulb agenesis. Classically, this syndrome affects men as a result of mutations in the *KAL* gene on the short

arm of the X-chromosome; however, women may present with amenorrhea and **anosmia**. This may be the result of mutations in numerous genes, resulting in X-linked, autosomal dominant, or autosomal recessive transmission. Recently, **GPR 54 has been implicated in the pathogenesis of GnRH deficiency in the setting of a normal sense of smell**.

ii. **Post-pill amenorrhea** was previously thought to represent a heterogeneous group of disorders, including profound suppression from oral contraceptive therapy. However, data suggest that **after discontinuation of combined p. 295p. 296oral contraceptive pills after taking the pill for 1 year will result in resumption of menses in an average of 32 days** and pregnancy achieved in <90 days. Additionally, resumption of menstrual cycles after using Depo-Provera (medroxyprogesterone acetate) for contraception may take 12 to 16 months.

c. Management

i. Removal of any organic lesion (e.g., tumor).

ii. Alleviation of the dysfunctional causes, such as weight loss, emotional conflict, and stress.

iii. If fertility is not a consideration and if simple measures are not successful in restoring ovulation, cyclic estrogen–progesterone therapy is indicated but should not be continued indefinitely. Therapy should be suspended for a few months each year to see if function has recovered.

2. **Hyperprolactinemia.** Hyperprolactinemia may alter ovarian function by a direct effect on the hypothalamus altering the pulsatile secretion of GnRH. Additionally, pituitary GnRH receptors may be decreased as a result of the hyperprolactinemia, resulting in reduced gonadotropin release. Moreover, elevated prolactin concentrations may have a lytic effect on the developing corpus luteum, further interfering with ovulation. Correction of hyperprolactinemia usually restores normal function of the hypothalamic–pituitary–ovarian axis.

3. **Adrenal disorders**

a. Increased cortisol production reduces the responsiveness to

GnRH.

b. Increased androgen production alters gonadotropin secretion; for example, a patient with virilizing congenital adrenal hyperplasia may exhibit a prepubertal GnRH response, resulting in an increased FSH response in comparison with the LH response.

4. Thyroid dysfunction. Disordered thyroid function (both hyperthyroidism and hypothyroidism) can cause anovulation with deranged menstruation. Hypothyroidism can also indirectly increase prolactin levels (by increased thyrotropin-releasing hormone incidentally stimulating prolactin release at the level of the pituitary) and subsequently lead to amenorrhea. Autoimmune thyroiditis may be associated with autoimmune oophoritis, and is also the most frequent autoimmune disorder associated with POF.

II. OVARIAN HYPERFUNCTION

A. Hyperandrogenism (Fig. 25-4)

Hyperandrogenism refers to excessive production of androgens by the ovary or the adrenals or either increased conversion of androgens, particularly testosterone, from steroid precursors by certain peripheral tissues via aromatization or an increased rate of utilization by androgen-responsive tissues. Hyperandrogenism is a common endocrinopathy and can present clinically as seborrhea, acne, infertility, hirsutism, or virilization. The most common finding associated with hyperandrogenism is the **PCOS**.

1. Polycystic ovary syndrome (see Chapter 26)

a. Pathophysiology

b. Diagnosis

c. Management. Therapy should be determined by the patient's goal.

i. If fertility is desired, induction of ovulation with clomiphene citrate is the choice of therapy. Recent literature indicates that in patients with PCOS and a BMI of 30.3 kg/m^2 and above, that letrozole results in higher ovulation rates (61.7% versus 48.3%, $p < 0.007$) and live birth rates (27.5% versus 10.1%, $p = 0.007$) in comparison to clomiphene citrate.

ii. If fertility is not a goal, low-dose combination oral contraceptive with an estrogen content of <50 μg is the

treatment of choice to suppress LH hypersecretion. The usual contraindications for oral contraceptive use should be applied. After one or two cycles of combination oral contraceptive therapy, the T and A plasma levels should be in the normal range if the hyperandrogenism is LH dependent.

iii. If oral contraceptive therapy is contraindicated, spironolactone may be utilized (give 25 to 200 mg/day until the first day of menses, then stop for p. 296p. 297p. 297p. 2987 days; resume on day 8, and repeat this cycle for 3 to 6 months). If the response is inadequate or absent, increase the dose stepwise to 400 mg/day. Tumors must be surgically removed.

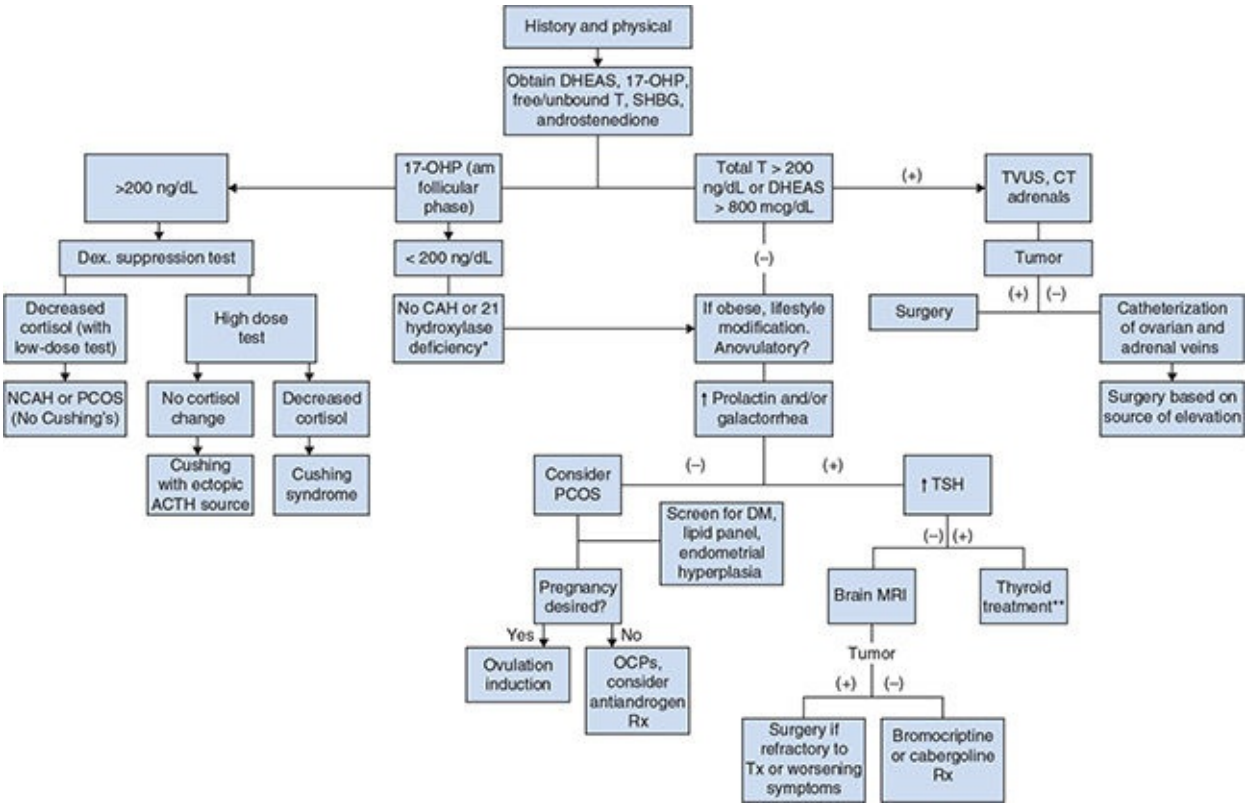

Figure 25-4. Algorithm for the diagnosis and management of hirsutism and hyperandrogenemia. *Rare forms of NCAH, including 3β-hydroxysteroid dehydrogenase deficiency, are not excluded here (17-hydroxypregnenolone must be obtained). **An increase in TRH associated with hypothyroidism can cause stimulation of prolactin secretion from the pituitary. ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; CT,

computed tomography; DEX, dexamethasone; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MRI, magnetic resonance imaging; NCAH, nonclassic adrenal hyperplasia; OCP, oral contraceptive pills; PCOS, polycystic ovarian syndrome; Rx, prescription; SHBG, sex hormone–binding globulin; T, testosterone; Tx, treatment; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; TVUS, transvaginal ultrasound. (Information derived from Givens JR. Ovaries. In: Wilson J, Foster DW, eds. *Williams Textbook of Endocrinology.* 7th ed. Philadelphia: WB Saunders; 1985; Schorge JO, Williams JW. Polycystic ovarian syndrome and hyperandrogenism: introduction. In: *Williams Gynecology*. New York: McGraw-Hill Medical; 2008:779–791.)

iv. Metformin, 850 to 1 000 mg/day, may be used to correct insulin resistance. Metformin also increases sex hormone–binding globulin, which binds to circulating free testosterone. Additionally, decreased insulin levels lead to lower levels of androgen production and can therefore help restore ovulation.

v. Flutamide is a nonsteroidal androgen receptor antagonist and is used primarily in the treatment of prostate cancer. An off-label use is the treatment of hirsutism, but is not the Food and Drug Administration recommended because its use is associated with hepatotoxicity. A recommended treatment regimen is 250 to 750 mg/day.

vi. Eflornithine irreversibly inhibits ornithine decarboxylase, an enzyme required to synthesize follicle polyamines necessary for hair growth. This medication can decrease hirsutism symptoms in a 4- to 8-week duration, but symptoms return once the medication is discontinued.

vii. Finasteride is a type two 5α-reductase inhibitor that prevents conversion of testosterone to dihydrotestosterone. A typical dose is 2.5 to 5 mg/day every 3 days and is Category X for pregnancy because it can cause hypospadias among other congenital defects.

viii. Spironolactone (Aldactone) is a potassium sparing diuretic that inhibits aldosterone, inhibits steroidogenic enzymes, and binds to androgen receptors located on the hair follicle. This medicine is relatively inexpensive and commonly prescribed. Irregular uterine bleeding, hyperkalemia, and gastrointestinal discomfort are common side effects. In all, 50 to 200 mg/day dosing is appropriate. **Contraception is mandatory** because incomplete virilization can occur in male fetuses.

2. **Combined adrenal and ovarian hyperandrogenism**
   a. **Pathophysiology.** Combined adrenal and ovarian hyperandrogenism may result from deficiency of the steroidogenic enzymes 3β-hydroxysteroid dehydrogenase, which converts the Δ5 to Δ4 compounds, including dehydroepiandrosterone (DHEA) to androstenedione, pregnenolone to progesterone, and 17-hydroxypregnenolone to 17-hydroxyprogesterone. This enzyme system is also deficient in the adrenals, but not in the peripheral tissues. Deficiency of the enzyme **17-ketosteroid reductase,** which converts androstenedione to testosterone and estrone to estradiol, is also associated with polycystic ovaries. These patients have high levels of **androstenedione** and estrone.
   b. **Diagnosis.** The diagnosis of 3β-hydroxysteroid dehydrogenase deficiency remains controversial but nevertheless requires clinical suspicion and documentation of an abnormally high precursor (pregnenolone, 17α-hydroxylase [17α-OH] pregnenolone, and dehydroepiandroandrosterone)/product (progesterone, 17α-OH progesterone, and androstenedione) ratio at the three critical steroidogenic steps. A firm diagnosis may not be practical in a clinical setting. Response to therapy can be followed using dehydroepiandrosterone sulfate (DHEAS) levels.
   c. **Management.** Deficiency of either of these enzyme systems induces androgenic polycystic ovaries as well as androgenic adrenals.
      i. If fertility is desired, the treatment of choice is glucocorticoid suppression using a low dose of DEX to suppress the adrenal source of DHEA and DHEAS. The initial dose should be 0.25 mg at bedtime.
      ii. The magnitude of the suppression of DHEAS need not be profound. The goal of therapy should be to bring the DHEAS level to within the normal range after 4 weeks of DEX administration. Cortisol level should range from 3 to 5 μg/dL. The overall guiding principle is to use the lowest dose of DEX that will suppress DHEAS levels to between 100 and 200 μg/dL. Some women are exquisitely sensitive to DEX; they may develop some of

the symptoms of Cushing syndrome if not carefully followed and the dose of DEX is not adjusted monthly. Some maintain suppression of DHEAS on 0.125 mg taken three times a week at bedtime.

iii. Therapy should be discontinued at the end of 1 year to evaluate whether continued therapy is necessary. If the DHEAS is not adequately suppressed with 0.25 mg of DEX, then one can add low-dose contraceptive therapy. This treatment suppresses DHEA from the ovaries and reduces the androgens that were not responsive to DEX.

3. **Primary adrenal and secondary ovarian hyperandrogenism**
   a. **Pathophysiology. Primary adrenal hyperandrogenism,** such as occurs in nonclassic 21-hydroxylase and 11β-hydroxylase enzyme deficiencies, may induce polycystic-appearing ovaries by the increased positive feedback on LH secretion as a result of increased E1 levels derived from the increased secretion of adrenal androstenedione.
   b. **Diagnosis.** Nonclassic 21-hydroxylase deficiency is diagnosed by comparing the magnitude of an exaggerated response of 17-hydroxyprogesterone following 25 μg of synthetic adrenocorticotropic hormone to a normogram of the responses of classic and nonclassic enzyme deficiency. **Basal T and A** are also elevated.
   c. **Management.** Treatment consists of adrenal suppression using a low dose of DEX (0.25 mg at bedtime), as previously described.
4. **Adrenal hyperandrogenism with decreased ovarian function**
   a. **Pathophysiology.** The **amenorrhea-galactorrhea syndrome** is frequently associated with hyperandrogenism. Prolactin induces adrenal androgen hypersecretion but inhibits steroidogenesis in the ovary.
   b. **Diagnosis.** Associated with hyperprolactinemia are depressed levels of T and dihydrotestosterone. Circulating DHEAS can be increased.
   c. **Management.** Correction of the hyperprolactinemia (see Chapter 7) corrects the androgen excess state from the adrenals

and restores normal function of the ovary.

B. Hyperestrogenism

1. Pathophysiology

a. The most common cause of estrogen excess is increased conversion from androgens (via aromatase) in peripheral tissues, such as the liver, skin, and fat.

b. Excess estrogen production in peripheral tissues can result from:

i. Increased substrate (hyperandrogenism)

ii. Increased percentage conversion of androgens (e.g., in the adipose of obese women)

iii. A combination of the above

c. Ovarian hypersecretion of estrogens results either from primary disease or from secondary hyperstimulation by human chorionic gonadotropin (HCG) secreted by a tumor, such as a teratoma or teratocarcinoma. Primary ovarian disorders causing hyperestrogenism include:

i. Functioning follicular cysts

ii. Granulosa-theca cell tumors of the ovary

2. Diagnosis. Excess estrogen is documented by increased levels in the blood or urine (or both) and by the clinical signs and symptoms resulting from the hormonal derangement, such as isosexual precocious development, advanced bone age, and abnormal uterine bleeding. Gonadotropins may be suppressed and thyroid-binding globulin and testosterone-estradiol–binding globulin increased. Assay for HCG is positive in those having an ectopic source.

3. Management

a. Therapy is directed to the specific etiologic factor.

b. Tumors of the ovary and tumors associated with ectopic production of HCG should be identified and removed.

c. Hyperandrogenic conditions should be corrected.

d. Efficacy of therapy should be monitored by specific estrogen assays.

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26 Polycystic Ovary Syndrome

Alice Y. Chang

I. OVERVIEW

Polycystic ovary syndrome (PCOS) is a condition of androgen excess and oligo-ovulatory or anovulatory cycles. It is the most common endocrine disorder in reproductive-aged women. The Rotterdam criteria classifies as many as 10% of reproductive-aged women with PCOS. The challenge for providers and patients is to make the diagnosis of PCOS based on a combination of symptoms, signs, and test results because there is no single test that can make the diagnosis. (There are limitations in sensitivity and specificity for many of the available diagnostic tests.) Even the name itself is misleading, when the condition is not caused by ovarian "cysts" but is characterized by the symptoms related to androgen excess, oligoanovulatory cycles, or the cardiometabolic consequences of insulin resistance. Treatment options should be tailored to an individual's symptoms and pregnancy planning. Finally, it is important to recognize the importance of screening for conditions commonly associated with PCOS. Especially given the significant increase in cardiovascular risk associated with the development of type 2 diabetes mellitus (T2DM) in women, the diagnosis of PCOS is a critical screening and prevention opportunity in the battle against heart disease, the leading cause of death for women in the United States.

II. DIAGNOSTIC CRITERIA

A. Rotterdam criteria (Table 26-1). Since 2003, PCOS is diagnosed when two of the following three major criteria are present: (a) oligoovulation and/or anovulation; (b) clinical and/or biochemical signs of hyperandrogenism; or (c) polycystic ovary morphology (PCOM). The diagnosis also requires the exclusion of other conditions based on clinical assessment and/or additional tests (see Sections III.A.2 and III.A.4).

B. National Institutes of Health criteria (Table 26-1). It is

important to recognize that many of the landmark studies characterizing insulin resistance, cardiovascular p. 301p. 302risk factors, and T2DM risk in PCOS required both hyperandrogenism and oligoanovulation. Women who meet National Institutes of Health criteria have greater metabolic and cardiovascular risk factors than women without hyperandrogenism or without anovulation.

TABLE 26-1 Rotterdam and NIH Criteria for PCOS

Rotterdam Consensus Criteria 2003	NIH Consensus Criteria 1990
Two of the three criteria below and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome)	Both 1 and 2
1. Oligo-ovulation or anovulation	**1.** Chronic anovulation and
2. Clinical and/or biochemical signs of hyperandrogenism	**2.** Clinical and/or biochemical signs of hyperandrogenism and exclusion of other etiologies
3. Polycystic ovaries: the presence of 12 or more follicles 2–9 mm in diameter and/or an increased ovarian volume >10 mL (without a cyst or dominant follicle) in either ovary	

NIH, National Institutes of Health; PCOS, polycystic ovary syndrome.

III. APPROACH TO THE HISTORY AND PHYSICAL EXAMINATION.

The diagnosis of PCOS can be challenging when women have already received treatment, such as hormonal contraception and/or mechanical treatment of terminal hair growth, and when ethnic/racial differences might increase or decrease the likelihood of terminal hair growth. The modified Ferriman-Gallwey score is the method used to visually assess hirsutism. Symptoms present since menarche and adolescence or at least throughout the twenties when not on hormonal contraception, pregnant, or breastfeeding are more consistent with women with PCOS characterized in research studies. Symptoms and signs of alopecia in an androgen-dependent distribution or acne, especially when acne persists into or starts

in adulthood, are more suggestive of hyperandrogenism. The physical examination should also look for signs of insulin resistance—acanthosis nigricans and skin tags.

A. Diagnostic testing (Table 26-2)

1. **Ovulatory status.** Oligoanovulation is established with a menstrual history of fewer than 9 periods/year or bleeding intervals >45 days. Anovulatory cycles are also suggested by more frequent bleeding (<21 days). If menses occurs monthly in 25- to 35-day intervals, a low midluteal (day 21) progesterone might support the diagnosis.
2. **If androgen excess is clinically present without virilization**, androgen concentrations do not need to be assessed. Clinical evidence of androgen excess includes a modified Ferriman-Gallwey score of terminal hair growth ≥8, evidence for alopecia or diffuse hair thinning or loss typically concentrated in a frontal/temporal/vertex distribution or significant acne. With severe hirsutism, a modified Ferriman-Gallwey score >15, and/or virilization, total testosterone and dehydroepiandrosterone sulfate (DHEAS) should be obtained to exclude concentrations suggestive of tumor (ovarian or adrenal).
3. **If androgen excess is not present by exam**, it is reasonable to assess for multiple biochemical tests for androgen excess because total testosterone is not a sensitive biomarker in women. In addition to total and free testosterone, additional androgens to assess include DHEAS and androstenedione concentrations. Any concentrations above the reference range provide evidence of hyperandrogenism.
4. **Exclusion of other conditions** is necessary to make the diagnosis of PCOS. Testing for pregnancy, hyperprolactinemia, and hypothyroidism should be performed in all evaluations for PCOS along with follicle-stimulating hormone to assess for primary ovarian insufficiency. Screening for **nonclassic congenital adrenal hyperplasia (NCCAH)** is ideally performed with an early morning, early follicular phase 17-hydroxyprogesterone (17-OHP). However, the diagnosis of NCCAH can be made with a random 17-OHP >1 000 ng/dL. A 60-minute cosyntropin stimulation test (250 μg) is needed to confirm the diagnosis if 17-OHP concentrations are near the upper limit of the normal range and will stimulate 17-OHP >1 000 ng/dL in

NCCAH. Because of the implications for pregnancy, corticosteroid treatment for infertility, and testing the partner for carrier status, screening for NCCAH is recommended in all evaluations for PCOS. If a woman with NCCAH presents with infertility and anovulatory cycles, treatment with corticosteroids can decrease the adrenal androgens and restore ovulation. *CYP21A2* genotyping of the partner is recommended to document whether the partner is a heterozygote carrier. If symptoms or signs of Cushing syndrome are present, the overnight 1 mg dexamethasone suppression test and midnight salivary cortisol test can detect milder or subclinical Cushing syndrome in women not taking oral contraceptives. A 24-hour urine for free cortisol can be obtained in women taking oral contraceptives. In women with secondary amenorrhea, evaluation might also include the progesterone challenge test for a withdrawal bleed and/or estradiol concentrations to assess for hypogonadotropic hypogonadism.

5. **Pelvic ultrasound.** If the other two diagnostic criteria are present, assessment of ovarian morphology is not necessary to make the diagnosis of PCOS or create p. 302p. 303a treatment plan. In addition, the presence of PCOM alone without any other symptoms or signs of PCOS does not establish a diagnosis of PCOS or suggest any other condition is present. **PCOM can be found in up to 20% of healthy young women without any symptoms of PCOS.** Pelvic ultrasound might be obtained by the reproductive endocrinologist in assessing treatment options for infertility and, if desired, risk for ovarian hyperstimulation syndrome.

TABLE 26-2 Diagnostic Evaluation in PCOS

Hyperandrogenism	
Androgen Excess Present by Exam (Acne, Alopecia, Ferriman-Gallwey ≥8)	**Androgen Excess Not Present by Exam**
Consider DHEAS, total testosterone (if severe hirsutism or any signs of virilization, screen for ovarian/adrenal tumors if DHEAS ≥700 μg/dL, or total testosterone ≥150 ng/dL)	DHEAS, total testosterone, free testosterone, androstenedione
Oligoanovulation	**Secondary Amenorrhea**
• Rule out pregnancy	Consider addition of:

• TSH, prolactin, FSH • Consider midluteal phase progesterone (day 21) if cycle length 25–35 d	**1.** Progesterone challenge test and/or estradiol concentration—assess for hypogonadotropic hypogonadism **2.** MRI pituitary—if hypogonadotropic hypogonadism diagnosed **3.** Pelvic ultrasound—anatomic defect
Pelvic Ultrasound	
• Not required for the diagnosis of PCOS • Consider in the absence of hyperandrogenism or oligoanovulation	
Exclusion of Other Diagnoses	
Suggested in All Evaluations	**Consider Based on History and Physical Examination**
Pregnancy, hyperprolactinemia, hypothyroidism (as above) Nonclassic congenital adrenal hyperplasia • Early A.M. and follicular phase 17-hydroxyprogesterone (17-OHP). • If 17-OHP <1 000 ng/dL but elevated, 250 μg cosyntropin stimulation test.	Cushing syndrome • 1 mg overnight dexamethasone suppression test • Midnight salivary cortisol × 2 • 24-hour urine free cortisol (if on oral contraceptives)
Assessment of Comorbidities	
All Adolescents and Women with PCOS	**Consider Based on History and Physical Examination**
1. Prediabetes/type 2 diabetes • 2-hour 75 g oral glucose tolerance test (OGTT) • If unable to do OGTT, HbA_{1c} **2.** Cardiovascular risk factors • Body mass index • Waist circumference • Blood pressure • Prediabetes/type 2 diabetes (as above) • Fasting lipid profile	**1.** Sleep-disordered breathing/obstructive sleep apnea (OSA) **2.** Depression/mood disorders
DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; MRI, magnetic resonance imaging; PCOS, polycystic ovary syndrome; TSH, thyroid-stimulating hormone.	

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B. Assessment for associated conditions and risk factors

1. **Prediabetes/T2DM.** It is well established that PCOS is strongly associated with **insulin resistance**, even in women who are not obese. Because of the increased risk for T2DM in PCOS and the greater prevalence of impaired glucose tolerance than impaired fasting glucose in PCOS, the Endocrine Society guidelines suggest that all adolescents and women with PCOS are screened with a 2-hour 75 g oral glucose tolerance test (OGTT) at least once and rescreened every 3 to 5 years or earlier if there is a change in risk factor status. A hemoglobin A_{1c} might be obtained if they are unable to complete an OGTT.
2. **Cardiovascular risk factors.** PCOS is associated with a greater prevalence of dyslipidemia, obesity, hypertension, and the metabolic syndrome. All adolescents and women with PCOS should be screened for calculation of body mass index (BMI) and measurement of waist circumference along with fasting glucose, lipids, and OGTT (as above).
3. **Obstructive sleep apnea.** Women with PCOS have a higher prevalence of sleep-disordered breathing than women without PCOS, even when controlling for BMI and obesity. Continuous positive airway pressure treatment of obstructive sleep apnea (OSA) in PCOS can improve insulin sensitivity and blood pressure. Women with PCOS with symptoms suggestive of OSA should be referred for diagnosis and treatment.
4. **Nonalcoholic fatty liver disease.** Based on current studies, it is not clear whether reports of nonalcoholic fatty liver disease (NAFLD) in PCOS are related to the associations with metabolic syndrome and insulin resistance and/or androgen excess. It is important to be aware of the potential for increased risk, although no specific screening strategies are recommended owing to the low sensitivity and specificity of serum markers of liver dysfunction and no specific treatment strategies to treat NAFLD though diet, exercise, and insulin sensitizers might be of benefit.

IV. APPROACH TO TREATMENT.

Selecting among treatment options is guided by an individual's primary symptom concerns and whether pregnancy is desired in the near future.

A. Hirsutism/acne. Setting expectations for treatment is one of the most important aspects of treating hirsutism. Terminal hairs already present will respond by growing more slowly and thinning in response to therapy. Only treatments such as laser treatment or electrolysis will permanently eliminate terminal hair follicles. However, unless therapy is initiated to lower androgens or interfere with androgen effect, new terminal hair follicles can continue to develop. In general, metformin therapy does not significantly affect symptoms of hyperandrogenism. Metformin can decrease circulating insulin levels and testosterone but has a minor effect on hirsutism compared to other treatments. With severe hirsutism that does not respond to first- and second-line therapies of hormonal contraceptives (HCs) or spironolactone, flutamide, or finasteride/dutasteride might be considered. However, flutamide must be used with great caution because of the black box warning regarding hospitalizations and deaths reported from hepatotoxicity. Finasteride/dutasteride might be considered in particular when alopecia is the predominant symptom and other strategies have not been effective.

1. **Hormonal contraceptives.** HCs (oral contraceptives, patch, or vaginal ring) are the first line treatment recommended for hirsutism, recognizing that ovarian androgen production is the source of approximately 80% of androgens in the premenopausal woman. Therefore, suppressing ovarian androgen production with any form of HC will significantly decrease androgen production. Oral contraceptives also have the added benefit of **increasing hepatic production of sex hormone–binding globulin that reduces the amount of free circulating androgens**.

   After 6 months of HC, an antiandrogen might be considered p. 304p. 305if additional effect is desired. There is no clear benefit of one type of HC over another. Continuous or extended-cycle therapy could be considered for greater hormonal suppression to avoid any rebound during the pill-free or placebo interval.
2. **Spironolactone.** Recommended starting dose is 25 to 50 mg twice daily, checking potassium after initiation and any dose increase. After 3 months of therapy, the dose might be increased to

100 mg twice daily. Contraception is advised to prevent fetal exposure during therapy.

B. Oligoanovulation

1. **HCs** are considered **first-line** treatment for the improvement of menstrual irregularity when this is a goal for the patient and contraception is also desirable.
2. **Metformin.** For women who cannot take or tolerate HCs, **metformin** is a **second-line** therapy for improving menstrual regularity. For women planning pregnancy or considering pregnancy in the near future, metformin can also increase the frequency of ovulatory cycles. It is important to recognize that metformin is effective in PCOS even when the OGTT demonstrates normal glucose tolerance.

C. Fertility. When seeking evaluation for infertility, women who are approaching or over 30 years of age should be referred to a reproductive endocrinology specialist to expedite evaluation and treatment. **Aromatase inhibitors and clomiphene** have been shown to achieve higher pregnancy rates compared to metformin.

D. Cardiovascular risk factors. In PCOS, **metformin** has been demonstrated in studies to improve insulin sensitivity and features of the metabolic syndrome as well as potentially facilitate weight loss. Although lifestyle changes have demonstrated the greatest reduction in the incidence of T2DM in high-risk individuals, metformin also decreased the incidence of T2DM greater than placebo. Metformin might also be considered for prevention of T2DM in women with PCOS who have prediabetes or a strong family history of T2DM.

E. Obesity. Obesity is commonly associated with PCOS and might further increase the health risks otherwise associated with PCOS and androgen excess. Obesity can also affect response to fertility treatments. Studies demonstrate that lifestyle changes can increase ovulatory frequency and pregnancy rates. Part of the effect of **metformin** in decreasing the development of T2DM might be mediated by weight loss. **Liraglutide** is a Food and Drug Administration–approved option for weight loss that can also improve insulin sensitivity and has been studied in small samples of women with PCOS. **Bariatric surgery** has also been studied in obese women with PCOS with improvement in menstrual regularity and androgen excess. Consideration of medical or surgical therapy for obesity should follow the same guidelines and criteria as individuals without PCOS.

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27 Male Reproductive Disorders in Adults

Vahid Mahabadi and Ronald S. Swerdloff

I. GENERAL PRINCIPLES

The human testis is an organ that is located outside the abdominal cavity with temperatures approximately 2°C lower than core body temperature, with dual function, endocrine (hormone production) and exocrine (sperm production). The testis is composed of parenchyma, which is surrounded by a solid capsule (tunica albuginea). Extension of tunica albuginea into the testicle as fibrous septa produces 200 to 300 pyramidal lobules, which contain coiled seminiferous tubules. Each testis contains 600 to 900 seminiferous tubules with an approximate length of 200 to 300 m and occupies 80% to 90% of the testicular mass. It has a huge reproductive capacity, with production of 10 to 20 million spermatozoa daily during male reproductive life. The seminiferous tubules are composed of Sertoli cells and germinal cells. The seminiferous tubules are interspersed within an interstitial space containing androgen-producing Leydig cells, blood vessels, lymphatics, nerves, macrophages, and fibroblasts. Each testes volume is approximately 15 to 30 mL with the length of 3.5 to 5.5 cm and width of 2 to 3 cm. Testicular function is regulated by a series of closed-loop feedback systems consisting of six main components: (a) extrahypothalamic central nervous system (CNS), (b) hypothalamus, (c) pituitary gland, (d) testes, (e) sex steroid–sensitive end organs, and (f) sites of androgen transport and metabolism.

A. Hypothalamic-pituitary function (Fig. 27-1)

1. **Extrahypothalamic CNS.** Extrahypothalamic brain tissues have both stimulatory and inhibitory effects on reproductive function. In the midbrain, cell bodies containing the biogenic amines, norepinephrine, and serotonin (5-hydroxytryptamine) as well as other neurotransmitters are connected to many areas of the hypothalamus, including the preoptic, anterior, and medial basal areas where gonadotropin-releasing hormone (GnRH)–containing neurons are located.

2. **Hypothalamus**
   a. **Pulsatile secretion of GnRH.** The hypothalamus is the integrating center for the regulation of GnRH. GnRH is a decapeptide released in predetermined regular pulses, which peak every 90 to 120 minutes into the portal circulation to stimulate pituitary gonadotropin synthesis and release. GnRH has a half-life of 5 to 10 minutes and, because of its low systemic concentration, is not easily measured in the systemic circulation. Continuous administration of GnRH causes cessation of gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) production, through inhibitory downregulation of GnRH receptors. Inhibition of gonadotropic secretion results in decreased serum testosterone (T) and estradiol (E_2) levels and thus has therapeutic applications in sex steroid–dependent conditions, such as prostate carcinoma, endometriosis, and precocious puberty. On the other hand, physiologic pulsatile administration of GnRH can establish normal production of LH and FSH in patients with hypothalamic-induced hypogonadism, such as those with Kallmann syndrome.
   b. **GnRH regulation.** The extrahypothalamic CNS, circulating androgens, and circulating peptide hormones, such as prolactin, activin, inhibin, and leptin, regulate GnRH synthesis and release. Local modulators of GnRH secretion include a number of neuropeptides, catecholamines, indolamines, nitric oxide, and so on. Kisspeptin, with signaling through the Kiss1 peptin receptor (KISS1R) is an important modulator in GnRH secretion.

p. 306p. 307

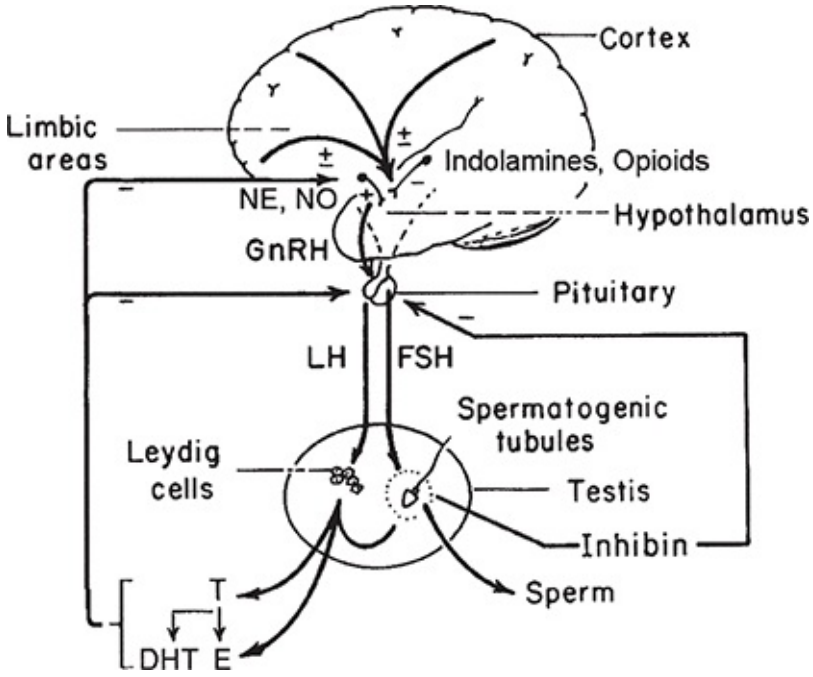

Figure 27-1. Hypothalamic-pituitary-testicular axis in the male. The hypothalamus is the integrating center for central nervous system (CNS) regulation of gonadotropin-releasing hormone (GnRH). Extrahypothalamic CNS input has both inhibitory and stimulatory influences on GnRH secretion. Neurotransmitters, such as norepinephrine (NE), dopamine (DA), opioid peptides, *y*-aminobutyric acid (GABA), serotonin, and melatonin, serve as regulators of GnRH synthesis and release from hypothalamus. The human testis is a dual organ with endocrine and reproductive functions. Testicular function is regulated by a series of closed-loop feedback systems involving higher centers in the CNS, hypothalamus, pituitary, and testicular endocrine and germinal compartments. DHT, 5*α*-dihydrotestosterone; E_2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NO, nitric oxide; T, testosterone. (Reprinted from Swerdloff RS, Wang C. The testes and male sexual function. In: Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine.* 22nd ed. Philadelphia: WB Saunders; 2004:1472–1483.)

T, directly or by its metabolic products, E_2 and dihydrotestosterone (DHT), has an inhibitory effect on GnRH, LH, and FSH secretion.

3. **Pituitary gland.** LH and FSH are large glycopeptides that, like thyroid-stimulating hormone and human chorionic gonadotropin (hCG), are produced from *α* and *β* chains. The *α* chain is identical in all four hormones, but the **biologic effects are exerted by the *β* chain**. The *α* and *β* chains are encoded by genes on different chromosomes. The *α* chain is encoded by a gene on chromosome 6 (6q12.21), FSH-*β* on chromosome 11 (11p13), and LH-*β* and hCG-*β* on chromosome 19 (19q13.32). LH and FSH are produced by gonadotropin cells in the pituitary gland and are secreted in a pulsatile pattern. The biologic activity of

gonadotropins depends on their degree of glycosylation, which increases their half-life in circulation. LH has a half-life of approximately 40 minutes, versus that of FSH of 4 hours and hCG of 5 hours.

a. LH binds to specific, high-affinity surface membrane receptors on Leydig cells. Binding is followed by G-protein–mediated events that stimulate T production within the testes.

b. FSH binds to receptors on Sertoli cells, stimulating production of a large number of specific proteins, including androgen-binding protein, inhibin, activin, plasminogen activator, γ-glutamyl transpeptidase, and protein kinase inhibitor. FSH, in conjunction with T produced by Leydig cells, works synergistically to promote spermatogenesis and to inhibit germ-cell apoptosis.

c. Gonadotropin regulation. The feedback regulation of LH production in man occurs by T and its metabolites E_2 and DHT. T mainly inhibits GnRH at the p. 307p. 308hypothalamus with mild suppressive action on LH, whereas E_2 has inhibitory effect at both the hypothalamus and pituitary levels. Inhibin and activin are glycoproteins involved in regulation of FSH secretion. Inhibin B, produced by Sertoli cells, enters the peripheral circulation and inhibits pituitary secretion of FSH. Activin stimulates FSH secretion and spermatogenesis. Both inhibin and activin are also thought to act locally as paracrine regulators of spermatogenesis.

Stressors during acute and chronic illness affect the hypothalamic-pituitary-testicular axis by increasing corticotropin-releasing hormone and cytokines, which, in turn, can decrease T production. Chronic fasting is another stressor decreasing T production by lowering leptin level as a hypothalamus pulse generator.

B. Testes function

1. Steroid hormone production and action

a. T production and secretion (Fig. 27-2). The testes are composed of interstitial steroid-secreting cells (Leydig cells)

and seminiferous tubules containing Sertoli p. 308p. 309cells and germ cells. Under the regulation of LH, Leydig cells are the main source of approximately 7 mg of T produced each day. The parent substance of T biosynthesis is cholesterol, which is mainly produced and stored in vacuoles of Leydig cells or via uptake from plasma low-density lipoprotein (LDL). T synthesis occurs through the $\Delta 4$ or $\Delta 5$ pathway, with the rate-limiting step being the LH-inducible conversion of cholesterol to pregnenolone by the enzyme P450scc, cholesterol 20,22-hydroxylase:20,22 desmolase activity (side-chain cleavage enzyme). The majority of produced T is immediately released to the blood, mainly via the spermatic vein, and smaller amounts are transported in the lymphatic system. In eugonadal men, **approximately 95% of circulating T** is produced by the testes and the reminder produced by **adrenal glands** and by peripheral conversion of adrenal gland precursors, such as **androstenedione**. The testes also produce equimolar amounts of epitestosterone, which is an inactive epimer of T. The ratio of T and epitestosterone in urine is used as a marker for exogenous T in athletes who are doping.

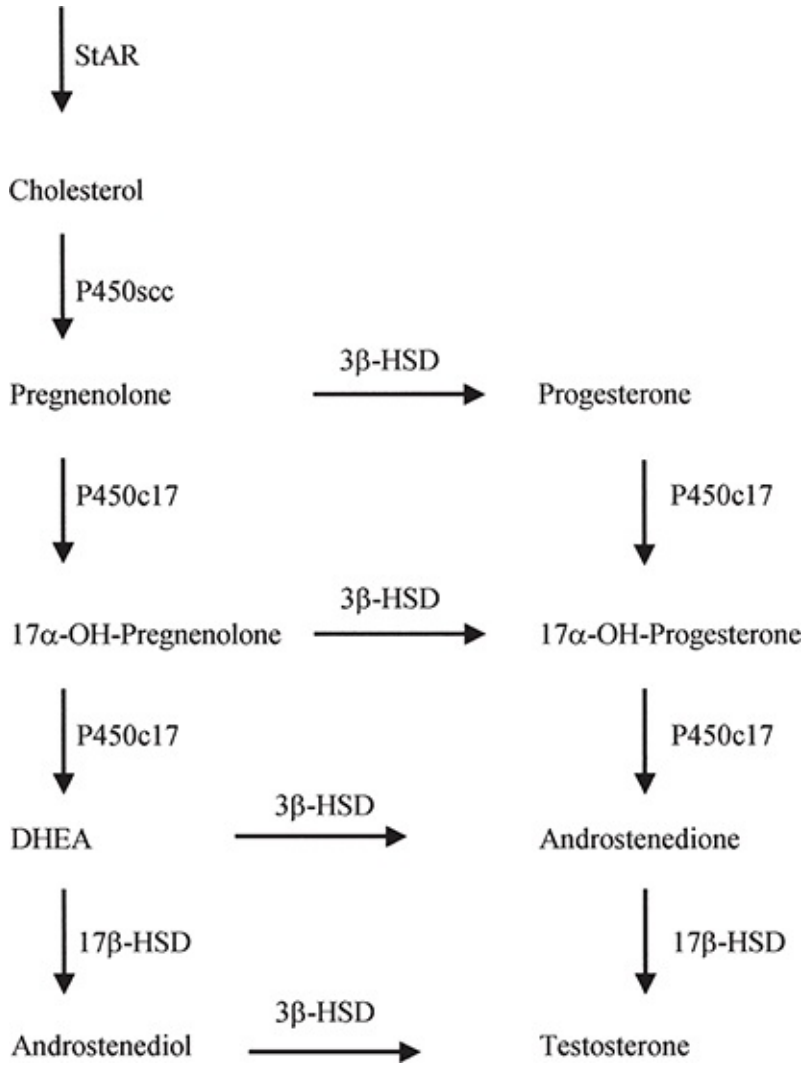

Figure 27-2. Testosterone synthesis in the testis. Steroidogenic acute regulatory protein metabolizes cholesterol from cellular stores to the mitochondria. Intratesticular pathways for synthesis of testosterone. Whereas both the Δ5 **(left)** and Δ4 **(right)** pathways exist, the Δ5 pathway predominates in the testes. DHEA, dehydroepiandrosterone; HSD, hydroxysteroid dehydrogenase; OH, hydroxy; StAR, steroidogenic acute regulatory protein. (Reprinted from Swerdloff RS, Wang C. The testes and male sexual function. In: Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine.* 22nd ed. Philadelphia: WB Saunders; 2004:1472–1483.)

b. T transport and binding proteins. The majority of circulating T is bound either strongly to sex hormone–binding globulin (SHBG) approximately (30% to 44%) or loosely to albumin (54% to 68%), whereas 0.5% to 3% remains unbound (free T). Unbound and albumin-bound T are available for cellular entry and are referred to as **bioavailable testosterone.** Despite binding to SHBG, the half-life of T in blood is only 10 minutes, and it is catabolized efficiently by the

liver and eliminated via the urine as 17-ketosteroids and sulfates.

Circulating SHBG is a large glycoprotein, which is encoded by a gene on chromosome 17 and produced by the liver. SHBG may also be produced in other tissues such as prostate and mammary glands, where it may have local functions. Hepatic production of SHBG is influenced by a number of physiologic and metabolic factors.

i. Sex steroids are important modulators of SHBG synthesis; **estrogens stimulate whereas androgens inhibit SHBG production, which explains the higher level of SHBG in premenopausal women**. The estrogen to androgen ratio is a major determinant of the hepatic production of SHBG.

ii. In patients with hepatic cirrhosis, estrogen levels are maintained despite a fall in androgen levels, leading to an increase in circulating SHBG. Because elevated SHBG levels tend to increase the total T levels without affecting the free or bioavailable T concentrations, total T levels may be normal in the presence of a moderate decrease in T secretion.

iii. Thyroid hormones influence SHBG levels. Decreased concentrations of thyroxine (T_4) or tri-iodothyronine (T_3) diminish SHBG, whereas hyperthyroid states are associated with high binding protein concentrations.

iv. Body mass and degree of adiposity influence SHBG concentrations. SHBG levels are **low** in obese and acromegalic patients. Much of this effect is **mediated by insulin, which is increased in such patients.**

c. **T conversion to E_2 and DHT (Fig. 27-3).** Daily T production is 5 to 7 mg (5 000 to 7 000 μg). About 40 to 50 μg of E_2 is produced daily in a eugonadal adult male. Three fourths of this is derived from peripheral aromatization of T by the enzyme **aromatase**, and the rest (~10 μg) is secreted directly by the testes (Leydig cells). DHT (200 to 300 μg) is mainly derived from peripheral conversion of T by **5α-reductase**. Two isozymes of 5-reductase have been identified in humans. Type I is predominantly found in the skin, liver, and testes,

whereas type II 5α-reductase predominates in the reproductive tissues, genital skin, and epididymis. T thus serves as a prohormone for both E_2 and DHT.

d. Androgen receptor binding. The androgen receptor (AR) gene is expressed on androgen-sensitive organs. The AR protein is distributed in both the cytoplasm and the nucleus. AR is a typical steroid receptor consisting of three main regions: a steroid-binding site, a DNA-binding site, and a regulatory region that influences messenger RNA (mRNA) transcription. The same receptor binds both T and, with 10-fold higher affinity, DHT. The DHT–AR complex is more thermostable and dissociates more slowly than the T–AR complex. p. 309p. 310T-receptor binding leads to development of the internal male genitalia in the fetus and stimulation of spermatogenesis. DHT binding is responsible for development and maintenance of male external genitalia, virilization, and secondary sex characteristics. Both T and DHT exert negative feedback on the hypothalamus and pituitary gland to decrease LH release.

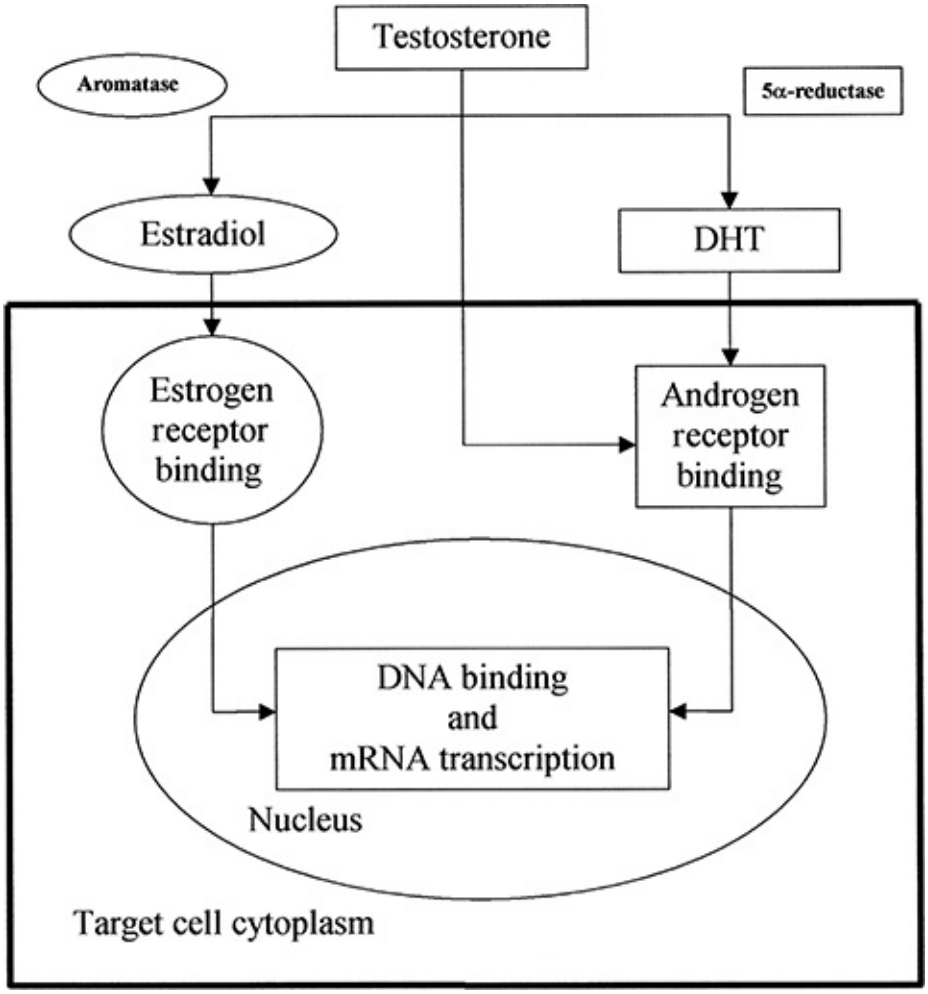

Figure 27-3. Conversion of testosterone to estradiol and dihydrotestosterone, and genomic effect on target tissue. DHT, dihydrotestosterone; mRNA, messenger RNA.

2. **Biologic effects of T:** T has different functions in different stages of life, which is mainly divided among fetal life, puberty, and adulthood. Leydig cells can be seen in the testis of the embryo around the eighth week of gestation, and T synthesis starts around the ninth week. In the embryo, through the effect of mainly DHT derived from in situ T on the Wülffian duct, growth of external genitalia, in particular the penis, occurs. Lack of T or the enzyme 5*α*-reductase can cause ambiguous genitalia or micropenis. During puberty, both T and DHT have very specific effects on body hair growth (virilization), stimulation of sebaceous glands (acne during puberty), stimulation of the larynx and elongation of the vocal cords (voice drop or break), and increase in muscle mass and strength (by stimulation of mRNA and protein synthesis). T and its

metabolites (DHT and E_2) also have effects on closure of the epiphysis, bone mass, hematopoiesis, prostate size and function, libido, behavior, aggressiveness, and spatial cognition. The effects of T on lipids show after puberty, when high-density lipoproteins (HDLs) fall in boys, and LDLs and triglycerides increase, whereas there are no gender-specific differences prior to puberty.

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3. **Spermatogenesis** is a complex process whereby a primitive stem cell, the type A spermatogonium, passes through a complex series of transformations to give rise to spermatozoa. In humans, the entire process of spermatogenesis and spermiogenesis takes 72 days.
   - **a.** The spermatogenic compartment consists of the Sertoli and germ cells. Sertoli cells are the target of local androgen and FSH stimulation, as well as the source of multiple paracrine regulators of spermatogenesis, and regulators of gonadotropin secretion (e.g., inhibin, activin).
   - **b.** LH or hCG administration stimulates an increase in intratesticular T and promptly initiates spermatogenesis. In the congenital and complete form of hypogonadotropic hypogonadism, treatment with hCG alone does not result in maturation of the seminiferous epithelium beyond the spermatid stage. In these patients, FSH alone will not initiate spermatogenesis, but FSH administration to hCG-primed hypogonadal men results in completion of spermatogenesis. Thus, FSH appears to be essential for spermiogenesis (development of spermatids into mature spermatozoa). In hypogonadotropic subjects primed with hCG and FSH, spermatogenesis can be maintained by hCG alone. Furthermore, in patients with incomplete or acquired hypogonadotropism (previously exposed to FSH), hCG alone may reinstate close to normal sperm counts.
4. **Paracrine control of testicular function and Leydig cell–Sertoli cell interaction.** The results of numerous studies suggest the existence of an **intratesticular Leydig cell–Sertoli cell axis**. The precise nature of this interaction remains unclear, but recent studies suggest that Sertoli cells exert both inhibitory and

stimulatory influences on Leydig cells. The interaction between the Sertoli cells and the maturing germ cells might be responsible for the orderly events of spermatogenesis.

II. MALE REPRODUCTIVE DISORDERS

A. Hypogonadism. Hypogonadism refers to a state of absolute or relative androgen deficiency. Major diagnostic categories are listed on Table 27-1, including primary hypogonadism (testicular insufficiency), secondary or hypogonadotropic hypogonadism (resulting from decreased GnRH or LH production), and androgen insensitivity (decreased action of androgens on target tissues).

1. **Clinical manifestations of androgen deficiency.** The time of onset of androgen deficiency influences clinical features.
   a. **Fetal onset.** Differentiation of the genitalia along male lines is an androgen-dependent process that occurs during the first trimester of gestation. During this time, placental hCG binds to LH receptors on Leydig cells and promotes T secretion. By the 13th week, pituitary secretion of LH in conjunction with hCG continues to stimulate T secretion. T deficiency or end-organ unresponsiveness during this critical developmental period results in pseudohermaphroditism. The degree of sexual ambiguity is determined by the extent of the androgen deficiency and can range from hypospadia to phenotypically female external genitalia (with a short vagina). If androgen secretion or action is diminished before birth but after the genitalia have differentiated along male lines, a small but anatomically intact phallus (microphallus) may be seen. The latter situation can be seen in congenital GnRH deficiency.
   b. **Prepubertal onset.** During the prepubertal period, GnRH, LH, and FSH are secreted at low levels. Puberty is heralded by increased nocturnal pulsation of GnRH and pituitary gonadotropins. The increase in LH and FSH leads to androgen production and spermatogenesis. The testes increase in size from 1 to 2 mL to 15 to 35 mL by adulthood, and secondary sexual characteristics develop. If androgen deficiency begins after fetal development but prior to the completion of puberty, the clinical presentation is that of delayed puberty, and secondary sex characteristics will fail to develop. The lack of T and its metabolite (E_2) results in delayed epiphysial closure.

Thus, growth of the long bones continues, and the patient develops eunuchoid proportions (arm span at least p. 311p. 3122 cm more than height and heel to pubis measurement more than 2 cm greater than pubis to crown measurement). If there is concomitant growth hormone deficiency, a eunuchoid habitus may not be present.

TABLE 27-1 Classification of Male Hypogonadism

Hypothalamic-Pituitary Dysfunction
Idiopathic GnRH deficiency, Kallmann syndrome, Prader-Willi syndrome, Laurence-Moon-Biedl syndromes (multiple)
Hypothalamic deficiency, pituitary hypoplasia
Trauma, postsurgical, postirradiation
Tumor (adenoma, craniopharyngioma, others)
Vascular (pituitary infarction, carotid aneurysm)
Infiltrative (sarcoidosis, histiocytosis, tuberculosis, fungal infection, hemochromatosis)
Systemic illness, malnutrition, anorexia nervosa
Autoimmune hypophysitis
Drugs (drug-induced hyperprolactinemia, sex steroids)
Testicular Disorders (Primary Leydig Cell Dysfunction)
Chromosomal (Klinefelter syndrome and variants, XX male gonadal dysgenesis)
Defects in androgen biosynthesis
Orchitis (mumps, HIV, other viral, leprosy)
Cryptorchidism
Myotonia dystrophica
Toxins (alcohol, opiates, fungicides, insecticides, heavy metals, cotton seed oil)
Drugs (cytotoxic drugs, ketoconazole, cimetidine, spironolactone)
Systemic illness (uremia, liver failure)
End-Organ Resistance (Impaired Androgen Action)
Androgen receptor defects
Postreceptor transduction abnormalities
5*α*-Reductase deficiency

GnRH, gonadotropin-releasing hormone.

c. Postpubertal onset. Because these patients have proceeded

through normal pubertal maturation, they have normal body measurements and normal voice but present with sexual dysfunction (i.e., decreased libido, impotence, and infertility), osteoporosis, anemia, muscle weakness, depression, and lassitude. These symptoms may be associated with loss of secondary sex characteristics (i.e., decreased facial, pubic, and body hair; decreased muscle mass and strength; increased adiposity; and small, soft testes). Gynecomastia can result from imbalance of serum T and E_2 (decreased T to E_2 ratio). The absence of chest hair, a sparseness of pubic hair, female escutcheon, and fine wrinkling of skin suggest severe long-standing hypogonadism. Less severe defects produce more subtle changes.

2. **Diagnosis of underandrogenization**
   a. **History.** A detailed developmental history pertaining to testicular descent, timing of puberty, frequency of shaving and body hair development, sinopulmonary complaints, and medical history focused on past and present systemic illnesses, sexually transmitted diseases, orchitis (in adulthood), prior irradiation treatment, prostate surgery, and drug use is important. A detailed sexual history regarding libido, erectile and ejaculatory function, masturbation, coitus, and fertility should be obtained.
   b. **Physical examination** includes assessment of height, arm span, hair pattern, fat distribution, and skin exam for wrinkling and acne. The genitourinary exam should include penis length, urethral integrity for hypospadia, digital rectal p. 312p. 313exam of the prostate (small, underdeveloped in prepuberty and atrophy of prostate in postpuberty hypogonadism), and scrotal exam for pigmentation, wrinkling, contents, proper fusion, and testicular descent. The normal size of testes ranges from 3.6 to 5.5 cm in length, 2.1 to 3.2 cm in width, and 15 to 35 mL in volume in Caucasian and African American men. In assessing T-responsive body hair, the clinician must take into account the patient’s genetic and racial background. Whereas Caucasians may need to shave daily, African Americans, Asians, and Native Americans may shave

less frequently. Last, but not least, the clinician needs to assess musculoskeletal system for underdevelopment, lack of or decreasing strength, muscle atrophy, excessive eunuchoid growth, and bones for osteopenia or osteoporosis.

c. **T level.** The clinical suspicion of low T secretion can be confirmed by measuring the serum total T level (normal range ~280 to 1 000 ng/dL). Because T is secreted in a pulsatile manner, a more accurate **measurement of serum T may be obtained by two separate measurements between 7 to 10 A.M.** Low serum T concentrations in the absence of clinical manifestations suggest a low SHBG level, which can be either a congenital or an acquired defect. A normal free T or bioavailable T measurement (albumin-bound and free T) is helpful in such cases.

d. **Anatomic localization of underandrogenization defect.** If serum T concentration is low (in the absence of low SHBG), the diagnosis of hypogonadism is confirmed, and the evaluation proceeds to identification of the anatomic level of defect. If underandrogenization exists in the absence of lower serum T levels, androgen resistance is suspected. A classification of underandrogenization according to the major sites of organ impairment is provided in Table 27-1. A summary of the laboratory changes in hypogonadism according to anatomic site is provided in Table 27-2.

   i. **Primary hypogonadism.** Primary testicular insufficiency is characterized by low serum T levels accompanied by elevated serum concentrations of LH and FSH. The disorder can result from a long list of conditions, including chromosomal abnormalities such as Klinefelter syndrome, enzymatic defects of androgen synthesis, and acquired defects as a result of trauma, infection, infiltrative diseases, autoimmune destruction, certain drugs, and malformations, such as cryptorchidism and anorchia. The androgen deficiency is usually accompanied by damage to the seminiferous tubules, resulting in azoospermia and infertility.

   ii. **Secondary hypogonadism.** Hypogonadotropic hypogonadism is characterized by low serum T levels and low serum concentrations of LH and FSH. Low

gonadotropin secretion can result from impaired hypothalamic secretion of GnRH or as a result of direct pituitary dysfunction. Functional defects may occur as a response to severe stress or illness, malnutrition, or drugs. Acquired destructive processes of the hypothalamus and pituitary p. 313p. 314gland include neoplasia, infiltrative processes, trauma, and irradiation. **Hyperprolactinemia** of any cause can produce hypogonadotropic hypogonadism, primarily by suppressing GnRH and LH secretion. Isolated GnRH deficiency, such as that associated with Kallmann syndrome and idiopathic hypogonadotropic hypogonadism, has been described. An algorithm for evaluation of such patients is suggested in Figure 27-4.

TABLE 27-2 Summary of Hormone Levels and Treatment in Major Diagnostic Categories of Hypogonadism

Category of Hypogonadism	FSH	LH	T	Treatment
Hypogonadotropic hypogonadism	↓	↓	↓	hCG or T to virilize, hCG and hMG for fertility
Primary testicular insufficiency	↑	↑	↓	T to virilize only
Isolated germinal cell damage	↑/N	N	N	None
T resistance	↑/N	↑/N	↑/N	None

↑, increased; ↓, decreased; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; LH, luteinizing hormone; N, normal; T, testosterone.

a) The distinction of hypothalamic from pituitary causes can be difficult. GnRH measurements are not practical because of the location in the portal system, low systemic concentration, and short serum half-life (5 to 10 minutes). GnRH deficiency may be suggested if androgen deficiency is accompanied by anosmia (Kallmann syndrome) or diabetes insipidus. Findings such as visual-field defects and panhypopituitarism are

more suggestive of pituitary disease. Further resolution requires magnetic resonance imaging (MRI) of the sella (hypothalamic-pituitary region) with and without contrast material.

b) Because both hypothalamic and pituitary diseases can result in a blunted or absent response of LH and FSH to an acute bolus of GnRH, this should not be used to distinguish hypothalamic and pituitary disorders. However, p. 314p. 315priming the pituitary with multiple properly spaced injections of GnRH will result in stimulation of LH secretion in patients with hypothalamic GnRH deficiency and could be of value in separating such patients from those with pituitary disease if localization of the primary defect is unclear. Because most patients with a pituitary basis for secondary hypogonadism have either hyperprolactinemia or a mass lesion on MRI, distinguishing between hypothalamic and pituitary causes by GnRH pulsing is rarely indicated.

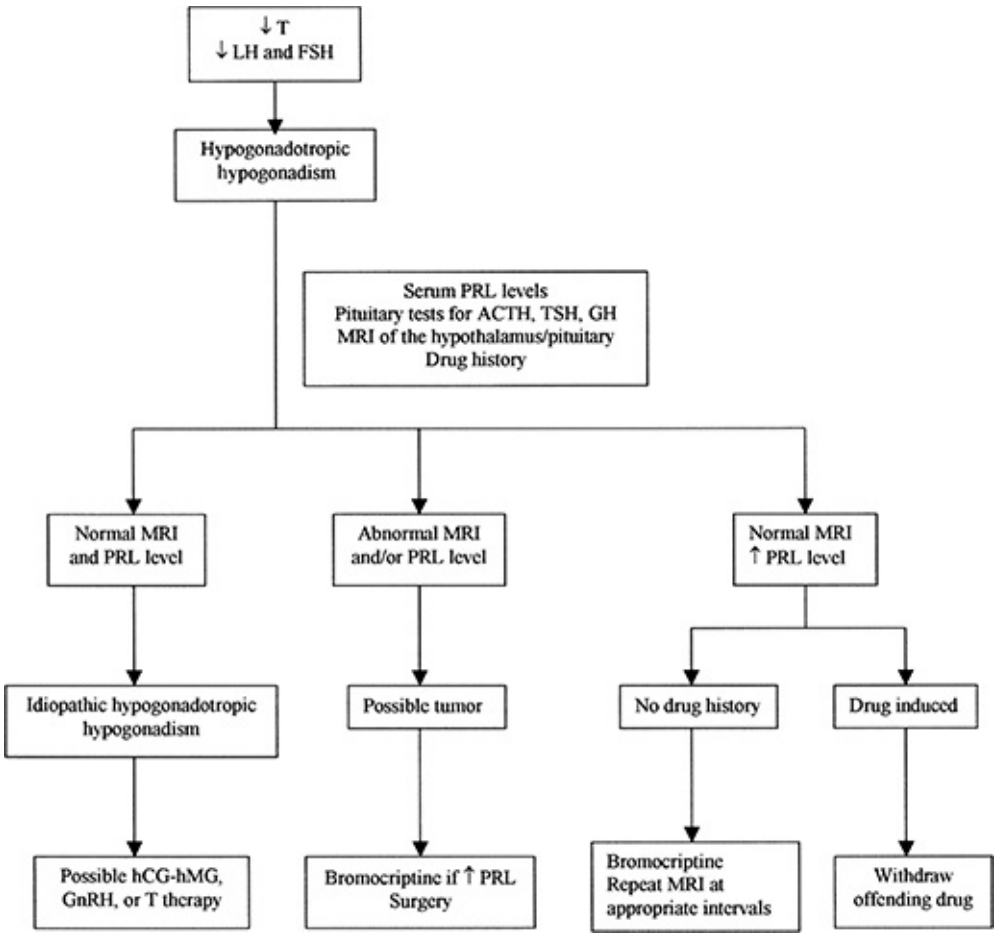

Figure 27-4. Evaluation and treatment of a patient with hypogonadotropic hypogonadism. ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone; MRI, magnetic resonance imaging; PRL, prolactin; T, testosterone; TSH, thyroid-stimulating hormone. (Modified from Swerdloff RS, Boyers SP. Evaluation of the male partner of an infertile couple: an algorithmic approach. *JAMA* 1982;247:2418. Copyright 1982 American Medical Association.)

3. **End-organ resistance:** Androgen resistance is caused by sporadic or familial mutations of the AR gene, which is located on chromosome X (Xp11–12), and approximately 250 different gene mutations have been recognized. It is estimated that 1 in 20 000 to 64 000 newborns have the AR defect. AR defects appear to be the most common cause of T resistance and have a characteristic hormonal pattern with elevated serum T and LH levels. Such patients often present with clinical manifestations ranging from complete testicular feminization (external genitalia are female, with the presence of testes in the inguinal canal) to Reifenstein

syndrome (identifiable as male at birth, with moderately ambiguous genitalia, gynecomastia, and azoospermia) and infertile-man syndrome (mild form with male external genitalia and descended testes with defective spermatogenesis and oligospermia). DHT should be measured when there is abnormal differentiation of external genitalia. Gynecomastia is common and is a result of excessive production of E_2 from both aromatization of circulating T and direct hypersecretion by the testis.

4. **5*α*-Reductase deficiency** is a disorder of sexual differentiation caused by a mutation of the gene for the enzyme 5*α*-reductase type II located on chromosome 2, which converts T to DHT. Despite a 46,XY karyotype, because of the lack of enzyme activity, these patients do not have a normal male phenotype, and the external genitalia may appear female. The testes are usually located in the labia majora, inguinal canal, or abdomen. The level of T is high, with low to undetectable DHT levels. DHT replacement is the potential treatment, although the US Food and Drug Administration (FDA) does not approve it for this purpose.
5. **Delayed puberty** is defined as puberty that has not started by age 14 in boys (2.5 years standard deviation from the norm). It is often challenging and difficult to distinguish delayed puberty from hypogonadotropic hypogonadism in the prepubertal age, thus it is a diagnosis of exclusion. Among hypogonadotropic males, basal serum LH, FSH, and T concentrations and the gonadotropin response to GnRH are indistinguishable from those of prepubertal boys. The following may be helpful.
   - **a.** Measure serum LH levels using the newest generation of highly sensitive immunofluorescent assays, which are often capable of separating normal prepubertal from hypogonadotropic concentration.
   - **b.** Progressive testicular growth and onset of virilizing signs indicate that puberty is progressing normally.
   - **c.** The presence of nocturnal LH release in early pubertal boys may help to establish that puberty has been initiated.
   - **d.** In isolated hypogonadotropism, the levels of adrenal steroids (dehydroepiandrosterone sulfate [DHEAS]) are normal relative to chronologic age. In constitutional delay, bone age is delayed, and serum DHEAS concentration is low.

e. Patients with constitutional delay in puberty have a history of slow growth velocity throughout childhood. In hypogonadotropism, growth velocity is normal in childhood and is normal or slightly slower during the prepubertal growth spurt, even though these individuals may eventually be taller with eunuchoid proportions.

6. **Treatment of androgen insufficiency.** The requirement for androgens varies at different stages of life, and it must be adjusted accordingly based on disease state, age, and current reproductive needs of the patient. Indications for androgen therapy are given in Table 27-3. Androgen replacement has risks and benefits, which again differ in different situations and stages of life. The benefits and risks of androgen replacement are summarized in Table 27-4.

In general, if the p. 315p. 316hypogonadism is caused by extratesticular factors, attempts should be made to correct these. Otherwise, libido, potency, and secondary sex characteristics can be restored by androgen replacement therapy. Patients with hypothalamic or pituitary processes causing secondary hypogonadism should be treated with T to restore virilization or with either gonadotropins (human menopausal gonadotropin [hMG], hCG) or pulsatile GnRH replacement therapy if restored fertility is required. It is important to emphasize that the gradual decline of T secretion can lead to the insidious onset of symptoms, such as loss of libido and potency, tiredness, lack of ambition and drive, hot flushes, and depression. It is equally important to realize that a patient who has never had adequate T secretion may claim that the levels of libido and potency he experiences are normal, because he does not have a basis for comparison.

TABLE 27-3 Indications for Androgen Therapy

Androgen deficiency (primary and secondary hypogonadism)
Delayed puberty in boys
Transsexuality (female → male)
Elderly men with low testosterone levels
Angioneurotic edema
Microphallus (neonatal)
Other possible uses or under investigation:
• Hormonal male contraception

- Wasting disease associated with cancer/HIV/chronic infection
- Postmenopausal female (in combination with estrogens)

a. Methods of androgen replacement. (Table 27-5). T is available in different forms and serves as a hormone and prohormone, which is **converted to DHT by 5*α*-reductase and E_2 by aromatase**. Patients need to be evaluated 3 months after treatment initiation and then annually for response to treatment as well as adverse effects.

i. T esters (injectable forms): Treatment usually commences with intramuscular injections of T enanthate or cypionate in a dosage of 50 to 100 mg weekly, or 150 to 200 mg every 2 weeks. Serum T levels should be within the mid-normal range when measured 5 to 7 days after an injection, and p. 316p. 317the patient should be free of symptoms of androgen deficiency throughout the interval between injections. For monitoring, measure serum T levels midway between injections. If the serum T level is >700 ng/dL or <350 ng/dL, the physician will need to adjust the T dose or frequency. The **optimum interval for injections** varies considerably, but **10 to 17 days is usual.** The patient is then encouraged to give his own injections. T:DHT and T:E_2 ratios are in the normal range in this mode of replacement if replacement is physiologic and biologically active in resolving sign and symptoms of hypogonadism. **Testosterone undecanoate (TU)** in oil is an injectable long-acting formulation approved by the FDA in the United States.

TABLE 27-4 Benefits versus Risks of Androgen Replacement Therapy

Benefits	Risks (Potential)
↑ Sexual motivation and performance	Acne, oiliness of skin
↑ Or maintains secondary sexual characteristics	Gynecomastia (aromatizable androgens)
↑ Muscle mass and strength	↑ Hematocrit
↓ Body fat including visceral fat	Sleep-related breathing disorders, apnea

↓ Bone resorption, ↑ bone formation, and maintains bone mass	↓ HDL cholesterol, ↓ HDL to total cholesterol ratio (cardiovascular risk?)
Improves mood parameters	Aggravates benign prostatic hypertrophy (?)
Improves quality of life	Stimulation of existing cancer of the prostate
Improves or prevents deterioration of cognition (?)	

↑, increased; ↓, decreased; HDL, high-density lipoprotein.

TABLE 27-5 Androgen Preparations

Type	Currently Available in the United States
Injectables	Testosterone enanthate, cypionate (100–200 mg every other week) Mixture of esters (e.g., testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, testosterone decanoate) Testosterone undecanoate injections (750 mg initially, followed by 750 mg after 4 wk, followed by 750 once every 10 wk)
Oral	Methyltestosterone[a] Testosterone undecanoate (under development), 80–160 mg/d in divided doses)
Buccal	Transbuccal testosterone tablets (60 mg/d in divided doses)
Implants	Testosterone pellets (75 mg, 3–6 inserted once every 4–6 mo)
Transdermal (gels/solutions)	AndroGel 1% (25 mg in 2.5 g packet) AndroGel 1.62% (20.25 mg in 1.25 g packet) Testim 1% (50 mg in 5 g packet) Fortesta 2% (10 mg/metered-dose pump) Axiron 2% solution (30 mg/metered-dose pump)
Nasal gel	Natesto (one pump actuation delivers 5.5 mg into the nostrils, total of 33 mg/d)

[a]Associated with severe hepatotoxicity.

ii. **Transdermal delivery. AndroGel** is supplied in two concentrations of AndroGel 1% that each 1.25 g contains 12.5 mg of T, versus AndroGel 1.62% that each 1.25 g contain 20.25 mg T. **Testim** is 1% T gel provided in tubes of 5 and 10 g that delivers 50 and 100 mg T, respectively. The third transdermal formulation is **Fortesta** 2% T gel supplied in metered-dose pump, which each pump depression deliver 0.5 g gel that contains 10 mg T. The last one is **Axiron 2%** T solution that comes in metered-dose pump and 1.5 mL delivers 30 mg T to the axilla. The

disadvantage is transfer to female partner and children.

iii. **Oral preparations.** Most oral T preparations are absorbed into the portal circulation and rapidly degraded by the liver. Synthetic oral 17-alkylated androgens, such as methyltestosterone, fluoxymesterone, and oxymetholone, **are not recommended** because they produce only partial androgenization. Methyltestosterone and fluoxymesterone have been associated with several hepatic disorders, including cholestatic jaundice, liver cell carcinoma, and the rare vascular disorder peliosis hepatis. **TU** (non–17-alkylated) is an oral T preparation; it has the advantage of lymphatic absorption, thus bypassing first-pass metabolism in the liver. The dose ranges between 40 and 80 mg p. 317p. 318orally two or three times daily with meals. It has variable clinical response in the same individual on different days, because it is very dependent on the fat in the diet for optimal absorption.

iv. **T implants** (Testopel). Three to six 75 mg pellets are implanted subcutaneously. They are capable of maintaining physiologic levels of T for 5 to 6 months. The main obstacle is implantation into the subdermal fat of the buttocks or lower abdominal wall, which has been associated with pellet extrusion, infection, and fibrosis.

v. **Nasal testosterone gel** (Natesto) that is administered into the nostrils (5.5 mg of T) by metered-dose pump applicator. The recommended dose is 11 mg three times daily. Despite lower risk of transfer to a partner or child, it has been associated with epistaxis, rhinorrhea, sinusitis, and nasal scab.

vi. **Buccal tablet (Striant SR),** which is 30 mg each and applied twice daily in the gum above the upper incisors. T is released and absorbed through the buccal mucosa to the systemic circulation. It is associated with taste alteration.

vii. **DHT** is used in Europe in the form of a topical gel. It may be useful in men with 5α-reductase deficiency, prepubertal gynecomastia, microphallus, and delayed puberty because it **cannot be aromatized to estrogen.** It has **not been associated with gynecomastia**, and reports have

suggested an actual **decrease in prostate size**. This may be advantageous in older men at risk for obstructive uropathy; however, because DHT is not aromatized to E_2, the long-term effects on bone density, cardiovascular disease, and cognition are not known.

b. **Potential adverse effects.** Androgen replacement is contraindicated in patients with androgen-sensitive neoplasia (breast and prostate carcinoma). Prostate enlargement is a potential complication, and patients with symptomatic prostatic hypertrophy should have surgical correction or medical control prior to starting replacement. It is important to measure prostate-specific antigen (PSA) and prostate size by digital rectal examination annually while on replacement. Development of or preexisting polycythemia (hematocrit > 52%) is an indication to withhold androgen replacement, because androgens **increase red cell production** either by stimulating erythroid precursors or by stimulating erythropoietin secretion. Because of neuromuscular effects of T on the upper airway, **apneic sleep disorders** may be exacerbated by androgens. Other side effects include **gynecomastia** secondary to aromatization to E_2, fluid retention, and acne. HDL cholesterol levels may be lowered; however, the long-term cardiovascular consequences are not known.

c. **Management of primary testicular failure.** Unfortunately, the majority of testicular disorders causing androgen deficiency are irreversible. Consequently, treatment consists of androgen replacement therapy alone.

d. **Management of secondary hypogonadotropic hypogonadism.** The initial aim in management is always to exclude tumors of the pituitary or hypothalamus, along with other treatable causes, such as thyroid disease, hyperprolactinemia, and offending drugs, by the appropriate investigations. Treatment of men with congenital hypogonadotropic hypogonadism usually begins at puberty. If fertility is not desired, T replacement can be given (as described above) to achieve masculinization without concern for any irreversible compromise of testicular function. If fertility is

desired, subsequent management involves replacement therapy with gonadotropins or GnRH infusion.

i. **Treatment with gonadotropins. When fertility is desired,** T is not given or withdrawn, and injections of hCG (purified from the urine of pregnant women) (1 500 to 2 000 IU) are given intramuscularly or subcutaneously three times a week for approximately 6 months. **hCG acts as LH** in binding to LH receptors and increasing testicular T production. If semen analyses show that sperm production has not commenced or is <7 to 10 million/mL, FSH, in the form of hMG (which is purified from the urine of postmenopausal women) or recombinant FSH, 75 IU three times a week, is p. 318p. 319added to the hCG regimen. Because FSH or hMG is more expensive than hCG, treatment usually begins with hCG alone, but combined therapy is often needed for 12 to 15 months. Once spermatogenesis is initiated, hCG alone may maintain normal sperm count. Recombinant human hCG and recombinant human FSH are now available with identical biologic and pharmacokinetic activities. Predictors of success are the testicular volume (>8 mL with better response vs. <4 mL with poorer outcome) and time of onset (onset of hypogonadism prior to puberty with less favorable outcome than after puberty).

ii. **Pulsatile administration of GnRH for treatment of hypothalamic hypogonadotropism.** GnRH could stimulate appropriate gonadotropin secretion only when the hormone was administered in an episodic mode and at a physiologic frequency. **Continuous administration was completely ineffective** in evoking the desired pattern of gonadotropin discharge. Using such a regimen of long-term episodic GnRH administration by means of a portable pump with an initial dose of 25 ng/kg/pulse every 2 hours subcutaneously, it has been possible to restore spermatogenesis in men with Kallmann syndrome and to induce clinical and biochemical changes of puberty in patients with delayed puberty because of hypothalamic GnRH deficiency. A similar approach has been used with

success in inducing ovulation in women with hypothalamic amenorrhea associated with idiopathic GnRH deficiency, anorexia nervosa, or competitive exercise. Although subcutaneous administration of GnRH has been reported to be effective, it is less practical and less effective than gonadotropin therapy.

e. **End-organ resistance.** There is **no known effective therapy** for the eunuchoidism resulting from androgen resistance. Patients with male phenotypes and gynecomastia usually require cosmetic surgery to remove breast tissue and to correct the more severe degrees of hypospadia.

7. **Specific disease states associated with primary hypogonadism**
   a. **Klinefelter syndrome.** Klinefelter syndrome is the most common disorder of sexual differentiation, occurring in about 1 of 500 to 1 000 men. It has been reported that approximately 10% of individuals with Klinefelter syndrome are diagnosed by karyotype screening at birth and childhood, and overall only 25% are diagnosed during life. The primary abnormality is the presence of two or more X chromosomes, usually in the form of a 47,XXY chromosomal complement (the classic form) or, less commonly, 46,XY/47,XXY (the mosaic form). The additional X chromosome(s) may be a result of nondisjunction during gametogenesis or nondisjunction in the zygote during mitosis.
      i. **Classic form.** Before the onset of puberty, the hypothalamic-pituitary-testicular axis functions normally. By 12 to 14 years of age, impaired Leydig cell function results in decreased T, increased gonadotropins, and hypogonadism. Testicular biopsy reveals pathologic hyalinization and fibrosis of the seminiferous tubules. Decreased testicular size and defective spermatogenesis are present in almost all patients with the classic form. Clinically, it is characterized by an unequivocally male phenotype, small penis size, small firm testes (with median volume of 4 mL, and always <12 mL), azoospermia, and decreased male pattern body and facial hair. If Leydig cell failure occurs prior to puberty, then patients manifest eunuchoid features. Gynecomastia is common and may be

caused by increased peripheral conversion of T to E_2 as well as decreased clearance of estrogens. Most patients come to medical attention after puberty with complaints of dyslexia, infertility, or gynecomastia. Obesity and varicose veins occur in one third to one half of patients with Klinefelter syndrome. There is an increased incidence of learning disability and social maladjustment, subtle abnormalities of thyroid function, diabetes mellitus, and abnormalities of pulmonary function. Taurodontism is common and may be associated with early tooth decay. Incidence of **breast cancer is 1 in 5 000, about 20 times that of normal men** but only one fifth that of women. Screening p. 319p. 320mammography is not recommended because of the low incidence. There are also higher incidences of germ-cell tumors and autoimmune disorders. These patients generally have a male psychosexual orientation and are capable of **functioning sexually as normal men**.

ii. **Mosaic form.** About 10% of patients with Klinefelter syndrome have the mosaic form, a less severe form of the disorder. As many as one fourth of these patients have normal testicular size, and only half have complete absence of spermatogenesis accounting for **rare instances of fertility**. Mosaicism may be limited to the testes and thus can only be diagnosed by testicular biopsy.

iii. The diagnosis of Klinefelter syndrome in patients with the classic 47,XXY is suggested by elevations of LH and FSH, and a low-to-normal T. A careful history will almost always demonstrate learning disabilities and varying degrees of dyslexia. From a standard laboratory perspective, a **high FSH level** (because of germinal compartment failure) **is the best demarcator between patients with Klinefelter syndrome and normal men**. If FSH is elevated, the condition can be rapidly confirmed by buccal smear and detection of Barr bodies (extra X chromosome), a chromosomal analysis performed on peripheral blood leukocytes, or by fluorescence in situ hybridization.

Mosaicism can be missed in some patients in whom the mosaic pattern is limited to the testes. Under these circumstances, only a chromosomal analysis of testicular cells provides a definitive diagnosis.

iv. Treatment with T will lead to masculinization and improvement of symptoms of hypogonadism; however, **infertility is irreversible,** despite hormone therapy.

b. **Gonadal dysfunction in patients treated with cancer chemotherapeutic agents.** With the advent of multiagent chemotherapy for malignant disorders and the ensuing increased survival, it has become apparent that germinal aplasia and resulting infertility may be a common side effect. Chemotherapeutic agents are not equivalent in their potential gonadal toxicity. The side effects depend not only on the specific class of drug used but also on the total dose used. Alkylating agents (cyclophosphamide, thiotepa, chlorambucil, nitrogen mustard, and melphalan) as a class produce dose-dependent germinal depletion. Procarbazine, most commonly used in the management of lymphoma, produces permanent germinal aplasia. Doxorubicin hydrochloride (Adriamycin) (500 mg/m^2), vincristine, and high-dose methotrexate do not have these side effects in humans.

c. **Radiation** to the pelvic region (e.g., prostate, bladder, testes, rectum, lymph nodes) often produces reversible germinal depletion between 50 and 400 rad; above 500 rad, germinal aplasia is usually permanent.

d. **Endocrine disruptors** (see Chapter 86). These are man-made drugs, toxins, and synthetic chemicals as well as natural phytoestrogens, which act on the endocrine system by mimicking, blocking, and/or interfering in some manner. They can cause gonadal toxicity by effect on the germinal epithelium, which is a rapidly dividing tissue like bone marrow and gastrointestinal tract, and susceptible to damage.

i. **Marijuana.** There is evidence that marijuana not only **lowers the plasma T level** by decreasing GnRH production but may also produce **gynecomastia** and **altered germinal maturation** in the testes. Crude marijuana contains plant estrogens that interfere with gonadal function, but there is little evidence that purified

tetrahydrocannabinol has any direct effect.

ii. **Fetal exposure to diethylstilbestrol and medroxyprogesterone acetate (Provera).** Fetal exposure to diethylstilbestrol (DES) and medroxyprogesterone acetate (MPA) can produce significant abnormalities of the male genital tract. In both rodents and humans, DES produces an increased incidence of epididymal cysts and testicular atrophy. MPA likewise can be associated with abnormalities of the external genital apparatus. Accordingly, a maternal history of drug exposure can be helpful in evaluation of the infertile male.

iii. **Miscellaneous.** Each year the list of environmental toxins shown to produce adverse effects on the testes grows. Dibromochloroperine, boron, dioxin (Agent Orange), and kepone are some of the better-known toxins.

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8. **Specific hypothalamic syndromes characterized by hypogonadotropic hypogonadism**

   a. **Kallmann syndrome.** Hypogonadotropic hypogonadism was first recognized by Kallmann, Schoenfeld, and Barrera in 1944. Kallmann syndrome has different genetic modes of transmission (X-linked, autosomal dominant with variable penetration, and autosomal recessive) and is characterized by isolated GnRH deficiency. During normal fetal development, GnRH neurons begin migration from the olfactory placode to the arcuate nucleus of the hypothalamus. Migration is interrupted or absent in Kallmann syndrome because of mutations in the *KAL1* gene, which encodes **anosmin,** a cell-adhesion protein that mediates migration. Approximately **50% of these subjects have midline craniofacial defects** (anosmia or hyposmia, cleft lip and palate), and may manifest increased frequencies of sensorineural deafness and ataxia, and renal defects. MRI of the brain may show anomalous or absent olfactory bulbs in up to 75% of cases. Women are affected much less frequently than men (4:1 male to female ratio). This makes the X-chromosomal inherited variant the most common form. **A positive family history is present in approximately 50% of cases**; relatives may have hypogonadism, and many manifest only one

of the associated midline defects. In teenagers who fail to enter puberty, these clinical markers can be useful to differentiate Kallmann syndrome from constitutional delay of puberty.

b. **Fertile eunuch syndrome (Pasqualini syndrome).** This term has been used to describe patients with partial GnRH deficiency that is enough to stimulate normal levels of FSH, but the LH levels are not completely normal, leading to eunuchoidism and delayed sexual development but normal-sized testes. These individuals appear to have sufficient gonadotropin to stimulate enough intratesticular T production for spermatogenesis, but not enough circulating T to adequately virilize the peripheral tissues. **Despite the name, these patients are frequently infertile.**

c. **Functional hypogonadotropism**

   i. Marked weight loss in patients with chronic diseases, such as malabsorption syndrome in gastrointestinal diseases (i.e., celiac disease), chronic renal insufficiency, tumor cachexia, severe systemic illnesses, and **anorexia nervosa,** are associated with hypogonadotropic hypogonadism. The underlying mechanisms remain to be elucidated but likely involve a combination of cytokine and/or glucocorticoid effects. One mechanism is decreased secretion of GnRH and consequent reduction in LH and FSH, which in turn causes T production and spermatogenesis to cease. This **may be a result of leptin deficiency** secondary to lack of enough adipocytes, which provides feedback to the hypothalamus indicating that the body fat is inadequate for reproduction. With correction of the underlying disorder and restoration of normal weight, usually long-term therapy is not required.

   ii. Exercise and stress also affect the hypothalamic-pituitary axis. **Basal T levels** were lower than normal in a study of joggers and **fell markedly after completion of a marathon**. T levels also fell in military personnel studied during stressful periods at officer candidate school. Women involved in strenuous exercise (e.g., joggers, athletes, and ballet dancers) can develop hypothalamic amenorrhea in a manner similar to that seen with anorexia nervosa. Pulsatile administration of GnRH restores normal gonadotropin

secretion and menstrual cycles in these patients, suggesting a defect in hypothalamic GnRH secretion.

iii. Chronic opiate administration for chronic pain syndrome as well as treatment of opioid dependence by methadone is associated with low T concentration and sexual dysfunction.

iv. Glucocorticoid administration for other chronic illness cause can lead to hypogonadism through the effect on the hypothalamus or pituitary, where serum LH does not increase.

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v. Antipsychotics, which are blocking dopamine D_2 receptors, allow uninhibited secretion of prolactin and subsequently gynecomastia, sexual dysfunction, and infertility.

d. **Miscellaneous hypothalamic syndromes.** Acquired hypogonadotropic hypogonadism can result from structural lesions affecting the hypothalamus (e.g., craniopharyngiomas and germinomas) and head trauma. In the majority of cases, hypogonadotropism as a result of infiltrative processes of the hypothalamus (e.g., sarcoidosis and hemochromatosis) has been shown to be that of GnRH deficiency. A few individuals have a pituitary cause, with impaired pituitary response to GnRH administration. The etiologic progression of hypogonadotropism seen in association with Prader-Willi and Laurence-Moon-Biedl syndromes appears to be caused by hypothalamic dysfunction in most cases. **Prader-Willi syndrome (see Chapter 16)** and **Angelman syndrome** are rare syndromes (1:20 000) characterized by combination of marked hypotonia, secondary hypogonadism, hyposomia, oligophrenia, facial dysmorphism, obesity, and type 2 diabetes mellitus. Prader-Willi syndrome is caused by a deletion on the long arm of the paternal chromosome 15, whereas in Angelman syndrome, the maternal chromosome 15 is deleted (15q11–13). There is no definitive treatment, and because of reduced cognitive abilities and abnormal behavior, T should be administered with caution. Life expectancy is decreased because of extreme obesity, which increases the risk of

cardiovascular disease. **Laurence-Moon-Biedl syndrome** is an autosomal recessive disorder characterized by obesity, hypogonadism, oligophrenia, retinitis pigmentosa, and polydactylism. At birth, undescended testes, micropenis, and hypospadia are frequently observed.

9. **Male senescence.** Unlike the abrupt gonadal failure of female menopause, men have a gradual decline in circulating androgens, adrenal androgen precursors, and growth hormones, (see Chapter 12) which have been shown in a number of cross-sectional and longitudinal studies, such as The Baltimore Longitudinal Study of Aging and The Massachusetts Male Aging Study (Table 27-6).
   a. Both total and free T gradually decline and are associated with elevated serum LH and FSH levels, indicating a primary defect within the testes. A second, partial defect in hypothalamic GnRH secretion may also exist, resulting in a blunted rise in LH and FSH relative to the lowered serum T concentration. The effects of low T are similar to those observed in younger men. These include decreased muscle mass, muscle strength, bone density, libido, and erectile function, and depressed mood. Body fat, especially visceral fat, is increased. E_2 is increased as a result of T aromatization in adipose tissue. p. 322p. 323Screening of older male population for low T level is not recommended, but testing should be utilized for men who have signs and symptoms of androgen deficiency. **Replacement therapy with T** has been shown to increase lean body mass, grip strength, bone density, quality of life, sense of well-being, and libido. However, erectile dysfunction is multifactorial in origin, with impaired vasodilatory function in the penis being a predominant factor in many older men. Thus, erectile dysfunction is often not improved despite androgen therapy.

TABLE 27-6 Hormonal Changes with Aging

GnRH-LH/FSH-T	CRH-ACTH-DHEA/S	GHRH-GH/IGF-1
↑ LH,[a] FSH	No change in ACTH	↓ GHRH message and receptor
↓ T (↓ Leydig	↓ DHEA and DHEAS	↓ GH secretory pulses

cells)		
↓ Free T	↓ DHEA and DHEAS response to ACTH ↓	↓ Circulating GH
↑ SHBG		↓ Serum IGF-1

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; DHEA, dihydroepiandrosterone; DHEAS, dihydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IGF-I, insulin-like growth factor type I; LH, luteinizing hormone; SHBG, sex hormone–binding globulin.

[a] ↓ LH pulse amplitude and ↓ responsiveness to GnRH.

b. Androgen precursors DHEA and DHEAS also decrease with age. Small studies have reported that **DHEA** administered to aging animals and humans may improve sense of well-being, enhance memory, decrease body fat, reduce risk of cardiovascular disease, prevent cancer, and provide beneficial effects on immune function. DHEA is sold as a dietary supplement without quality control by FDA in the United States and is available without prescription, but efficacy is modest and long-term safety has not been established.

c. Hormonal changes may contribute to male frailty; however, it is not known whether the changes represent a physiologic or a pathologic process. There is ongoing debate as to whether androgen replacement is beneficial in male senescence, but new guidelines recommend it for symptomatic men with classic androgen deficiency (see above). On the other hand, experts recommend against T therapy in patients with breast or prostate cancer, palpable prostate nodule or induration, PSA > 3 ng/dL, symptomatic severe benign prostate hyperplasia, erythrocytosis (hematocrit > 52%), hyperviscosity, untreated obstructive sleep apnea, and uncontrolled severe heart failure. The PSA threshold may be lowered for African Americans and patients with family history of prostate cancer.

B. Male infertility. Infertility is defined as a lack of conception following 1 year of frequent unprotected intercourse. The causes of male infertility can be divided into six main areas (Table 27-7): **(a)** hypothalamic disease (secondary hypogonadism) accounting for 1% to 2% of causes; **(b)** testicular disease (primary hypogonadism), 30% to 40%; **(c)** posttesticular defects (disorders of sperm transport), 10% to

20%; **(d)** sexual dysfunction, 1% to 2%; **(e)** systemic illnesses (uncommon); and **(f)** nonclassifiable, 40% to 50%. All evaluations for infertility must include a thorough assessment of both the man and the woman, because in many cases, abnormalities of reproductive function exist in both partners. A population-based study by the World Health Organization (WHO) found the following distribution of causes when evaluating infertile couples: male factors 23%, ovulatory dysfunction 18%, tubal damage 14%, endometriosis 9%, coital problems 5%, cervical factors 3%, and unexplained 28%.

1. **Evaluation.** An algorithmic approach to the evaluation of a man for infertility is presented in Figure 27-5.
   a. **History.** History should focus on sexual development, puberty, school performance, symptoms of hypogonadism (loss of body hair and loss of libido), chronic illnesses, infections, sexually transmitted diseases, previous surgery, drug and environmental exposures, and a detailed sexual history. Many drugs are associated with impaired spermatogenesis and/or Leydig cell dysfunction. Among them, the most important are the alkylating drugs (cyclophosphamide and chlorambucil). Antiandrogens (flutamide, cyproterone, and spironolactone), ketoconazole, and cimetidine cause testicular dysfunction by inhibiting testicular androgen production or actions. Environmental toxins may be an underappreciated cause of infertility. The pesticide dibromochloropropane is a well-known cause, as are lead, cadmium, and mercury. The possibility that chemicals with estrogenic activity, including phytoestrogens, may lower sperm counts has attracted much attention recently, although direct proof of an effect is lacking. The suspicion of such an effect originated with observations that sperm counts had decreased over the past several decades. However, a recent meta-analysis suggested that although decreases in sperm counts have occurred on a local basis, there has been no worldwide decline.

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   b. **Physical exam** should include assessment of secondary sex characteristics, developmental defects, gynecomastia, and detailed genitourinary exam.
   c. **Semen analysis.** Semen analysis is the cornerstone in the assessment of a male partner of an infertile couple. A normal

semen analysis should prompt a thorough evaluation of the female partner. At least 2 to 7 days of sexual abstinence is recommended prior to collection of the specimen in a clean container. The semen specimen should be kept warm (between 20°C and 37°C) (as close to body temperature as possible) and transported to the laboratory within 1 hour of collection, and the start of the investigation not exceed 3 hours from the collection. At least two samples should be collected 1 to 2 weeks apart, and any abnormal semen analysis should be repeated after an appropriate period of abstinence. Table 27-8 lists the parameters assessed in a basic semen analysis, and normal reference ranges are listed in Table 27-9. Evaluation of the semen specimen includes assessment of the following.

i. **Volume.** The volume of the ejaculate is mainly contributed by seminal vesicles and prostate gland. The normal volume varies between 1.5 and 5 mL. A low volume with azoospermia or oligospermia may be caused by genital tract obstruction. Congenital absence of vas deferens may be diagnosed by physical examination and a low semen pH, whereas ejaculatory duct obstruction is diagnosed by finding dilated seminal vesicles on transrectal ultrasound.

ii. **pH.** Of importance is the balance between the alkaline seminal vesicular secretion and the acidic prostatic secretion. A value of 7.2 is considered p. 324p. 325p. 325p. 326a low normal threshold. A low pH suggests occlusion of the ejaculatory ducts or congenital bilateral absence of the vas deferens or contamination of the specimen with urine.

TABLE 27-7 Common Causes of Male Infertility

Cause	Percent of Patients
Hypothalamic-pituitary disease	1–2
Isolated hypogonadotropic hypogonadism	
Hypopituitarism (tumors, hyperprolactinemia)	
Hemochromatosis, others	
Testicular Dysfunction	30–40

Chromosomal (XXY or variants)	
Cryptorchidism	
Varicocele	
Orchitis (mumps, tuberculosis, cytomegalovirus)	
Drugs (alkylating agents and other cytotoxic drugs)	
Irradiation	
Toxins	
Hyperthermia	
Autoimmune testicular disease	
Y-chromosome deletions or substitutions	
Sexual Dysfunction	1–2
Retrograde ejaculation	
Erectile dysfunction	
Problems with Sperm Transport	10–20
Epididymal obstruction/dysfunction	
Congenital absence of the vas	
Young syndrome	
Vasectomy	
Systemic Illness	Less common
Debilitating disease (e.g., renal failure, liver failure, HIV)	
Not Known	40–50

Data from Baker HWG. Male infertility. In: De Grout LJ, ed. *Endocrinology*. Philadelphia: WB Saunders; 1994:2404; De Kretser DM. Male infertility. *Lancet* 1997;349:787.

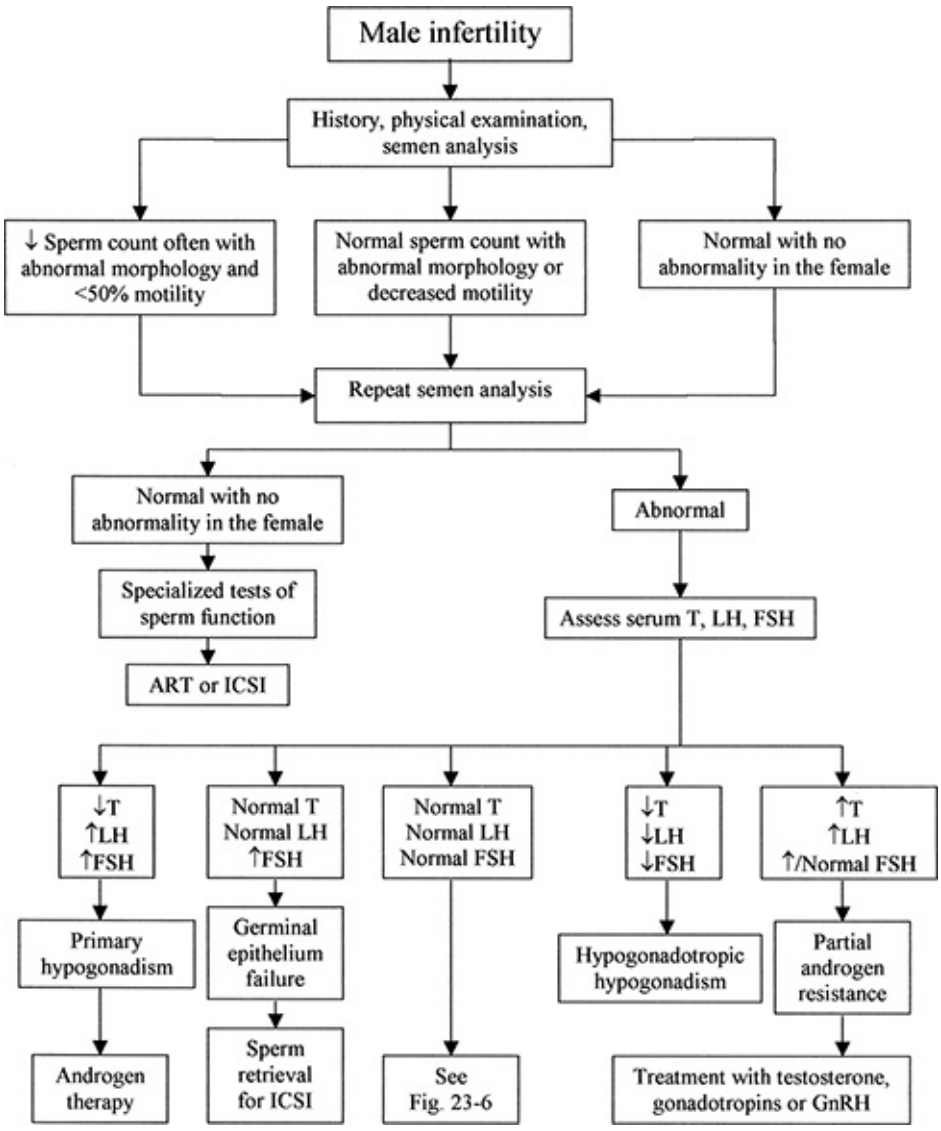

Figure 27-5. Algorithmic approach to the diagnosis and management of male infertility. ART, assisted reproductive technology; FSH, follicle-stimulating hormone; ICSI, intracytoplasmic sperm injection; LH, luteinizing hormone; T, testosterone. (Reprinted from Swerdloff RS, Wang C. The testes and male sexual function. In: Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine*. 24th ed. Philadelphia: WB Saunders; 2012:1472–1483.)

TABLE 27-8 Male Infertility: Basic Semen Analysis

Volume
pH
Microscopy: agglutination, debris
Sperm: concentration, motility, morphology, vitality
Leukocytes
Immature germ cells
Sperm autoantibodies (if agglutination present)

(Sperm/semen biochemistry sperm function tests)

TABLE 27-9 Semen Analysis: Reference Ranges

Parameter	Reference Range
Semen volume	>1.5 mL
Sperm	
Concentration	>15 million/mL
Total count	>40 million/ejaculate
Motility	>40% motile
	>32% progressively motile
Morphology	>15% normal[a]
Vitality (live)	>75%
Leukocytes	<1 million/mL

[a]This value is based on using the strict criteria for assessment of sperm morphology in studies using in vitro fertilization as an endpoint.

Modified from WHO: *Laboratory Manual for Examination of Human Semen and Sperm Cervical Mucus Interaction.* 2010.

iii. **Microscopy for debris and agglutination.** The presence of agglutination suggests autoantibodies to sperm. This should be confirmed by the mixed antiglobulin reaction or the immunobead test. A clinically significant immune disorder is suggested when >50% of spermatozoa are coated with autoantibodies.

iv. **Sperm count, motility, and morphology**

a) A **normal** sperm count is defined as >**15 million/mL of semen**, although a moderate decrease (moderate oligospermia) in sperm concentration (10 million/mL) is compatible with fertility, provided sperm motility and morphology are normal. A sperm count <5 million/mL is defined as severe oligospermia. Azoospermia is the complete absence of sperm.

b) **Sperm motility.** Sperm is assessed by microscopy and classified as progressive, nonprogressive, or nonmotile. At least 40% of spermatozoa should be motile, and 32% should demonstrate progressive motility. Decreased motility can occur with structural or metabolic defects of

sperm or can represent a hostile semen environment. Specific defects of ciliary structure or function in both the respiratory and the reproductive tracts have been identified (i.e., Kartagener syndrome, immotile cilia syndrome), resulting in infertility associated with a severe reduction in sperm motility. Despite its subjective nature, **sperm motility is one of the best semen correlates of infertility in the oligospermic patient**. If sperm motility is poor, subsequently, sperm vitality should be assessed to determine whether the immotile spermatozoa are alive or dead. The presence of vital but immotile cells may be indicative of structural defect in felagellum, whereas necrozoospermia (high percentage of immotile and dead cells) refer to epididymal pathology.

c) **Sperm morphology.** A new strict morphologic criteria system has been endorsed by the WHO, which includes length, width, length/width, area occupied by the acrosome, and neck and tail defects.

v. **Leukocyte count.** The white blood cells (mainly polymorphonuclear leukocytes) are present in seminal fluid. Elevation with cutoff (>1 million/mL in the semen) may suggest infection. Culture and antibiotic treatment are often of low yield.

vi. If indicated, more specialized analysis may be performed, such as computer-aided sperm analysis, sperm biochemistry analysis (including fructose), sperm p. 326p. 327function tests such as the acrosome reaction, and penetration assays such as the zona-free hamster penetration test.

d. **Hormonal assessment.** All abnormal semen analyses should be repeated. If the repeat analysis shows severe oligospermia or azoospermia, basal serum T, LH, and FSH should be measured on a morning serum sample to rule out hypogonadism. The evaluation and management of patients with primary (high LH, FSH, and low T) and secondary (low

LH, FSH, and T) Leydig cell dysfunction and end-organ resistance to androgen have been discussed in Section II.A.2.3. If LH is low, the serum prolactin level should be measured to rule out prolactin-induced hypogonadotropism. Patients with isolated FSH elevations have isolated germinal compartment failure and respond poorly to therapy. An algorithm for the workup and treatment of males with normal hormonal values is given in Figure 27-6.

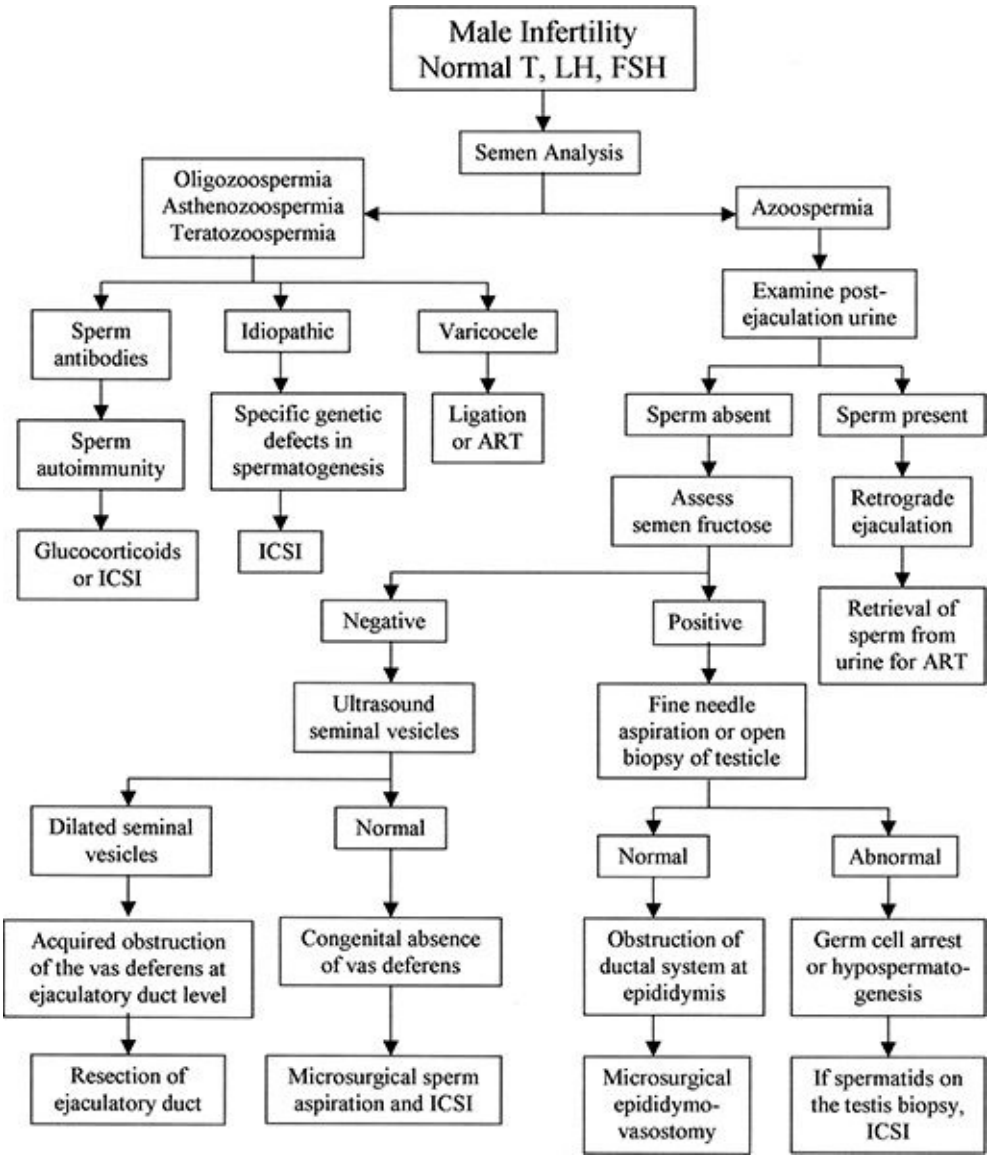

Figure 27-6. Algorithmic approach to the diagnosis and treatment of male infertility in patients with normal serum hormone concentrations. (Reprinted from Swerdloff RS, Wang C. The testes and male sexual function. In: Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine*. 24th ed. Philadelphia: WB Saunders; 2012:1472–1483.)

e. Azoospermia with normal-sized testes, serum T, LH, and FSH. These patients usually have retrograde ejaculation or an obstruction of the ejaculatory system. A postejaculation urine sample should be checked for spermatozoa.

i. Retrograde ejaculation is suspected by the presence of autonomic neuropathy and is most commonly seen in patients with diabetes mellitus. The presence of large numbers of sperm in postejaculation urine specimens confirms the diagnosis.

ii. Obstructive azoospermia. The absence of sperm in the postejaculation urine suggests obstructive azoospermia or impaired spermatogenesis. Recognition of obstructive disorders is important because therapy must be directed to surgical correction of the disorder.

a) The combination of absence of the vas deferens (normally palpable in the scrotum as an elongated tube) on physical exam, low seminal fluid volume, and acidic pH is suggestive of congenital absence of vas deferens and seminal vesicles. Congenital absence of the vas deferens is associated with the cystic fibrosis regulator gene (*CFRG*) in Caucasian men. Seminal fructose, normally produced by the seminal vesicles and transported into the vas deferens by the ejaculatory ducts, is absent on biochemical analysis.

b) If semen fructose is normal, a high percentage of these cases will prove to have an obstruction of the epididymis proximal to the entry of the ejaculatory ducts. The finding of normal-sized testes with or without palpable enlargement of the caput epididymis almost certainly indicates obstructive disease. If surgery is contemplated, exploration of the scrotum with visualization of the epididymis may demonstrate epididymal obstruction, and microsurgical correction of the obstruction or collection of spermatozoa for intracytoplasmic sperm injection (ICSI) may be attempted.

c) If exploration fails to demonstrate an obstruction, then testicular biopsy may be required to determine

intratesticular defect.

f. **Oligospermia with normal-sized testes, serum T, LH, and FSH.** A normal hormonal pattern is seen in the majority of oligospermic patients. Varicocele, reproductive tract infection, and sperm antibodies should be ruled out by physical exam and laboratory tests before the diagnosis of idiopathic infertility is made. Varicocele will be discussed separately in Section C. The remainder of these patients with oligospermia and normal hormonal profile are categorized as having idiopathic oligospermia and account for most male infertility.

g. **Normal sperm count but impaired sperm morphology or motility**

   i. Dead sperm (necrozoospermia) can be identified with supravital stains or assessed indirectly by the hypo-osmotic swelling test, which assesses the fluidity of the plasma membrane.

   ii. Abnormal sperm motility or morphology is usually seen in oligospermic specimens, but can occur in men with normal counts. Abnormal forms indicate impaired spermatogenesis.

2. **Treatment.** It is essential that the female partner be thoroughly evaluated along with the male partner. Treatment of a female partner can often compensate for male factor subfertility of mild-to-moderate decreases in semen parameters.

   a. There are a number of causes of **irreversible infertility with no available therapy.** This is true for most instances of primary hypogonadism or those involving damaged seminiferous tubules, including Klinefelter syndrome, **microdeletions of the Y chromosome, Sertoli cell–only syndrome**, and idiopathic infertility associated with **azoospermia.**

   b. Secondary hypogonadism may be managed with gonadotropins, GnRH infusions, and correction of underlying causes as outlined in Section II.3.d.

   c. **Assisted reproductive techniques**

      i. **Intracytoplasmic sperm injection.** This technique involves the direct injection of a single spermatozoon into the cytoplasm of a human oocyte. The overall fertilization rate is approximately 60%, and the clinical pregnancy rate per cycle is between 20% and 40%. ICSI can be performed

with p. 328p. 329sperm obtained from ejaculate, epididymal aspiration, testicular biopsy, or fine-needle aspiration.

ii. Intrauterine insemination and in vitro fertilization have low efficacy rates.

iii. The introduction of ICSI has made it possible for men with severe oligospermia and azoospermia to father children, but the genetic risks must be considered. Examples include transfer of the *CFRG* gene and microdeletions of Y chromosome. Genetic counseling and molecular genetic tests should be undertaken prior to ICSI therapy. Fortunately, to date, there has been no reported increase in the incidence of birth defects with ICSI in comparison with natural conception.

C. Varicocele. A varicocele is an abnormal tortuosity and dilatation of the veins of the pampiniform plexus within the spermatic cord. Incompetence of the venous valvular structure produces increased hydrostatic pressure and dilatation of the veins. Because the left spermatic vein, which is one of the longest veins in the body, inserts directly at a perpendicular angle into the left renal vein, (thus the left side is more prone to varicosity) **90% of varicoceles occur on the left side**. Right-sided varicoceles have been described, but they are usually associated with bilateral varicosity because collateral veins permit venous reflux from the left.

1. **Detection.** Moderate- to large-sized varicoceles are easily detected by physical examination of the spermatic cord ("bag of worms" appearance). Small varicoceles usually enlarge when the patient is asked to perform a Valsalva maneuver. Occasionally, mild exercise or standing for 30 minutes can be used to bring out a latent varicocele. However, ultrasonography, thermography, and radionucleotide methodology are now commonly used as noninvasive alternatives to corroborate the diagnosis.
2. **Infertility and indications for varicocelectomy.** The role of varicocele in the etiology of infertility remains unclear and controversial.
   a. **Incidence.** A varicocele is present in **approximately 15% to 20% of the male population**, and the majority of these men have no testicular dysfunction or infertility. Therefore,

physicians must be relatively conservative in their diagnostic and therapeutic approaches to men with varicocele. The presence of a varicocele alone is not evidence of testicular dysfunction and, therefore, does not constitute an indication for varicocelectomy. However, among infertile men, the incidence of varicocele has been reported to be 30% to 40%, suggesting an etiologic link.

b. **Selection for treatment.** Although the presence of varicocele can be associated with normal semen parameters and normal fertility, most men with varicocele and presumptive infertility have abnormal semen parameters, including low sperm concentration and abnormal sperm morphology. The causal relationship between varicocele and male infertility has been ascribed to increased testicular temperature, delayed removal of endogenously produced toxic metabolites, hypoxia, and stasis. A 1992 WHO study of 9 034 men found varicocele to be associated with an increase in abnormal semen, decreased testicular volume, impaired sperm quality, and a decline of Leydig cell hormone secretion. Interestingly, spontaneous pregnancies were equal in couples with and without a varicocele. Treatment of a varicocele by surgery or vein embolism/occlusion has been reported to improve semen quality; however, whether varicocele ligation will improve pregnancy rates in the female partner remains controversial. A large prospective study by the WHO compared pregnancy rates among infertile couples in which the male partner with a varicocele underwent immediate varicocele ligation, as opposed to ligation delayed for 1 year. The study suggested that varicocele ligation was beneficial, with a 34.8% first-year cumulative pregnancy rate in the immediate-treatment group, compared with 16.7% in the delayed-treatment group. However, there were flaws in the design and follow-up of patients in this trial. Furthermore, the first-year cumulative pregnancy rate of the delayed-treatment group was only 20%. Other studies have suggested that there are no significant differences in spontaneous pregnancy rate between couples treated for varicocele and untreated couples. Therefore, the use of varicocele ligation should be p. 329p. 330presented

to the infertile couple with knowledge of yet uncertain efficacy. If there is a response to ligation, the response rate may be better in younger couples and in couples whose infertility is of shorter duration. The presence of atrophic testes, elevated FSH, and severe oligospermia/azoospermia suggests severe germinal damage, and consequently treatment for the varicocele is unlikely to aid fertility.

D. Male sexual dysfunction. Normal sexual function is a complex process that is dependent on higher cortical centers of the brain, which control fantasy and sexual thought; the autonomic nervous system, which controls erection and ejaculation; the pelvic vascular flow; and hormonal balance. Sexual dysfunction may be a manifestation of a decreased libido, erectile dysfunction, ejaculatory difficulties, or a combination of these factors.

1. **Hypoactive sexual desire disorder,** with the prevalence of 5% to 15% in men, may result from alcoholism, medications (selective serotonin reuptake inhibitors, opioid analgesics, antihypertensives, 5α-reductase inhibitors, and antiandrogens), psychological factors such as depression, anxiety, and relational problems, or it may be caused by medical conditions such as hypogonadism or systemic illnesses.
2. **Ejaculatory difficulties**
   - **a.** Premature ejaculation (based on new *Diagnostic and Statistical Manual of Mental disorders [DMS-5]*, Fifth Edition definition is ejaculation within 1 minute of vaginal penetration) is the most common sexual disorder in men 18 to 59 years of age. Psychological factors, including anxiety or medications (especially adrenergic agents), are common causes.
   - **b.** Delayed ejaculation is referred to inability to ejaculate in a reasonable time period, which interferes with sexual and emotional satisfaction associated with distress.
   - **c.** Retrograde ejaculation is failure of semen passing through the urethra despite orgasm, and most commonly is associated with the transurethral resection of the prostate, followed by diabetes-induced autonomic neuropathy as second.
3. **Erectile disorder** is defined as the inability to maintain an erection of sufficient duration and firmness to complete satisfactory intercourse. The prevalence and incidence of endocrine disruptors has been studied in two cross-sectional studies, the

Massachusetts Male Aging Study (MMAS) and the National Health and Social Life Survey (NHSLS). The prevalence is increasing with age, and it is estimated that it affects 20 to 30 million men in the United States and 150 to 200 million worldwide.

a. Normal erectile physiology. Nerve impulses prompted by excitatory stimuli travel from higher areas of the brain, down the spinal cord, to the thoracolumbar cortex. This leads to parasympathetic relaxation of the penile arterioles and cavernosal smooth muscles as a result of increase in endothelium-derived relaxing factor (nitric oxide). Expansion of the cavernosal muscles leads to compression of the penile venous outflow against the tunica albuginea, causing further expansion of the penis. Tactile sensation from the shaft results in additional parasympathetic stimulation.

b. Etiology. Causes of erectile disorder include psychological factors (more common in younger men), vascular insufficiency (more common among older men), neuropathy, hormonal impairment (hypogonadism and hyperprolactinemia), generalized fatigue from systemic illnesses, or use of drugs (antihypertensives, antihistamines, and psychotropics). Erectile disorders may be multifactorial in origin and may be difficult to treat. For instance, although T levels decrease with aging, the increased incidence of atherosclerosis leads to vascular disease and may play a more prominent role in erectile disorder in the elderly. It is also considered to be a marker of cardiovascular disease.

c. Evaluation. Couples should be evaluated together. A complete social, medical, and sexual history, including drug and medication history, should be obtained and a detailed physical examination performed. The presence of morning erections, by history or documented with the use of a RigiScan portable home monitor, may aid differentiation between organic and psychological causes. Obvious associated conditions, such as paresis, developmental defects, or atrophic testes, may infrequently be found on examination. Blood work entails p.

330p. 331a chemistry panel, including glucose, serum T level, and thyroid function tests, if indicated. More specialized tests, such as the penile brachial index, penile injection of 10 mg prostaglandin E_1 (PGE_1) or 10 mg papaverine, may be used to assess vascular sufficiency. Bioesthesiometry or electromyography can be used to assess sensory innervation and the presence of neuropathy.

d. Medical management. Cells in the corpus cavernosum produce nitric oxide (NO) during sexual arousal in response to nonadrenergic, noncholinergic neurotransmission. NO stimulates the formation of cyclic guanosine monophosphate (cGMP), leading to relaxation of smooth muscle of the corpus cavernosum and penile arteries, engorgement of the corpus cavernosum, and erection. Oral phosphodiesterase-5 inhibitors (sildenafil, vardenafil, and tadalafil) lead to persistent cGMP-stimulated relaxation of the corpora cavernosa. If taken 1 to 2 hours before intercourse, they are effective in 60% to 80% of patients. Response rate in men with diabetes mellitus is somewhat lower (~50%). The most serious side effect is cardiovascular collapse, especially in those with underlying coronary artery disease or on nitrates. Trazodone, which has serotonergic and α-adrenergic properties, may be effective in one third of patients but causes sedation. Intracavernosal injections of PGE_1 (papaverine) and PGE_1 intraurethral suppositories are available. Surgical treatments include penile implants or revascularization procedures. Revascularization of the penis and venous ligation for venous leakage has a high rate of failure and is recommended only under special circumstances.

E. Gynecomastia. Gynecomastia refers to male breast enlargement because of proliferation of glandular and stromal tissue. It is a common disorder affecting **approximately 70% of pubertal males**. More than 30% of men > 40 years of age have some palpable breast tissue.

1. **Normal breast development.** In both male and female fetuses, epithelial cells proliferate into ducts that will eventually form the areola of the nipple at the surface of the skin. Both male and

female breasts are equivalent at birth, and the male breast, when stimulated by estrogen, will progress through the same stages of development as the female breast. Up to **90% of male newborns have transient gynecomastia** as a result of exposure to high maternal levels of hCG, estrogen, and progesterone, which stimulate breast tissue.

2. **Detection of gynecomastia.** Special attention should be given to medications, drug and alcohol abuse, and other chemical exposure. Presence of systemic illnesses, such as hyperthyroidism, liver disease, and renal failure, should be sought. Rapid, recent breast growth should be more concerning. Finally, the clinician should inquire about fertility, erectile dysfunction, and libido in order to evaluate hypogonadism as a potential cause. Physical examination should be done in supine position with palpation from the periphery to the areola and can usually distinguish glandular tissue from pseudogynecomastia (adipose or other nonglandular tissue) on the basis of texture and shape of the breast. The glandular mass should be measured in diameter, which is diagnosed by the finding of subareolar breast tissue of 4 cm or greater. Gynecomastia is usually bilateral but may be asymmetric. It is important to differentiate unilateral benign gynecomastia from carcinoma of the breast. Concerning findings include unusual firmness, a fixed mass, skin dimpling, nipple retraction and bloody nipple discharge, ulceration, and local adenopathy. Testicular exam is essential. Bilateral small testes are indicative of testicular failure, whereas testicular asymmetry or mass suggests the possibility of neoplasm.
3. **Classification**
    - **a.** Pseudogynecomastia
        - **i.** Adipose tissue
        - **ii.** Neoplasm
        - **iii.** Neurofibromatosis
    - **b.** Gynecomastia
        - **i.** Newborn: physiologic exposure of fetus to estrogens
        - **ii.** Prepubertal onset
            - **a)** Drugs
            - **b)** Idiopathic
            - **c)** Neoplasms (feminizing adrenal carcinoma)

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iii. Pubertal onset
- **a)** Normal external genitalia
  - **1)** Pubertal gynecomastia
  - **2)** Klinefelter syndrome
  - **3)** Pubertal macromastia
- **b)** Ambiguous external genitalia
  - **1)** Mixed gonadal dysgenesis
  - **2)** Androgen-resistant syndromes
  - **3)** T biosynthetic defect
  - **4)** True hermaphroditism

iv. Postpubertal onset
- **a)** Idiopathic
- **b)** Testicular failure
- **c)** Drugs: alcohol, spironolactone, estrogens, digitalis preparations, androgens, chorionic gonadotropin, cimetidine, flutamide, mitotane, methyldopa, isoniazid, phenothiazine, amphetamines, diethylpropion, reserpine, marijuana, diazepam, and cytotoxic agents
- **d)** Cirrhosis
- **e)** Thyrotoxicosis
- **f)** Chronic renal failure
- **g)** Refeeding after starvation
- **h)** hCG-secreting neoplasms
- **i)** Leydig cell tumors
- **j)** Feminizing adrenal carcinoma

4. **Pathophysiology.** The common denominator in disorders characterized by gynecomastia is an **imbalance between circulating estrogens and androgens**. Estrogens have a stimulatory effect on breast tissue, whereas androgens have an inhibitory role. Relative or absolute excess of circulating estrogens or a deficiency of circulating androgens leads to breast enlargement. Mechanisms for this imbalance include increased production of estrogens, increased aromatization of estrogen precursors, displacement of estrogens off SHBG, drugs with estrogen-like effect, and exogenous estrogen exposure. Decreased circulating androgens may result from decreased synthesis, increased metabolism, or a relative deficiency associated with

androgen-resistant syndromes.

5. **Specific clinical syndromes**
   a. **Puberty.** Gynecomastia develops in approximately 70% of normal boys during puberty. The condition usually begins between 12 and 15 years of age and spontaneously abates in 90% of those afflicted within 3 years of onset. Serum E_2 concentrations are often high in relation to T in boys with pubertal gynecomastia, resulting in a high E_2 to T ratio. This ratio returns to normal adult values as puberty progresses.
   b. **Adulthood.** About 30% to 40% of patients over 40 years of age have some palpable breast tissue. With advancing age, circulating concentrations of total and free T decrease along with a rise in serum LH. However, serum E_2 concentrations are maintained, resulting in an altered E_2 to T ratio. Increasing adiposity may also contribute by increasing peripheral aromatization of androgens to E_2. Finally, SHBG increases with age in men. Because **SHBG binds estrogen with less affinity than T**, the bioavailable E_2 to T ratio may increase in the obese older male. Diagnosis requires exclusion of other causes of gynecomastia.
   c. **Hypogonadism.** Gynecomastia occurs more commonly in men with primary testicular failure, but can also be seen in patients with secondary hypogonadism. Serum T concentrations are low, whereas serum estrogens are usually normal or slightly elevated, resulting in an increased E_2 to T ratio.
      i. In primary testicular failure, such as Klinefelter syndrome, serum T level is reduced, and serum LH is increased. **A high LH level stimulates aromatase activity in the testes,** resulting in increased testicular E_2 production and an increased E_2 to T ratio. In secondary hypogonadism, p. 332p. 333for example, Kallmann syndrome, low levels of T and unopposed estrogen effects from the normal conversion of adrenal precursors to E_2 result in increased E_2 to T ratio.
      ii. Serum prolactin is normal in most patients with

gynecomastia, and **enlarged breasts do not develop in most patients with hyperprolactinemia**. Prolactin may occasionally contribute to gynecomastia by causing secondary hypogonadism and alterations in the ratio of circulating estrogens and androgens.

d. Cirrhosis. Approximately 50% of patients with cirrhosis have gynecomastia; 65% have testicular atrophy; and 75% experience decreased libido. The T production rate is decreased, although total serum T concentrations may not reflect this decrease because of increased SHBG. Adrenal androstenedione production rate is increased, which may result in higher E_2 levels. Serum E_2 levels are high normal, but serum **estrone (E_1) levels are quite elevated** because of increased peripheral conversion of androstenedione to E_1. Thus, increased aromatization of an abundant adrenal substrate along with impaired T secretion leads to a high estrogen to androgen ratio.

e. Thyrotoxicosis. Approximately **30%** of men with Graves disease have clinically detectable **gynecomastia**. Gynecomastia regresses when euthyroidism is restored. Patients often have elevated estrogen, which might be the stimulatory effect of thyroid hormone on peripheral aromatase activity. Thyroid hormones also increase SHBG. This results in elevation of both total serum T and E_2. Because serum T binds more avidly than E_2 to SHBG, free E_2 may be relatively increased compared to free T, resulting in an increased E_2 to T ratio.

f. Hormone-secreting tumors

i. Feminizing adrenal carcinoma. This is a rare tumor that directly secretes E_2. The incidence of gynecomastia is close to 100%. Other adrenal neoplasms can secrete excess DHEA, DHEAS, and androstenedione that can then be aromatized peripherally to E_2.

ii. Leydig cell tumor. Leydig cell tumors constitute only 1% to 3% of all testicular tumors. Approximately 25% of the reported cases have had associated gynecomastia. These tumors are associated with isosexual precocity (if they occur prior to puberty) and may secrete E_2 directly. Less than 10% of Leydig cell tumors are malignant, but when

present, metastatic sites include the lung, liver, and retroperitoneal lymph nodes.

iii. **Germ-cell tumors.** These are the most common cancers in males between 15 and 35 years of age, and they are divided into seminomatous and nonseminomatous subtypes. A variety of malignant tumors originating in the germinal elements of the testis as well as extragonadal germ-cell tumors have been shown to secrete hCG, which stimulates aromatase activity in Leydig cells to produce an excess of E_2. Nontesticular tumors can also produce hCG and stimulate E_2 by the same mechanism.

iv. Certain chorionic tumors and hepatocellular carcinoma may transform circulating precursors into estrogens.

g. **Refeeding gynecomastia.** Prisoners of war during World War II, when refed, acquired tender gynecomastia that regressed spontaneously within 1 to 2 years. Similarly, gynecomastia can develop during recovery from anorexia nervosa, starvation, or any prolonged illness accompanied by substantial weight loss. The mechanism of refeeding gynecomastia is activation of the hypothalamic-pituitary-testicular axis and restoration of gonadal function, which results in transient elevation of E_2 to androgens.

In men with hypogonadism as a result of malnutrition, both the gonadotropin secretion and Leydig cell function appear to be impaired. During refeeding, pituitary and gonadal function return to normal.

h. **Drugs**

i. Synergistic action with estrogen because of intrinsic estrogen-like properties of the drug,

ii. The production of increased endogenous estrogen, or

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iii. Excess supply of an estrogen precursor (e.g., T or androstenedione) that can be aromatized to estrogen.

a) Spironolactone, cimetidine, and flutamide can produce gynecomastia by competitive displacement of DHT from its intracellular receptor (AR blocker). Spironolactone has the ability to **block androgen production** by inhibiting enzymes in the T synthetic pathway (i.e., 17α-

hydroxylase and 17,20-desmolase), like ketoconazole. Spironolactone can also displace E_2 from SHBG, thereby increasing free estrogen level.

b) Digitoxin has inherent estrogen-like properties. In contrast, digoxin does not act as an estrogen agonist. It may occasionally produce gynecomastia through a "refeeding" mechanism in debilitated men with congestive heart failure.

c) T administration, probably by its conversion to estrogens, may cause gynecomastia. However, nonaromatizable androgens, such as methyltestosterone, have been reported to produce gynecomastia, suggesting that additional mechanisms may be operative.

d) A wide variety of agents that act on the CNS can raise serum prolactin, induce a secondary hypogonadal state (GnRH deficiency), and cause gynecomastia.

e) Many chemotherapeutic agents, such as busulfan, nitrosourea, and vincristine, may cause Leydig cell and germ-cell damage, resulting in primary hypogonadism.

f) Alcohol causes gynecomastia by several mechanisms; it is associated with increased SHBG and decreases free T, thus increasing the E_2 to T ratio. Alcohol also increases hepatic clearance of T and has a direct toxic effect on testes.

g) Marijuana decreases GnRH production and subsequently lowers T production, which through the imbalance of E_2 to T ratio causes gynecomastia.

h) Protease inhibitors used in the treatment of HIV infection are associated with gynecomastia.

6. Evaluation of the patient with gynecomastia

a. Exclude breast carcinoma. Localized areas of irregularity, firmness, or asymmetry in the mass suggest the possibility of early breast carcinoma and should be an indication for biopsy. In advanced stages, signs such as ulceration and adjacent adenopathy may be evident.

b. A thorough drug history is important.

c. Gynecomastia may be the first sign of a hormone-secreting tumor of the testis or adrenal gland. The testes should be

examined carefully for neoplasms. A variety of tumor markers are useful as screening tests, for example, measurement of β-hCG for hCG-secreting tumors of the testis or serum DHEAS for adrenal carcinoma.

d. Laboratory evaluation. In general, all patients with gynecomastia should have **serum T, E_2, LH, FSH, and β-hCG** measured. If β-hCG and E_2 are markedly elevated, this suggests a neoplasm. In this case, testicular ultrasound is warranted. If no testicular source is detected, additional imaging studies are required to detect nontesticular tumors that produce β-hCG. If T is low but LH is high and E_2 is normal to high, this indicates primary hypogonadism, and if the history suggests Klinefelter syndrome, a karyotype is needed for a definitive diagnosis. On the other hand, low T, low LH, and normal E_2 levels imply secondary hypogonadism, and hypothalamic and pituitary causes should be investigated. If T, LH, and E_2 are all elevated, then diagnosis of androgen resistance should be considered.

7. Treatment. (a) Start the treatment as soon as possible. Reduction mammoplasty is required if the gynecomastia is cosmetically or psychologically disabling. (b) No medications have been approved for the treatment of gynecomastia. (c) Pubertal gynecomastia will be resolved in 90% of cases by 17 years of age. (d) In many other conditions such as hyperthyroidism, hypogonadism, and drugs, correction of the underlying cause can lead to regression of gynecomastia.

a. There are three classes of off-label medical treatment for gynecomastia: **androgens** (T, DHT, and danazol), **selective estrogen receptor modulators** **p. 334p. 335****(SERMs)** (tamoxifen, raloxifene, and clomiphene citrate), and **aromatase inhibitors** (testolactone).

b. In patients with hypogonadism, because of primary testicular dysfunction, T can be administered to decrease progression of gynecomastia, presumably by suppressing LH-mediated secretion of E_2 from the testes and restoring the T to E_2 ratio.

Exogenous T may itself produce gynecomastia by aromatization to E_2.

c. Danazol appears to be less effective than tamoxifen in clinical trials. In Europe, DHT preparations, because it is nonaromatizable, are available and are associated with some success in uncontrolled studies.

d. The role of SERMs **(tamoxifen**, **raloxifen,** and **clomiphene)** in the management of gynecomastia remains unclear despite encouraging reports. Tamoxifen 10 mg twice daily for 3 months showed relief of gynecomastia-induced breast tenderness, and caused partial regression of glandular tissue in 80% of men.

e. Aromatase inhibitors, such as **testolactone**, can be effective in the early proliferative phase of the disorder, but further studies are needed with more potent aromatase inhibitors, such as letrozole, fadrozole, anastrozole, or formestane.

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28 Disorders of Sexual Development in the Pediatric and Adolescent Male

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I. NORMAL SEXUAL DEVELOPMENT

A. Fetal

1. **Sex determination.** In humans, the process of sex determination commits the undifferentiated gonads to develop into testes or ovaries, usually by the seventh week of gestation, depending on the presence or absence of the Y chromosome and the sex-determining region on the Y-chromosome gene, *SRY*. Several transcription factor genes are required for the early development of the bipotential gonads (*SF1*), Wilms tumor 1-KTS isoform (*WT1-KTS*), and chromobox homolog 2 (*M33*) (Fig. 28-1). *SF1* and *WT1* act in concert to affect the expression of male-specific genes downstream of SRY, and a double dose of the dosage-sensitive sex-reversal adrenal hypoplasia congenita X-linked gene (*DAX1*) may impair testis development by interfering with the SF1/WT1 synergy. SRY must reach a threshold level before male sex determination occurs; otherwise, the ovary-determining pathway will initiate in the bipotential gonad. Although the regulation of SRY expression is not completely known, genes that appear to play a role in promoting expression of SRY include *WT1-KTS*, *GATA4/FOG2* (Friend of *GATA2*), *GADD45γ*, *MAP3K4*, *M33*, and the insulin receptor tyrosine kinase family. There are additional genes downstream of SRY that are crucial components of the male sex-determining pathway. These genes include SRY-box 9 gene (*SOX9*), anti-Müllerian hormone (AMH), fibroblast growth factor-9 (FGF9), and Doublesex and MAB-3-related transcription factor 1 (DMRT1). SRY expression in gonadal somatic cells initiates the

differentiation of Sertoli cells, which aggregate around the germ cells to form seminiferous tubular cords and the interstitial space of the testes. The Leydig cells, fibroblasts, and the typical vasculature of the male gonad make up the interstitial space of the testes. The process of sexual differentiation follows, with the gonads releasing sex-specific signaling molecules or hormones.

In humans, mutations in *WT1* gene lead to defective development of the external genitalia and the kidneys (Denys-Drash and Frasier syndromes). A double dose of *DAX1* gene leads to complete gonadal dysgenesis in 46,XY individuals. *SOX9* may be required to potentiate the action of SRY, because mutations in *SOX9* cause 46,XY gonadal dysgenesis in the autosomal dominant condition called camptomelic dysplasia, characterized by skeletal, cardiac, and renal abnormalities. **46,XY patients harboring SF1 mutations have complete gonadal dysgenesis or ambiguous genitalia** together with either normal or impaired adrenal function. More information on sex development and its disorders is presented in Chapter 29.

2. **Sex differentiation**
   a. **Hormonal regulation.** Male phenotypic differentiation is dependent on the action of **three hormones: AMH** (also known as Müllerian-inhibiting substance), and the two steroid hormones **testosterone** and **dihydrotestosterone**. SF1 regulates adrenal and gonadal expression of many of the genes and enzymes involved in steroidogenesis. AMH and testosterone are secreted by the fetal testis, and testosterone is converted to dihydrotestosterone by the enzyme 5α-reductase within the testis and in peripheral tissues. Testosterone biosynthesis by the Leydig cells is controlled by enzymes, and deficiency of these enzymes can p. 336p. 337lead to abnormal genital development in males (Fig. 28-1). **AMH** produced by the Sertoli cells of the fetal testes causes the regression of the Müllerian ducts. **Testosterone**, which peaks at 20 weeks of gestation, stimulates the growth and differentiation of the Wolffian ducts into the epididymis, vas deferens, and seminal vesicles. Development of the male external genitalia from 6 weeks of gestation onward is under the influence of **dihydrotestosterone**. Formation of the penis

and scrotum is completed by 12 to 14 weeks' gestation. From the second-trimester onward, further development of the male external genitalia is dependent on the fetal pituitary gonadotropin secretion, which stimulates testosterone production.

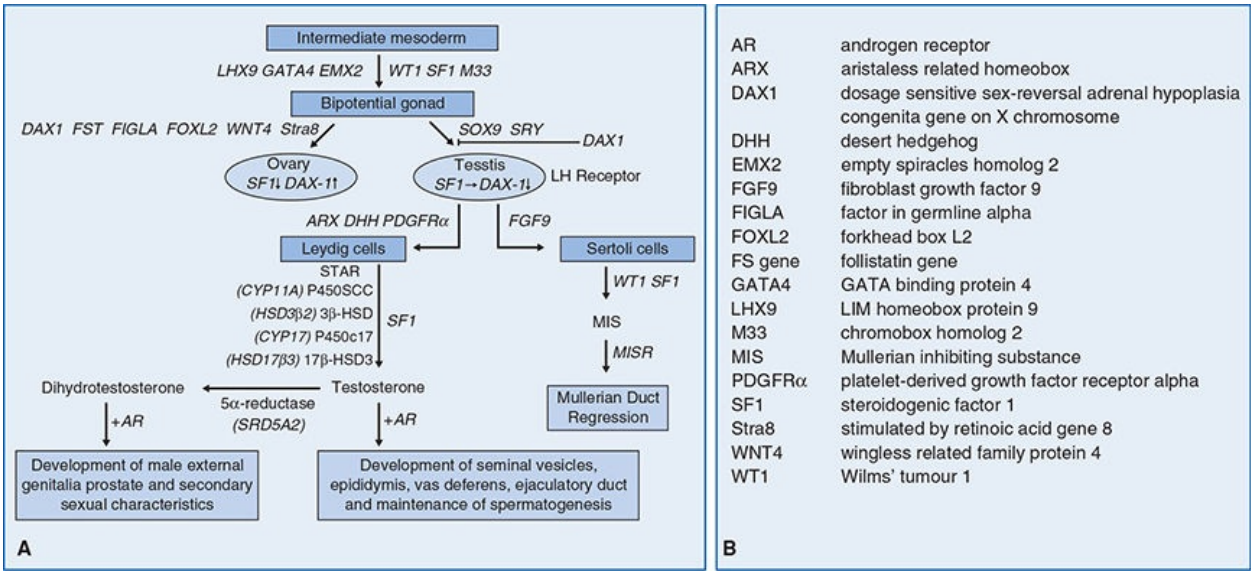

Figure 28-1. **A.** Pathway of sexual differentiation. **B.** Genes involved in sex development.

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b. Germ-cell differentiation. Around 4 weeks' gestation, primordial germ cells proliferate and localize in the genital ridge, then undergo DNA methylation to differentiate based on the surrounding somatic environment (e.g., in males, to become testes under the influence of Sertoli and Leydig cells). The germ cells in the testes enter a state of mitotic arrest after differentiation and remain so until after birth, whereas the germ cells of the ovary enter meiosis at 11 weeks' gestation. Stra8 (stimulated by retinoic acid 8) is a protein required for meiotic initiation in both sexes. Stra8 expression is, as anticipated, stimulated by retinoic acid (RA), and the three major RA receptor isotypes are expressed in the gonads in both sexes. In the male, CYP26B1, along with another meiosis suppressor NANOS2, decreases RA and Stra8, resulting in the germ cell entering into mitotic arrest, whereas in the female, activation of

Stra8 by RA results in meiosis.

c. **Development of the pituitary gonadotrophs.** Migration of the gonadotropin-releasing hormone (GnRH)–producing neurons from the medial olfactory placode to the hypothalamus is mediated by the neuronal migration factors. There are also genes that are involved in the regulation of GnRH synthesis and secretion. Mutations in these pituitary transcription factors genes result in **multiple pituitary hormone deficiency** and hypogonadotropic hypogonadism. GnRH is detectable in the hypothalamus by 9 weeks' gestation.

d. **Testosterone secretion.** It is unclear what regulates testosterone secretion by the fetal testes between 8 and 12 weeks. Testosterone secretion is most likely independent of pituitary gonadotropin stimulation during this period of fetal development. After 13 weeks of gestation, testosterone secretion and subsequent penile growth are regulated by pituitary luteinizing hormone (LH) and human chorionic gonadotropin (hCG) present in the fetal circulation. Fetal testosterone secretion peaks at about 20 weeks of gestation and then progressively falls toward late gestation, coinciding with the decline in LH and hCG in the fetal circulation. Failure of testosterone secretion at this time results in micropenis in the newborn infant.

e. **Testicular descent.** In humans, descent of the testes into the scrotum occurs during the second and third trimesters, and a biphasic model of testicular descent has been proposed:

   i. The first phase of descent occurs at 8 to 15 weeks of gestation and is called the trasnsabdominal phase. The descent is the result of release of the testis by regression of the craniosuspensory ligament and thickening of the gubernaculum along the migration path to scrotum.

   ii. The second phase occurs at 26 to 35 weeks of gestation and is called the inguinoscrotal phase. This phase is dependent on testosterone secretion and binding of testosterone to the androgen receptor. The testes descend into the scrotum in 97.3% of term infants, 79% of preterm infants, and 99% of 1-year-old infants.

B. Infancy and childhood

1. **Mini-puberty.** During the first few months after birth, a transient

rise in the circulating LH and follicle-stimulating hormone (FSH) concentrations is usually seen in infants of both sexes. The rapid withdrawal of placental sex steroids leads to a disturbance of the balance of negative feedback between sex steroids and GnRH release from the hypothalamus, resulting in an abrupt increase in

p. 338p. 339the circulating levels of LH and testosterone, with a smaller elevation of FSH concentrations. These levels remain elevated for the first 3 months after delivery in male neonates. This “mini-puberty” of infancy induces the transformation of gonocytes into Ad (dark) spermatogonia in the process of germ-cell differentiation. This process is impaired in children with cryptorchidism (resulting in persistence of gonocytes) and androgen resistance syndrome. Cryptorchidism is associated with an increased risk of infertility and testicular cancer in adult life, with gonocytes undergoing malignant transformation.

2. **Quiescence during childhood.** After this “mini-puberty,” the hypothalamic-pituitary-gonadal axis undergoes a long period of relative quiescence until late childhood, when pubertal development occurs. Three hypotheses have been proposed to explain the suppression of the hypothalamic-pituitary-gonadal axis during childhood and the mechanism of the onset of puberty. The first is the “gonadostat” hypothesis, based on the concept of changing sensitivity of the regulatory system of gonadotropin secretions to the negative feedback by gonadal sex steroids in childhood and adolescence. The onset of puberty is the result of decreasing sensitivity of the “gonadostat” to the negative feedback of small amounts of gonadal steroids secreted by the gonads during the peripubertal period. The challenge of the “gonadostat” hypothesis comes from the finding that a similar pattern of suppressed circulating gonadotropin levels has been found in agonadal patients. The second hypothesis proposes that the sexual quiescence during childhood before the onset of puberty is a result of central neural inhibition of GnRH release independent of the negative feedback of gonadal steroids. The last hypothesis or “desynchrony theory” proposes that the lack of GnRH stimulation of the pituitary in prepubertal children is a result of the desynchronization of the discharge or “firing” of the GnRH neurons.

C. Puberty

1. **Gonadarche** marks the maturation of the hypothalamic-pituitary-gonadal axis between 9 and 14 years of age in boys. During childhood, there is gradual amplification of GnRH pulse frequency and amplitude that is of great importance in stimulating the secretion of gonadotropins mediating sexual maturation in adolescence. With the onset of puberty, there is increasing pulsatile secretion of LH, initially mainly at night, which is associated with a testosterone rise in boys. The pulsatile secretion of LH stimulates the Leydig cells of the testis to produce testosterone, which is then converted either by aromatization to estradiol or by 5*α* reduction to dihydrotestosterone. Testosterone production from the testes progressively increases, and this hormone is responsible for the development of secondary sexual characteristics and metabolic changes at puberty. The first clinical sign of puberty is testicular enlargement, as shown by a testis length ≥ 2.5 cm or a volume >3 mL. The sexual maturity rating according to Marshall and Tanner is shown in Table 28-1. The adult testes produce about 6 to 10 mg of testosterone per day, with a small amount of testosterone synthesized in extratesticular tissue or via peripheral conversion. LH and FSH are required for the development and maintenance of testicular function. The coordination of testosterone output is under the tight control of both positive feed-forward and negative feedback mechanisms. FSH and testosterone have little effect in boys until spermarche, when these hormones act on the Sertoli cells to secrete many paracrine factors to support the initiation of spermatogenesis, which involves a process of differentiation from the spermatogonia to the mature spermatozoa. Maintenance of spermatogenesis requires the action of testosterone and the supportive action of FSH. **Dihydrotestosterone is not essential in maintaining spermatogenesis**, because patients with 5*α*-reductuse deficiency have normal spermatogenesis and may be fertile. Sertoli cells are important in supporting germ-cell development, and androgen receptor transcription is upregulated by FSH, underscoring a synergistic effect of both FSH and testosterone in spermatogenesis. Mature spermatozoa may be present at Tanner stage 3, when the mean testicular volume is 11.5 mL.

   The onset of puberty is triggered by removal or diminution of

central inhibition and an increase in stimulation of the GnRH neurons. Gene transcripts of p. 339p. 340both kisspeptin-1 and its receptor, GPR54 are upregulated in the hypothalamus with onset of puberty. Kisspeptin-1 is a potent stimulus for GnRH-induced gonadotropin secretion. **Neurokinin B** and **dynorphin** may stimulate kisspeptin secretion through co-expression of all three peptides from **KNDy neurons**. Transsynaptic inhibitory influences on GnRH secretion include GABAergic and opiatergic innervation, vasoactive intestinal peptide, corticotrophin-releasing factor, and melatonin. Disruption of TGF*α*–erbB1 and NRG–erbB4 signal complexes results in delayed puberty. The TGF*α*–erbB1 signaling complex has been implicated as the cause of precocious puberty associated with hypothalamic hamartoma. Leptin may act as a permissive signal for the onset of puberty, but through indirect neuronal pathways.

TABLE 28-1 Stages of Puberty in Boys

			Age		Testicular volume (cm^3)	
Stage	**Genitals**	**Pubic hair**	**Mean**	**SD**	**Mean**	**SD**
I	Preadolescent: testes, scrotum, and penis are about the same size and proportion as in early childhood.	Preadolescent: vellus over pubes is no further developed than that over abdominal wall (i.e., no pubic hair).			4.98	3.63
II	Scrotum and testes have enlarged, and there is a change in texture of scrotal skin and some reddening of scrotal skin.	Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly at base of penis.	11.7	1.3	6.74	3.54
III	Growth of penis has occurred, at first mainly in length but with some increase in breadth; there has been further growth of testes and scrotum.	Hair is considerably darker, coarser, and more curled and spreads sparsely over junction of pubes	13.2	0.8	14.68	6.32
IV	Penis is further enlarged in length and breadth, with development of glans; testes and scrotum are further enlarged; there is also further darkening of scrotal skin.	Hair is now adult in type, but area covered by it is smaller than in most adults; there is no spread to medial surface of thighs.	14.7	1.1	20.13	6.17
V	Genitalia are adult in size and shape; no further enlargement takes place after stage V.	Hair is adult in quantity and type, distributed as an inverse triangle; there is spread to medial surface of thighs but not up linea alba or elsewhere above base of inverse triangle.	15.5	0.7	29.28	9.10

SD, standard deviation.
Adapted from Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970;45:13; Daniel WA Jr, Feinstein RA, Howard-Peebles P, et al. Testicular volumes of adolescents. *J Pediatr* 1982;101:1010; Penny R, Goldstein IP, Frasier D, et al. Overnight follicle stimulating hormone (FSH) and luteinizing hormone (LH) excretion in normal males. *J Clin Endocrinol Metab* 1976;43:1394.

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Twin studies have also suggested a genetic influence on the

timing of puberty. An effect of nutritional factors and body composition on the time of onset of puberty is supported by the **earlier age of puberty in moderately obese children**, and by delayed maturation of the reproductive endocrine system in states of malnutrition and chronic illness. Very vigorous physical conditioning and training may independently affect puberty onset and progression in girls but not in boys. Children adopted from developing countries and living in advanced societies have early puberty as a general feature. Exposure to endocrine-disrupting chemicals with estrogen agonistic and androgen antagonistic effects may affect the timing of puberty.

2. **Adrenarche** refers to the increase in the secretion of adrenal androgens, coinciding with the development of the zona reticularis of the adrenal beginning at 7 to 8 years of age in boys. The androgens predominantly secreted are dehydroepiandrosterone (DHEA) and its sulfate (DHEAS). Adrenarche is characterized by maturational increases in 17-hydroxylase and 17,20 lyase and a low 3β-hydroxysteroid dehydrogenase activity of the adrenal gland. The secretion of adrenal androgens continues to increase until mid-puberty. Adrenocorticotropic hormone (ACTH) rather than pituitary gonadotropins mediates this change. Adrenarche and gonadarche are responsible for pubic and axillary hair development.
3. Stages and reference values of sex hormones during pubertal development
   a. **Stages of pubertal development** (Table 28-1)
   b. **Reference levels of sex steroids** (Table 28-2)

II. CLINICAL DISORDERS

A. Undescended testes

1. Classification
   a. **A retractile testis** is one that is not located in the scrotum when the child is initially examined, but can be easily manipulated into the scrotum. A retractile testis is the result of a strong cremasteric reflex and is not observed in the neonatal period.
   b. **An ectopic testis** is located in the perineum, medial surface of the thigh, abdominal wall, or, rarely, over the dorsum of the penis. Treatment of this rare condition is always surgical, and

patients usually have a poor prognosis for fertility.

c. **A cryptorchid testis** may be intra-abdominal (10%), in the inguinal canal (20%), or in the superficial inguinal pouch (40%). A testis in the superficial inguinal pouch differs from a retractile testis in that it cannot be manipulated into the scrotum. The remaining cases are obstructed testes (30%) resulting from blockage of the path of descent by a fascial cord between the inguinal pouch and the scrotal inlet.

d. An **acquired undescended testis** may appear 3 to 4 months after birth, when the gonadotropin levels decline. The condition also occurs in 5- to 10-year-old boys when the elongation of the spermatic cord is inadequate for the change in size of the inguinoscrotal region with growth. Sometimes the fibrous remnant of the process vaginalis impairs the elongation of the spermatic cord.

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TABLE 28-2 Serum Concentrations of Sex Steroids for Normal Related to Tanner Stage of Sexual Development

Stage	T (ng/dL)[a]	DHT (ng/dL)[a]	Δ4 (ng/dL)[a]	DHEA (ng/dL)[a]	DHEAS (μg/dL)[a]	E_1 (ng/dL)[a]	E_2 (ng/dL)[a]	P (ng/dL)[b]	17-OHP (ng/dL)[b]
I	10 ± 1	3.3 ± 1.3	55.0 ± 7.5	205.4 ± 31.7	41.5 ± 31.7	1.06 ± 0.28	0.75 ± 0.28	36.0 ± 5.0	65.0 ± 5.0
II	85 ± 5	9.2 ± 6.7	60.0 ± 10.0	306.5 ± 91.6	62.7 ± 35.6	1.56 ± 0.31	1.05 ± 0.29	37.0 ± 4.0	67.5 ± 10.0
III	121 ± 17	20.0 ± 10.0	70.0 ± 10.0	402.4 ± 99.7	73.0 ± 48.8	2.14 ± 0.20	1.58 ± 0.53	34.0 ± 4.0	70.0 ± 5.0
IV	493 ± 42	35.0 ± 13.3	95.0 ± 17.5	375.5 ± 98.9	103.0 ± 55.7	3.34 ± 0.62	2.19 ± 0.78	54.0 ± 10.0	95.0 ± 10.0
V	605 (260–1,000)	41.7 ± 18.3	117.5 ± 15.0	542.8 ± 112.7	123.4 ± 48.2	3.15 ± 0.70	2.07 ± 0.53	45.0 ± 4.0	140.0 ± 25.0

Δ4, androstenedione; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; E_1, estrone; E_2, estradiol; 17-OHP, 17-hydroxyprogesterone; P, progesterone; T, testosterone.

[a]Mean value ± standard deviation (range).

[b]Mean value ± standard error of mean (range).

Data from Bidlingmaier F, et al. Plasma estrogens in childhood and puberty under physiologic and pathologic conditions. *Pediatr Res* 1973;7:901; Root AW. Endocrinology of puberty. I. Normal puberty. *J Pediatr* 1973;83:1; Lee PA, Migeon CJ. Puberty in boys: correlation of plasma levels in gonadotropins (LH, FSH), androgens (testosterone, androstenedione, dehydroepiandrosterone and its sulfate), estrogens (estrone and estradiol), and progestins (progesterone and 17-hydroxy progesterone). *J Clin Endocrinol Metab* 1975;41:556; DeParetti E, Forest MG. Pattern of plasma dehydroepiandrosterone sulfate levels in humans from birth to adulthood: Evidence for testicular production. *J Clin Endocrinol Metab* 1978;47:572; Pang S, et al. Dihydrotestosterone and its relationship to testosterone in infancy and childhood. *J Clin Endocrinol Metab* 1979;48:821; Friedman IM, Goldberg E. Reference materials for the practice and adolescent medicine. *Pediatr Clin North Am* 1980;27:193.

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2. Clinical features of cryptorchidism

a. **Incidence.** Cryptorchid testes are found at birth in 2.7% of term infants and 21% of preterm infants. Spontaneous descent of the testes occurs in the majority of these infants so that only 0.9% of 1-year-old boys have cryptorchid testes.

b. **Pathology.** The histopathology of cryptorchid testes is characterized by a diminution of the number of mature or

differentiating germ cells, disturbances of tubular structure, and increases in interstitial tissue by the second and third years of life. Germ-cell abnormalities are seen in 2%, 20%, and 45% of testicular biopsies at the time of surgery when orchidopexy is performed at 1, 2, and 4 years of age, respectively. In addition to testicular damage and infertility, there is an increased risk of developing testicular germ-cell tumors (relative risk, 5.2). Twelve percent of patients with testicular cancer have a history of cryptorchidism.

c. **Associated disorders.** Although cryptorchidism can occur in isolation, it may be associated with disorders of sex chromosomes and autosomes, ambiguous genitalia, malformations of the urinary tract, and disorders such as Prader-Willi, Noonan, Bardet-Biedl, Aarskog, and Cornelia de Lange syndromes. Bilateral cryptorchidism can also occur in patients with hypopituitarism or isolated hypogonadotropic hypogonadism.

d. **Pathophysiology.** An impaired hypothalamic-pituitary-gonadal axis has been proposed as the cause for cryptorchidism, but has not been uniformly found by all investigators. An immune cause for cryptorchidism has also been suggested. In most instances, an inherent testicular dysfunction or dysgenesis may be the cause of cryptorchidism. Cryptorchidism resulting from abnormal production of INSL3, AMH, and testosterone is rare. **Maternal gestational smoking** is associated with **increased risk** of cryptorchidism.

3. Evaluation

If no testis is palpable in a male infant, the possibilities of 46,XX disorder of sex development and congenital bilateral anorchia should be excluded. Infants with anorchia have normal male external genitalia. Testicular damage resulting from torsion or vascular accident could have occurred after the third month of gestation. These children can be differentiated from children with bilateral intra-abdominal testes by measurement of basal testosterone and the lack of increase in the serum testosterone 72 hours after an intramuscular (IM) injection of hCG (5 000 IU/1.73 m^2). About 30% of undescended testes are not palpable. Ultrasonography has a diagnostic sensitivity of 90% to 95% for testes in a canalicular location, but this technique is not adequate

for intra-abdominal testes. For the detection of intra-abdominal testes, magnetic resonance imaging (MRI), gadolinium-enhanced magnetic resonance angiography, or laparoscopy may be necessary.

4. **Treatment.** No intervention should be considered before 6 months of age because of the possibility of spontaneous descent.
   a. **Medical.** Medical therapy has a limited role in the management of cryptorchidism. hCG (1 000 to 6 000 IU/week for 5 weeks) is not particularly effective in children <3 years of age, and intranasal GnRH (1 200 μg/day in divided doses for 4 weeks) is effective in only 20% to 25% of cases, with a significant risk of relapse even after initial descent of the testes.
   b. **Surgery.** In patients without spontaneous testicular descent, orchidopexy should be performed after 6 months but no later than 18 months of age. A biopsy should be obtained at the time of surgery because of the possibility of dysgenetic gonads and malignancy.
5. **Long-term prognosis**
   a. **Retractile testes.** Although retractile testis is generally conceived as a benign condition that does not require treatment, there is increasing evidence that **lower average spermatogonia and Sertoli cell number, and increased tubular degeneration** are found in retractile testes.
   b. **Cryptorchidism.** Fertility is significantly decreased in bilateral cryptorchidism and is unrelated to the age of orchidopexy. Fertility is impaired in approximately 30% of patients with unilateral cryptorchidism, and the risk is increased if p. 343p. 344the testes were intra-abdominal, varicocele is present, or if a partner has a fertility problem. A paternity rate of up to 70% to 90% has been reported in men with unilateral cryptorchidism postorchidopexy. In patients with bilateral cryptorchidism, approximately 75% have abnormal semen analyses, and the rate of infertility is high. A recent report suggested that low-dose GnRH analog given by nasal spray every other day for 6 months following successful orchidopexy appears to improve semen quality in adult life as compared to controls. Infertile patients with prior cryptorchidism tend to have higher FSH, lower sperm density, and lower inhibin B levels than fertile patients. There is an

increased risk of testicular cancer following bilateral (odds ratio, 5.8) or unilateral (odds ratio, 2.7) cryptorchidism. Thus, early surgical correction of cryptorchidism is important because **(a)** any mass in the testis can be detected early, **(b)** the rate of infertility is decreased, and **(c)** the risk of cancer of the testis may be decreased.

B. Micropenis

1. **Definition.** A micropenis is defined as a penis whose stretched length is >2.5 standard deviations (SDs) below the mean stretched penile length of children of the same age in published normative data (Table 28-3). Undescended testes can be present in children with micropenis.
2. **Etiology** (see Section II.D)
   a. Children with **isolated gonadotropin deficiency** (with or without anosmia) and **congenital idiopathic hypopituitarism** present with micropenis at birth. This is because penile growth in utero is dependent on testosterone secretion, which is regulated by pituitary gonadotropin after 13 weeks of gestation.

TABLE 28-3 Stretched Penile Length in Normal Males

	Stretched penile length (cm)	
Normal male	Mean ± SD	Mean − 2.5SD
Newborn		
30 wk	2.5 ± 0.4	1.5
34 wk	3.0 ± 0.4	2.0
Term	3.5 ± 0.4	2.5
0–5 mo	3.9 ± 0.8	1.9
6–12 mo	4.3 ± 0.8	2.3
1–2 yr	4.7 ± 0.8	2.6
2–3 yr	5.1 ± 0.9	2.9
3–4 yr	5.5 ± 0.9	3.3
4–5 yr	5.7 ± 0.9	3.5
5–6 yr	6.0 ± 0.9	3.8
6–7 yr	6.1 ± 0.9	3.9
7–8 yr	6.2 ± 1.0	3.7
8–9 yr	6.3 ± 1.0	3.8
9–10 yr	6.3 ± 1.0	3.8
10–11 yr	6.4 ± 1.1	3.7

Adult	13.3 ± 1.6	9.3

SD, standard deviation.
Data from Lee PA, Mazur T, Danish R, et al. Micropenis. I. Criteria, etiologies and classification. *Johns Hopkins Med J* 1980;146:156.

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b. It may be seen in children with **congenital central nervous system (CNS) defects,** including midline facial defects, septo-optic dysplasia, and pituitary agenesis.

c. Many **syndromic disorders** are associated with micropenis. Prader-Willi and Bardet-Biedl syndromes are commonly associated with gonadotropin deficiency. Micropenis resulting from primary hypogonadism is seen in Klinefelter, Noonan, Robinow, Cornelia de Lange, Down, and fetal hydantoin syndromes.

d. Micropenis resulting from **partial androgen insensitivity** is usually associated with varying degrees of genital ambiguity (see Chapter 30 for diagnosis and management).

e. Idiopathic. In some children, no obvious cause for the micropenis can be found.

3. Management

After evaluation (see Chapter 24), testosterone enanthate or cypionate, 25 mg IM monthly for three doses, can stimulate the growth of the penis into the normal range in infancy and early childhood. Further assessment and treatment of these patients are required in adolescence.

C. Gynecomastia is defined as excessive proliferation of stromal and glandular tissue of the breasts in a male.

1. Etiology (Table 28-4)

a. Physiologic gynecomastia can occur in the neonatal period, at the time of puberty, and with old age. Breast enlargement in newborns results from the effect of maternal or placental estrogens, and most cases resolve in a few weeks. Gynecomastia may be present in **70% of pubertal boys**. It is usually bilateral but may be unilateral or asymmetrical. An imbalance of androgens to estrogens ratio at puberty has been implicated as the cause of pubertal gynecomastia. Enhanced

aromatization of androgens to estrogens is important in the pathogenesis of gynecomastia associated with obesity in puberty and aging.

TABLE 28-4 Causes of Gynecomastia

1. Physiologic
   - Newborn, puberty, and old age
2. Defects in androgen action or production
   - Androgen resistance syndrome
   - Klinefelter syndrome
   - Congenital anorchia
   - Defects in testosterone biosynthesis
   - Acquired testicular failure
3. Tumors
   - Estrogen-secreting tumors of adrenal gland or testis
   - hCG-secreting tumors
   - Prolactinoma
4. Drugs
   - Spironolactone, cimetidine, digitalis, phenothiazines, tricyclic antidepressants, aromatizable androgens, growth hormone, exposure to hormone-containing cosmetic creams and hair products, tea tree oil and lavender oil.
5. Endocrine disorders
   - Familial aromatase hyperactivity
   - Obesity
   - Thyrotoxicosis
6. Trauma or refeeding
7. Idiopathic

hCG, human chorionic gonadotropin.

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b. Gynecomastia is present with defects of the androgen receptor in which serum testosterone levels are high while there are defects in androgen action. Gynecomastia can be found in patients with **androgen deficiency,** as in Klinefelter syndrome, congenital anorchia, defects in testosterone biosynthesis, and acquired testicular failure. These conditions are associated with low testosterone concentrations, an elevation of serum LH, and variable increases of serum estrogen as a result of direct testicular secretion or peripheral aromatization of adrenal precursors. The abnormal testosterone

to estrogen ratio predisposes the patients to the development of gynecomastia.

c. Breast enlargement can be caused by estrogen-secreting testicular or adrenal **tumors,** hCG-secreting tumors (germinomas from the liver, CNS, and testis), or prolactinoma.

d. Gynecomastia can be as a result of the effects of **drugs.** Spironolactone inhibits testosterone biosynthesis, and cimetidine blocks the binding of androgen to its receptor. The mechanisms for digitalis-, phenothiazine-, and antidepressant-induced gynecomastia remain unknown.

e. Familial aromatase hyperactivity is inherited as an autosomal dominant condition characterized by prepubertal or peripubertal gynecomastia in males and precocious puberty in female members of the affected family.

f. Idiopathic gynecomastia refers to breast enlargement in prepubertal children in whom no cause can be found despite extensive investigations. The excessive use of **tea tree oil** and **lavender oil** has been reported to cause prepubertal gynecomastia.

g. Trauma and recovery from severe **illnesses** associated with weight loss can also cause gynecomastia.

2. **Evaluation.** A detailed history and physical examination will help in evaluating the cause of gynecomastia. A careful examination should be performed to exclude pseudogynecomastia (excess fat in the absence of glandular tissue proliferation). Incomplete masculinization indicates androgen resistance or defects of testosterone biosynthesis. Unilateral testicular enlargement is suggestive of testicular neoplasm. Clinical features suggestive of the rare breast malignancy in males include nipple discharge, skin changes, and hard fixed masses outside the areolar region. Physical signs and karyotyping will identify Klinefelter syndrome. Prepubertal gynecomastia is rare, and one should look for a pathologic etiology or environmental exposure when it occurs. Hormonal assays should include serum testosterone, estradiol, prolactin, LH, FSH, and β-hCG. An elevated serum prolactin in a child or adult usually points to a prolactinoma, but gynecomastia is rare as a primary presentation of prolactinoma.
3. **Treatment.** The treatment of gynecomastia should be aimed at the underlying disorder. Patients with pubertal gynecomastia should be

reassured that the condition persists for only 2 years in 27% of cases and for 3 years in 7.7%. Studies have been published on efficacy of agents, including **dihydrotestosterone, aromatase inhibitors, and estrogen receptor modulators**. Aromatase inhibitors studied include testolactone (150 mg three times daily for 2 to 6 months) and anastrozole (1 mg daily for 3 to 6 months). Raloxifene treatment (60 mg daily for 3 to 9 months) and tamoxifen treatment (10 mg twice daily) have shown some efficacy, but the long-term side effects are unknown. Late treatment is ineffective. If there is no regression and the adolescent experiences psychosocial distress or persistent pain, alternative treatments to consider would be surgery or liposuction to remove glandular and adipose tissue.

D. Delayed puberty

1. **Definition**. Delayed puberty is a term applied to boys when pubertal changes fail to develop after 14 years of age (2 SD above the mean age for the onset of puberty).
2. **Etiology** (Tables 28-5 and 28-6). The etiology of delayed puberty can be divided into genetic, functional, or organic defects of the hypothalamic-pituitary-gonadal axis. The etiology can be further classified into hypergonadotropic (primary testicular defect) or hypogonadotropic (hypothalamic or pituitary defects) hypogonadism. The discussion of these conditions in this chapter will not be exhaustive.

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TABLE 28-5 Genetic Defects in the Three Components of the Hypothalamic-Pituitary-Gonadal Axis

Compartment	Disease	Gene
Hypothalamus	X-linked Kallmann syndrome	*KAL1*
	Autosomal dominant Kallmann syndrome	*FGFR1*
	Other genes causing Kallmann syndrome	*PROK2*, *PROKR2*, *CHD7*, *FGF8*, *WDR11*
	Morbid obesity, hypogonadism	Leptin gene Leptin receptor Prohormone convertase 1 (*PCSK1*)
	Adrenal deficiency, hypogonadotropic	*DAX1*

	hypogonadism	
	Disorder of sexual development, hypogonadotropic hypogonadism	*SF1*
	Prader-Willi syndrome	del pat chr15q11–13
	Bardet-Biedl syndrome	3 mutant alleles in 2 of 11 genes (*BBS* genes and *MKKS*)
Pituitary	Septo-optic dysplasia	*HESX1*
	Isolated hypogonadotropic hypogonadism	*GNRHR*, *GNRH1*, *GPR54*, *TAC3*, *TACR3* *FSHβ*, *LHβ*
	Disorder of pituitary organogenesis	*PROP1*, *LHX3*, *LHX4*, *PTX2*, *SOX3*
Gonad	Gonadotropin resistance	FSHR, LH/hCGR
	Autosomal recessive delay in puberty	Mutations in steroid enzyme pathway genes
	Disorder of sexual development, gonadal dysgenesis	*SF1*
	Autoimmune polyendocrine syndrome	*AIRE*
	Galactosemia	*GALT*
	Cystic fibrosis	*CFTR*
	Myotonic dystrophy	(CTG)n expansion of DMPK (CCTG)n expansion intron 1 of ZNF9
	Noonan syndrome	*PTPN11, KRAS, SOS1, RAF1*
	Klinefelter syndrome	47,XXY

a. **Functional hypogonadism** is usually as a result of hypothalamic dysfunction of the axis. Acute or chronic systemic disease will suppress the hypothalamic-pituitary-gonadal axis. Patients with chronic renal failure, connective tissue disorders, cardiac disease, or acquired immunodeficiency syndrome are commonly affected. In such patients, stress, altered nutrition, and inflammatory cytokines play a significant role. Cystic fibrosis, celiac disease, and chronic inflammatory bowel disease are chronic illnesses that can result in significant undernutrition if the patient is not adequately treated. Chronic elevations of cortisol, catecholamines, or cytokines (such as interleukin-6) resulting from chronic illness and inflammation act in concert to suppress the GnRH-pituitary-gonadal, thyrotropin-releasing hormone (TRH)/thyroid-stimulating hormone (TSH)/tri-iodothyronine, and growth hormone–releasing hormone

(GHRH)/growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axes and to modulate energy metabolism. With chronic illness, progressive hypogonadotropic hypogonadism develops, primarily affecting LH pulse amplitude rather than frequency. These patients have low sex steroid levels. Anorexia p. 347p. 348nervosa, although more common in females, can also occur in males, resulting in delayed puberty because of the effect on the hypothalamic GnRH pulse generator. Severe childhood hypothyroidism can also delay the onset of puberty. Functional hypogonadism is more common and much better documented in females. Psychotropic drugs, such as phenothiazines, risperidone, and tricyclic antidepressants, cause a rise in serum prolactin by blocking endogenous dopamine receptors. Abuse of opiates and cocaine leads to anorexia, decreased food intake, and hyperprolactinemia. Constitutional delay in growth and puberty are discussed in Chapters 14 and 29.

TABLE 28-6 Organic and Functional Disorders of the Hypothalamic-Pituitary-Gonadal Axis

Compartment	Functional	Organic
Hypothalamic	Anorexia nervosa Psychogenic Constitutional delay in growth and puberty Drug use Chronic systemic illness Undernutrition	Hypothalamic and suprasellar tumor Infiltrative disease Head trauma CNS infection Cranial irradiation
Pituitary		Pituitary tumor Pituitary apoplexy Infiltrative disease (lymphocytic or xanthomatous hypophysitis) Head trauma Hemosiderosis and hemochromatosis Cranial irradiation Congenital hypopituitarism
Gonadal		Chemotherapy and radiation Infection (mumps, sexually transmitted disease) Vanishing testes syndrome/congenital anorchia

	Trauma (torsion)

CNS, central nervous system.

b. Hypogonadotropic hypogonadism can present with delayed puberty, failure of progression of puberty, or failure to attain reproductive function, depending on the severity of the gonadotropin deficiency. The cause in the majority of cases remains unknown.

i. Nonorganic **isolated gonadotropin deficiency (idiopathic hypogonadotropic hypogonadism [IHH]) patients** have normal growth until adolescence, when their growth velocity decreases because of the absence of sexual development. They have characteristic eunuchoid proportions (arm span greater than height by >5 cm). Sporadic or autosomal recessive isolated gonadotropin deficiency without anosmia is rare. About half of patients with isolated gonadotropin deficiency do not have a family history of the disorder. Isolated gonadotropin deficiency can be associated with anosmia (Kallmann syndrome), midline facial defects, micropenis (stretched penile length <2.5 cm in neonates and <4 cm in children before puberty), and cryptorchidism.

ii. Kallmann syndrome is an inherited disorder of neuronal migration characterized by hypogonadism and **anosmia**. Autosomal dominant, p. 348p. 349autosomal recessive, and X-linked recessive inheritance patterns have been described, indicating heterogeneity. The condition is reported to occur in approximately 1 in 10 000 males and 1 of 50 000 females. The gene underlying the X-linked form of the disease, *KAL1*, has been localized to chromosome Xp22.3 and encodes a protein named anosmin-I. MRI scans in patients with Kallmann syndrome have demonstrated absence or hypoplasia of the olfactory bulbs, and hypoplastic or rudimentary olfactory sulci. Other symptoms associated with Kallmann syndrome include synkinesia, cerebellar ataxia, eye-movement abnormalities, sensorineural deafness, spatial attention abnormalities,

spastic paraplegia, and mental retardation. Somatic defects such as cleft lip and palate, renal agenesis, and pes cavus have also been described. The underlying mechanism is a defect in the hypothalamic pulsatile release of GnRH. Serum LH and FSH rise to normal levels with repetitive administration of GnRH in virtually all patients with KS, but not in patients with panhypopituitarism. Studies have indicated that the incidence of genetic defects within the coding region of the *KAL1* gene in patients with sporadic GnRH deficiency is low (5% to 8%), suggesting that the X-linked form of inheritance represents the least common form of isolated gonadotropin deficiency.

The autosomal dominant form of Kallmann syndrome is a result of mutations in the fibroblast growth factor receptor-1 (*FGFR1*) gene, localized to chromosome 8p11.2–12. There is a wide range of phenotypic spectrum in patients with FGFR1 mutations, and about half of patients have only IHH and hyposmia without other associated features. Additional gene mutations have been identified as causing KS.

iii. **Hypogonadotropic hypogonadism-23 with or without anosmia (also known as fertile eunuch syndrome or Pasqualini syndrome)** is characterized by eunuchoidism, small- to normal-sized testes, with the absence of mature Leydig cells as a result of mutations in the luteinizing hormone β-polypeptide gene (LHB), located at 19q13.33. Spermatogenesis may persist, and hence, fertility is possible, although sperm count, morphology, and motility may be low. The patients exhibit a normal clinical and biochemical androgenic response to hCG. They have subnormal testosterone secretion and low-normal basal and GnRH-stimulated serum FSH concentration, but poor LH response. Hypogonadotropic hypogonadism-23 is believed to be inherited in an autosomal recessive pattern.

iv. A variety of GnRH abnormalities have been reported in patients with IHH. These abnormalities affect GnRH synthesis, secretion, or function. Pituitary agenesis or hypoplasia has been reported in a few patients with congenital adrenal hypoplasia, and this has been shown to

be due to a loss of function mutations of the *DAX1* gene.

v. Heterozygous GnRH receptor mutations may be found in as high as 20% of familial cases of normosmic IHH patients.

vi. There are now a number of nuclear transcription factors that are known to be important in the embryonic development and definitive function of the anterior pituitary gland (thyroid transcription factor I gene, PITX1, PITX2, and the LIM-class homeodomain transcription factors LHX3 and LHX4). Affected patients have multiple pituitary hormone deficiency. Homozygous and heterozygous missense mutations within the HESXI homeodomain lead to the condition known as **septo-optic dysplasia**. Pituitary dysfunction, including hypogonadotropic hypogonadism, is variable and can be progressive. Patients with *PROP1* gene mutations exhibit secondary hypogonadism in addition to deficiencies of GH, PRL, and TSH. Patients with mutations in the *POU1F1* gene do not have gonadotropin deficiency. Both an overdosage of SOX3 or underdosage of SOX3 can result in hypopituitarism. Neuroradiologically, these patients have the features of congenital hypopituitarism, with hypoplastic adenohypophysis, transaction of pituitary stalk, and ectopic position of the posterior pituitary bright signal on MRI.

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vii. **Idiopathic hypopituitarism** is a heterogeneous group of disorders that can occur sporadically or can be inherited. Congenital idiopathic hypopituitarism presents in early infancy with severe fasting hypoglycemia, neonatal hepatitis-like syndrome, hyponatremia, and micropenis in males. Perinatal trauma and hypoxia have been implicated as a cause in 50% to 60% of patients presenting with idiopathic hypopituitarism in later childhood. MRI in patients with congenital hypopituitarism and idiopathic hypopituitarism in childhood may show hypoplasia or absence of the adenohypophysis, transection of the pituitary stalk, and ectopic position of the posterior pituitary. The patients usually have multiple anterior pituitary hormone deficiencies but normal posterior pituitary function. The

anterior pituitary secretory responses to hypothalamic-releasing factors vary from patient to patient and with time.

viii. **Prader-Willi** syndrome (see Chapter 16) and **Bardet-Biedl** syndrome are commonly associated with gonadotropin deficiency. Bardet-Biedl syndrome is characterized by hypogonadism, obesity, mental retardation, polydactyl, and retinitis pigmentosa. The syndrome occurs when there are three mutant alleles in two of eleven genes (*BBS* genes and *MKKS*).

ix. **Organic hypogonadotropic hypogonadism**

a) **Pituitary tumors** are less common in children than in adults. They can be secreting or nonsecreting (functional). The most common pituitary tumors are prolactinomas, followed by nonsecreting tumors.

b) **CNS disorders,** including tumors (craniopharyngioma, suprasellar astrocytoma, optic nerve glioma, germinoma, teratoma, and histiocytosis), congenital defects (midline facial defects, septo-optic dysplasia, and hydrocephalus), infection (meningitis and encephalitis), and infiltrative decreases (autoimmune lymphocytic hypophysitis and sarcoidosis xanthomatous hypophysitis), can lead to hypothalamic-pituitary dysfunction. A Rathke pouch cyst and empty sella syndrome can also lead occasionally to pituitary dysfunction.

c) **Radiation treatment** for leukemia or brain tumor can damage the hypothalamic-pituitary axis. The anterior pituitary hormone first affected by radiation is GH, followed by the gonadotropins and ACTH. A radiation dose of 2 700 to 3 500 rad is sufficient to produce GH deficiency, and a dose in excess of 4 500 rad can lead to panhypopituitarism. Post-traumatic brain injury hypopituitarism is increasingly being recognized (see Chapter 6).

x. Hypogonadotropic hypogonadism can be present in patients with **thalassemia major** and **hemochromatosis** because of iron deposition in the hypothalamus and pituitary as a result of repeated blood transfusions.

c. **Hypergonadotropic hypogonadism** results from primary testicular failure, leading to increase in serum LH and FSH. The

gonadotropin concentrations may not be markedly elevated in childhood until after adolescence (Tables 28-5 and 28-6).

i. **Klinefelter syndrome** (see Chapter 13) occurs in 1 in 500 males.

ii. **Noonan syndrome** (see Chapter 14) occurs in 1 in 1 000 to 1 in 2 500 live births, and the karyotype is normal.

iii. **Acquired testicular failure** can result from viral orchitis caused by mumps, coxsackie virus B, or echovirus. Cytotoxic drugs, especially alkylating agents and methylhydrazines, result in profound disturbance of the morphology of the germinal epithelium. Permanent damage to the germ cells occurs more frequently in postpubertal than in prepubertal boys, because the **prepubertal testis is relatively insensitive to the cytotoxic effect of these drugs**. Damage can also result from direct testicular irradiation. There is also a high incidence of gonadal dysfunction following the combination regimen of high-dose cyclophosphamide and total-body irradiation used in preparation for bone marrow transplantation.

3. **Evaluation**

a. A **diagnostic evaluation** should be performed **when puberty is delayed beyond 14 years of age** in boys. Points worthy of note in the history p. 350p. 351include chronic illness, neurologic symptoms, anosmia, history of hypoglycemia and hepatitis in infancy, and family history of delay of growth and sexual maturation. The physical examination should include a full neurologic evaluation. Impaired vision, nystagmus, microphthalmia, and hypoplastic optic disk on funduscopic examination should suggest a diagnosis of septo-optic dysplasia. Retinitis pigmentosa, polydactyly, and mental retardation in an obese child point to a diagnosis of Bardet-Biedl syndrome. One should also look out for features of other syndromic disorders and midline facial defects. The presence of micropenis indicates gonadotropin deficiency of prenatal onset.

b. **Initial laboratory investigations** should include LH, FSH,

testosterone, and other tests such as prolactin, bone age and skull radiographs, and/or MRI, blood count, sedimentation rate, renal and liver function tests, thyroid function, and cortisol levels if indicated. Low FSH and LH levels suggest a problem in the hypothalamus or the pituitary, whereas elevated FSH and LH concentrations suggest a primary testicular defect.

c. **Genetic testing** is performed to confirm the diagnosis of genetic syndromes. Karotyping may be used to confirm Klinefelter syndrome. To evaluate for Prader-Willi syndrome (deletion of 15q11–q13 in 50% of cases), methylation analyses may be performed.

d. **Combined pituitary study** using the arginine/GHRH test, GnRH, and TRH after sex steroid priming should be performed if there is a strong suspicion of hypopituitarism (see Chapter 13). Clinicians prefer the use of alternative GH stimulatory tests to reduce the risk of hypoglycemia (see Chapter 14). Most recently, an orally administered GH secretagogue receptor agonist (macimorelin) has shown promise as a GH stimulant. MRI of the sella should be considered to evaluate for tumors and pituitary structural defects. Hypopituitarism resulting from an organic cause in the CNS often can be associated with posterior pituitary dysfunction. The possibility of diabetes insipidus, therefore, should be evaluated (see Chapters 10 and 13).

e. The **differentiation of isolated gonadotropin deficiency from constitutional delay** of growth and puberty (CDGP) is a difficult challenge for pediatricians. Clinically, children with isolated gonadotropin deficiency have normal height and growth velocity, whereas children with CDGP are usually short. In both conditions, the basal LH and FSH are low without any disturbance of the secretion of other anterior pituitary hormones. **Assessment of the serum LH and FSH response to GnRH is not helpful.** An impaired prolactin response to TRH observed in isolated gonadotropin deficiency can be useful in distinguishing this condition from CDGP; but there is a considerable overlap between the two groups. Using a highly sensitive fluoroimmunometric assay, it has been found that **nocturnal augmentation of pulsatile LH or FSH secretion** (estimated in frequent blood sampling studies) **is**

absent in patients with Kallmann syndrome. Frequent blood sampling is not clinically practical in children. Genetic studies can be helpful in identifying the genetic defect in familial cases of multiple pituitary hormones deficiencies.

4. **Management.** Induction of secondary sexual characteristics in patients with hypogonadism can be achieved by replacement with a testosterone preparation at 14 years of age.
   a. **IM testosterone** (enanthate or cypionate) can be given (50 mg every 4 weeks; then increased by 50 mg every 6 months to a dose of 200 mg every 2 to 3 weeks). IM testosterone enanthate/cypionate results in supraphysiologic concentrations of testosterone a few days after injection, followed by a fall to a nadir by 10 to 14 days. In some patients, there may be cyclical skin changes (crops of acne) and mood disturbances (behavior problems).
   b. Newer methods of testosterone administration, which may be suitable for induction of puberty, include transdermal application of **testosterone gels.**
   c. **Oral testosterone** undecanoate (not available in the United States).

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   d. In older boys or men with hypogonadotropic hypogonadism, **hCG** or recombinant human LH **(hLH)** and pulsatile GnRH infusion are alternatives to testosterone replacement when fertility is desired (see Chapter 27). hCG or hLH should be given in an initial dose of 1 000 IU twice weekly by IM injection; the dose is increased to 2 000 to 3 000 IU twice weekly over a period of 2 to 3 years. hCG alone induces only moderate increase in the size of the testes, to about 8 mL. Human menopausal gonadotropin or **recombinant human FSH (hFSH),** 75 IU by IM or subcutaneous route, two to three times per week, might be required to induce spermatogenesis and further growth of the testes during the second and third years or when fertility is desired. Recombinant hCG, hLH, and hFSH can also be given by the subcutaneous route.
   e. **GnRH** given in a **pulsatile** manner every 90 minutes subcutaneously or intravenously induces puberty in hypogonadotropic hypogonadal boys. However, this form of

treatment is expensive and technically difficult to administer. Pulsatile GnRH (2 to 20 μg) subcutaneously every 90 minutes can be used to induce spermatogenesis in males with hypothalamic hypogonadotropic hypogonadism, but this is no more effective than the combination of gonadotropins.

f. **In patients with combined GH and gonadotropin deficiency, puberty may be induced after initiation of GH treatment.** Pubertal induction with exogenous testosterone stimulates growth through direct effects on the growth plates. In the setting of GH deficiency, exogenously administered testosterone's potential for this action is greatest when GH replacement is optimized.

g. Patients with CDGP can be reassured; however, treatment is frequently offered because the patient experiences significant social and psychological distress. Patients in whom short stature is the dominant problem can be offered oxandrolone (1.25 to 2.5 mg) at night for 3 to 4 months or a more prolonged course using a lower dose (0.05 mg/kg/day). Such a regimen allows earlier growth acceleration without compromising final adult height. In cases where the absence of sexual development is causing social/psychological difficulties, testosterone enanthate (100 mg IM monthly for three doses) will bring about some penile enlargement and pubic hair growth. A further short course of testosterone can be given after 3 to 4 months. Frequently, spontaneous pubertal development occurs within a year of starting testosterone treatment. In a randomized controlled trial, letrozole (a specific aromatase inhibitor) in a dose of 2.5 mg orally daily together with testosterone therapy has been shown to improve the final height of adolescents with CDGP compared to those treated with testosterone alone. However, the potential deleterious side effects on bone density have to be taken into account when manipulating growth by inhibiting estrogen action.

h. Cryopreservation of sperm retrieved from adolescent patients with Klinefelter syndrome (KS) by microdissection testicular sperm extraction together with intracytoplasmic sperm injection and in vitro fertilization techniques have given such patients hope for future fertility. Postponement of testosterone replacement in adolescence may be necessary if one wants to

retrieve viable sperms at this stage.

E. Precocious sexual development (see Chapter 23)

1. **Definition.** Puberty is considered precocious if secondary sexual characteristics occur **before 9 years of age in boys**. The most important long-term consequence in these children is short stature, because rapid skeletal maturation leads to early epiphyseal fusion. In true or **central precocious puberty (CPP),** there is premature activation of the hypothalamic-pituitary-gonadal axis. **Incomplete (pseudo and peripheral) precocious puberty** refers to development of secondary sexual characteristics in boys before 9 years of age as a result of autonomous secretion of androgens or hCG.
2. **Etiology**
   a. **Central precocious puberty** (Table 28-7)
      i. **Idiopathic** CPP is diagnosed when no organic cause can be found for the disorder. It accounts for 10% to 75% of all cases in boys, which is p. 352p. 353in contrast to girls, in whom >90% of cases are idiopathic. In one study from Israel, about half of the boys with CPP (n = 21) and early puberty (n = 44) have the **slowly progressive variant**. They have a prolonged course of puberty, and their final height is not impaired.

TABLE 28-7 Etiology of Central Precocious Puberty

Idiopathic	Sporadic
	Familial autosomal dominant (rare)
CNS tumors	Optic and hypothalamic gliomas
	Hypothalamic hamartoma
	Ependymoma
	Pineal region tumor
CNS lesions	Hydrocephalus
	Septo-optic dysplasia
	Arachnoid cyst
	Cerebral atrophy
	Head trauma
CNS infection	Epilepsy meningitis,

encephalitis, abscess Cranial irradiation and cancer chemotherapy Fetal alcohol syndrome Maternal uniparental disomy of chromosome 14 Williams syndrome Secondary to virilizing disorders such as congenital adrenal hyperplasia, hormone-secreting neoplasms
CNS, central nervous system.

ii. **CNS lesions** may be a cause of CPP. CNS lesions or tumors (glioma, ependymoma, astrocytoma, **hypothalamic hamartoma**, germinoma, and teratoma) in the posterior hypothalamus, tuber cinereum, third ventricle, and pineal region can disturb the regulatory mechanism by infiltration, compression, or interruption of neuronal connections within the hypothalamic-pituitary-gonadal axis to cause precocious puberty. In some patients, hypothalamic hamartoma may be a source of GnRH. Patients with hypothalamic hamartoma typically develop "gelastic" seizures that are quite resistant to anticonvulsant treatment. **CNS infection** can cause early sexual development and can be associated with the presence of hydrocephalus. Sexual precocity following **head injury** may also occur, although hypopituitarism is more common.

iii. Any **virilizing condition** can cause early activation of the hypothalamic-pituitary-gonadal axis because of exposure to androgens, leading to rapid advancement of bone age. Patients with congenital adrenal hyperplasia (CAH) are exposed to excessive amounts of adrenal androgens. If glucocorticoid suppression is inadequate, this may lead to accelerated skeletal maturation, which may trigger the onset of CPP. On the other hand, cases of gonadoptropin suppression and small testes in adult men with CAH have also been reported.

b. Incomplete (pseudo and peripheral) precocious puberty (Table 28-8)

i. Virilizing **CAH** causes precocious pseudopuberty because of increased adrenal androgen production, resulting in

sexual maturation (e.g., 21-hydroxylase, 11-hydroxylase deficiency).

ii. Virilizing **adrenal tumors,** usually adrenocortical carcinoma, are rare in childhood (see Chapter 23).

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TABLE 28-8 Causes of Incomplete Precocious Puberty in Boys

1. Gonadotropin-independent sexual precocity
   - Familial male-limited precocious puberty (FMPP)
   - McCune-Albright syndrome and other activating *GNAS* gene mutations
   - *DAX1* gene mutation
2. Premature adrenarche
3. hCG-secreting tumors located within and outside (hepatic, testicular, and retroperitoneal) the central nervous system
4. Increased androgen secretion from the adrenal gland or testes
   - Congenital adrenal hyperplasia
   - Virilizing adrenal tumors
   - Leydig cell adenoma (may contain somatic activating mutations of LHR or Gsp oncogenes)
   - Corticosteroid resistance syndromes
5. Heterosexual development
   - Feminizing adrenal tumors
   - Environmental exposure to estrogen and drugs
   - Familial aromatase hyperactivity
   - 3β-Hydroxysteroid dehydrogenase and 17-ketoreductase deficiency

LHR, luteinizing hormone receptor.

iii. **Cushing syndrome** as a cause of virilization is also rare.

iv. **Van Wyk-Grumbach** syndrome is a well known but very rare presentation of precocious puberty in association with chronic hypothyroidism. The pathogenesis is unknown. The precocious puberty can be associated with hyperprolactinemia and galactorrhea. This syndrome has been postulated to be the result of a hormonal overlap phenomenon, with overproduction of gonadotropins as well as TSH. An alternative hypothesis is that the condition arises from weak intrinsic FSH activity associated with the extreme TSH elevation. **In contrast to CPP, the bone age is delayed in Van Wyk-Grumbach syndrome**.

v. **Interstitial cell (Leydig cell) tumors** of the testes secrete testosterone and typically present with unilateral testicular enlargement. They are usually benign. Tumors can arise **from adrenal rest tissue** in the testes, or the adrenal rest tissue can increase in size during adrenarche or secondary to CAH, leading to testicular enlargement. Although most Leydig cell tumors presenting with incomplete precocious puberty are sporadic in nature, somatic activating mutations of the stimulatory G protein (Gsp oncogenes) resulting in constitutively activation of the LH receptor may result in Leydig cell hyperplasia and tumor.

vi. **hCG** can be produced by hepatoblastomas, retroperitoneal tumors, and germ-cell tumors. hCG-secreting tumors account for 4% of cases of sexual precocity in males and are reported more commonly in Asian people. Frequently, germ-cell tumors are intracranial and show marked contrast enhancement on computed tomography (CT) brain scan because of their high vascularity. Elevated levels of ***β*-hCG** and ***α*-fetoprotein** can be found in the blood and cerebrospinal fluid. These patients have pubertal testosterone concentrations stimulated by hCG, and suppressed serum FSH levels. In some patients, mildly elevated serum LH is found because of cross-reaction with hCG in some LH radioimmunoassays; however, LH does not increase in response to GnRH stimulation.

vii. **Premature adrenarche** has conventionally been defined as the development of pubic hair with or without axillary hair before 9 years of age in boys. In the United States today, boys have testicular and pubic hair p. 354p. 355development at a younger age than in the past. Girls are affected 10 times as frequently as boys, but no explanation for the unequal sex ratio has been forthcoming. An increase in frequency of premature adrenarche has been reported in children with cerebral dysfunction, and both sexes are equally affected. Premature adrenarche is also

more frequently observed among children with obesity and Prader-Willi syndrome. In some patients, the early development of secondary sexual hair is associated with normal adrenal androgen concentrations for their chronologic age, suggesting that premature adrenarche may be the result of increased sensitivity to androgens in peripheral tissues. Premature adrenarche is associated with increased body odor as well as oily skin and hair, but there is no penile enlargement. Premature adrenarche has no adverse effects on the onset and progression of gonadarche or on final adult height if bone age is not particularly advanced. However, children with premature adrenarche who have advanced bone age may have decreased final adult height.

The serum DHEA and DHEAS levels in children with premature adrenarche are higher than normal for their chronologic age, but the levels are still in the normal pubertal range. These children may have **impaired insulin sensitivity**, increased serum total and free IGF-1 concentrations, and **unfavorable lipid profiles**. Premature adrenarche is a **diagnosis of exclusion**. Patients with borderline elevation of adrenal steroid precursor concentrations (17α-hydroxyprogesterone [17-OHP] > 6 nmol/L) should undergo an ACTH stimulation test (250 μg cosyntropin intravenously and measuring the 17-OHP levels at 30 and 60 minutes). An ACTH-stimulated 17-OHP level > 30 nmol/L is diagnostic of late-onset 21-hydroxylase deficiency. **The prevalence of late-onset CAH among patients with premature adrenarche is not well defined and ranges from 7% to >40%**.

viii. Familial male-limited precocious puberty (FMPP), formerly known as testotoxicosis, is an inherited form of gonadotropin-independent sexual precocity caused by an activating mutation in the luteinizing hormone receptor (LHR) gene. FMPP is characterized by sexual development with pubertal sex hormone concentrations and spermatogenesis in the absence of a pubertal pattern of pituitary gonadotropin secretion. Clinically, FMPP patients exhibit secondary sexual development, with growth of the

penis and evidence of adrenarche, but have **small, soft testes**. In contrast to patients with CPP, patients with FMPP have **elevated serum testosterone levels**, but exhibit an absence of pulsatile, nocturnal LH (immunoreactive and bioactive), and FSH secretion or pubertal gonadotropin response to GnRH. Testicular biopsies have revealed an abundance of mature Leydig cells with varying degree of spermatogenesis and seminiferous tubule maturation as well as germ-cell degeneration in some tubules. Testicular Leydig cell nodules have been reported in some patients. The pattern of inheritance supports a sex-limited autosomal dominant transmission with >90% penetrance, and female carriers do not demonstrate any endocrine abnormalities. Activating mutations have been identified in the third cytoplasmic loop, transmembrane helices II, V, and VI of the LHR.

The Gs*α*-protein subunit couples >20 different receptors to stimulation of adenylate cyclase, and mutation in this gene can result in loss of function (pseudohypoparathyroidism type 1a) or gain in function as in McCune-Albright syndrome.

ix. **Androgens** prescribed in the past for aplastic anemia may cause accelerated growth and penile enlargement.

3. **Diagnosis**

a. A detailed history should uncover the timing of the onset of excessive growth, body odor, oiliness of skin and hair, pubic hair, and genital development. History of CNS infection and the pattern of sexual development in other family members may be helpful. Children with a CNS cause for the sexual precocity frequently have neurologic symptoms.

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b. In the physical examination, the height, weight, and pubertal staging must be accurately documented. Penile enlargement without significant testicular enlargement is helpful in identifying patients with incomplete precocious puberty. Hypertension, abdominal mass, and Cushingoid features are suggestive of an adrenal tumor. A full neurologic evaluation and funduscopic examination are essential. Unilateral testicular

enlargement is suggestive of a testicular malignancy.

c. Hormonal assays should include serum testosterone and basal and peak serum LH and FSH response to GnRH (if available). Patients with CPP have a peak serum LH and FSH in the pubertal range, with the LH response greater than the FSH response. Using a conventional radioimmunoassay, it was found that even an LH to FSH ratio of 3 was not sensitive enough to establish a diagnosis of precocious or normal puberty in boys. With the use of two-site fluoroimmunometric assay or other sensitive immunochemiluminometric assays, a basal LH cutoff of 0.6 IU/L and a GnRH-stimulated LH > 9.6 IU/L have been found to be sensitive indices to establish a male pubertal gonadotropin profile. Although the GnRH test is helpful in distinguishing incomplete from CPP, it is not helpful in identifying the underlying CNS pathology. Additional hormone tests, including thyroid function as well as adrenal steroid levels, should be ordered if adrenal tumor or hyperplasia is suspected.

d. Bone age radiography and cerebral CT or MRI of the sella should be performed on all patients with suspected CPP. CT scan or MRI of the adrenal area is indicated if the presence of an adrenal tumor is suspected.

e. All patients with midline CNS tumors and sexual precocity should have a measurement of **β-hCG and α-fetoprotein** in the serum and also in the cerebrospinal fluid, if possible, to exclude the existence of germ-cell tumors.

f. Molecular genetic studies will be helpful in patients with gonadotropin-independent sexual precocity.

4. Treatment

a. CPP. One possible sequela of CPP is a variable attenuation of adult stature depending on the age of onset. Treatment with medroxyprogesterone acetate and cyproterone acetate is no longer recommended for the treatment of CPP. Indications for GnRH analog treatment for CPP include **(a)** CPP with one or two signs of puberty before 9 years of age; **(b)** pubertal GnRH-stimulated gonadotropin levels; **(c)** rapidly progressive puberty; **(d)** compromised predicted adult height; and **(e)** psychological or behavioral reasons.

i. Monthly depot options include depot leuprolide acetate, 100

to 150 μg/kg, or depot triptorelin, 80 to 100 μg/kg given IM every 4 weeks. Treatment can be discontinued at 11 to 12 years of age, and there is prompt reactivation of the hypothalamic-pituitary-gonadal axis, allowing puberty to progress. The height gain from cessation of therapy to final height is negatively correlated with the bone age at the end of treatment, and boys will grow about 9.9 ± 3.3 cm after interruption of treatment.

ii. Longer acting **GnRH agonists include 3-month depot** leuprolide acetate (11.25 or 30 mg), 2-month long-acting goserelin (10.8 mg), 3-month depot triptorelin (11.25 mg), and 12-month histrelin subcutaneous implant (50 mg). These formulations have demonstrated successful suppression of puberty; however, the efficacies of these long-acting depot preparations in improving final adult height have not been adequately documented.

iii. **Subnormal growth velocity**, which is occasionally observed in some children with precocious puberty treated with a GnRH agonist, is likely to be due to “catch-down” growth. This is the observation of a fall-off in growth velocity after a period of rapid growth is suppressed. An alternate explanation is that these patients have already passed the pubertal growth spurt because of the advanced skeletal maturation. Serum IGF-1 levels are usually normal in such children.

iv. In a recent review, 78% of patients treated with depot GnRH analog reached a final height in their target height range, and they had normal body proportions. Therapy offers the greatest advantage for those children in whom

p. 356p. 357the onset of puberty occurs before 6 years of age, those who demonstrate rapidly accelerating bone age, those with the lower genetic height potential, or those with the largest difference between the target and predicted height. Obesity occurs with a high rate in boys with CPP. No negative effects on bone mineral density or fertility have been reported. Semen analysis in a limited number of CPP patients treated with GnRH analogs had revealed normal sperm count, motility, and morphology.

However, in boys with CPP resulting from hypothalamic hamartoma and treated with GnRH analog, the testicular volume remained smaller than normal posttreatment and took up to 5 years after stopping treatment before the testicular size became normalized. Treated patients should be followed up into adulthood.

v. Patients with CPP with poor predicted adult height despite GnRH analog treatment can be **treated with GH**. Preliminary results are encouraging.

vi. Children with an organic cause for their CPP should have treatment of their underlying pathology in addition to GnRH agonist therapy. Both boys and girls with CPP have been found to have **hypothalamic hamartomas**, which are slow growing and seldom associated with neurodevelopmental or gross neurologic deficit. Young patients with hamartoma of the tuber cinereum typically present with **gelastic seizures** that respond poorly to anticonvulsants. **Conventionally, surgery is not recommended**, and conservative symptomatic management with anticonvulsants for epilepsy and GnRH analog for precocious puberty has been the treatment of choice. Occasionally, such children progress to having intractable seizures despite anticonvulsant treatment in later childhood and adolescence. An innovative **surgical approach** (transcallosal, transseptal, and transventricular) through the third ventricle under stereotactic and magnetic resonance guidance has allowed safe and complete removal of these hamartomas and control of the intractable seizures.

b. Incomplete precocious puberty

i. Among patients with incomplete precocious puberty are those with premature adrenarche who do not require any treatment. Treatment of patients with an androgen-secreting tumor should be directed at the tumor. Patients with CAH should be given glucocorticoid and mineralocorticoid replacement. GnRH analog treatment can be started if CPP develops during the treatment of CAH. Leydig cell tumors of children are always benign, but radical orchiectomy remains the treatment of choice. Intracranial germ-cell tumors are very radiosensitive, and combination

chemotherapy is advised if ventriculoperitoneal shunting is done for hydrocephalus. Even after definitive treatment for incomplete precocious puberty, spontaneous onset of CPP can occur because of the advanced skeletal maturation. GnRH agonist therapy is indicated if that occurs.

ii. Children with FMPP (testotoxicosis) have been treated with **medroxyprogesterone acetate** (100 to 150 mg IM every 2 weeks) or **ketoconazole**, an antifungal agent that blocks androgen synthesis (200 mg every 8 hours). Adult height exceeded pretreatment predicted height by 5 to 13 cm in five patients with FMPP treated with ketoconazole for a mean duration of 6.2 years. A combination of **spironolactone**, which blocks androgen action (1 to 3 mg/kg every 12 hours), and **testolactone**, an aromatase inhibitor (5 mg/kg every 6 hours, increasing to 10 mg/kg every 6 hours), can also achieve short- and medium-term control of testosterone secretion. Measurement of testosterone and estradiol levels is not helpful in monitoring treatment with this combination of drugs. Elevation of circulating gonadotropins when a patient is treated with ketoconazole or spironolactone/testolactone combination can be managed by the addition of **GnRH agonist** therapy. The results of 6 years of treatment with spironolactone, testolactone, and deslorelin in FMPP yielded encouraging results. More recently, a combination of the **antiandrogen bicalutamide with anastrazole or letrozole** in two patients demonstrated clinical effectiveness in slowing bone age advancement and adrenarche.

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29 Early, Precocious, and Delayed Female Pubertal Development

Christopher P. Houk and Peter A. Lee

I. EARLY AND PRECOCIOUS PUBERTY

A. General principles

Puberty is the period of time when sexual maturity and fertility is established. Precocious puberty (PP) has traditionally been defined as the early onset of pubertal changes (based on chronologic age). Minimal, isolated pubertal changes, such as isolated breast or isolated pubic hair development, do not necessarily indicate the onset of puberty. The diagnosis of PP in girls requires that early onset of progressive breast development be associated with both an accelerated growth rate (premature growth spurt) and advanced skeletal maturation (determined by a bone-age radiograph). In girls, these early changes may or may not be accompanied by pubic hair. The presence of pubic hair alone is not an indication that puberty has begun.

These caveats make it difficult to make sense of recent studies showing that initial pubertal changes in girls seem to occur at increasingly younger ages. These contemporary studies have also identified distinct racial differences in the timing of puberty, with African Americans showing a tendency to earlier pubertal onset than Hispanics, which in turn begin puberty earlier than Caucasians and Asians when all races are taken together. Data suggest that the average age of the onset of breast development is around 9.5 years, with as many as 5% of girls showing some breast development before their eighth birthday.

Definitions that relate to the onset of specific aspects of puberty include **pubarche**—the beginning of pubic (sexual) hair growth, **adrenarche—**the initial rise of adrenal androgen secretion, a frequent cause of pubarche, **thelarche—**the first physical evidence of pubertal breast growth and development, whereas **gonadarche** is the

onset of pubertal gonadal (ovarian) function in response to upregulation of hypothalamic-pituitary function. When early breast growth is the only physical finding, the diagnosis of **premature thelarche** can be made, and clinical follow-up is indicated to monitor progression particularly those presenting with breast development in the first 2 years of life. Although the majority of girls with breast development before their eighth birthday have isolated premature thelarche, it is important to recognize that isolated premature thelarche may be the first manifestation of what becomes progressive PP. Thelarche may also develop early and progress slowly to a poorly described condition referred to as nonprogressive or intermittent precocious puberty. Nonprogressive PP is characterized by impressive early breast changes that are not associated with an upturn in growth velocity, advancement in skeletal maturity, or development of a pubertal hypothalamic-pituitary-gonadal (HPG) axis, whereas intermittent PP is characterized by intervals of progression that are not sustained.

When pubic hair develops without breast development, this is not PP but is referred to as **premature pubarche.** Although premature pubarche may be the first manifestation of adolescent ovarian hyperandrogenism (a portion of these patients later develop the polycystic ovarian syndrome [**PCOS**]), early development of sexual hair without breast growth or advanced skeletal maturation is usually considered isolated premature pubarche, a consequence of benign **premature adrenarche** caused by an early rise of adrenal androgen secretion characteristic of puberty. This pubertal variant is seen in as many as **20% of girls**. Other diagnoses in addition to PCOS that may initially present with isolated premature pubarche include **congenital**

p. 359p. 360adrenal hyperplasia, or sex steroid–secreting tumor—entities that all manifest an excessive advancement in skeletal maturity. Accelerated somatic growth that is not accompanied by breast or pubic hair growth is unrelated to sex steroid secretion.

1. **Premature thelarche** (isolated early breast development) is a variant of normal development, presenting most frequently during the first 2 years of life. When it begins after 3 years of age, isolated breast development is most commonly a marker of either nonprogressive or progressive puberty, and should be followed and

not labeled as benign thelarche.

a. **Clinical features.** Palpable and visible breast tissue can persist from the neonatal period into the first several years of life, because there is relatively more ovarian sex steroid secreted at this age. Most breast tissue that develops in the first few months of life regresses by the first birthday. Thelarche that appears to progress after the first birthday typically waxes and wanes, usually becoming quiescent around 36 months of age. Although unusual, breast growth from infancy may persist until the onset of normal puberty at the usual age. When occurring during mid-childhood (ages 3 to 5 years), thelarche may be the consequence of **transient estrogen release by an ovarian cyst**. Breast development that occurs as a consequence of ovarian cyst estrogen release typically regresses within a few weeks, as estrogen levels decline, although some patients have shown recurrent ovarian cysts. By definition, isolated premature thelarche is not accompanied by accelerated linear growth, advancement in skeletal maturity, or development of pubic hair.

b. **Treatment.** Treatment is not indicated for isolated thelarche. The child with isolated thelarche should be followed at least initially at 4- to 6-month intervals to ensure that breast development is not the first manifestation of progressive PP, which subsequently shows progressive breast growth, accelerated growth rate, and advanced skeletal maturation.

2. **Premature pubarche** (early development of sexual hair, pubic, or axillary). Isolated early sexual hair occurs as a result of benign **premature adrenarche** (premature pubertal secretion of adrenal androgens). However, early sexual hair may herald significant **hyperandrogenism**. This may involve ovarian hyperandrogenism and may evolve into the PCOS or, more rarely, mild forms of congenital adrenal hyperplasia or sex steroid–secreting tumor. In the two latter conditions, growth rate can be significantly accelerated, and bone age significantly advanced. In contrast, children with premature adrenarche show a normal growth rate and normal or only mildly advanced skeletal maturities. In females, excessive androgens may cause early progressive sexual hair, acne, and oily skin. Without treatment, these characteristics can progress in the pubertal years and result in hirsutism and amenorrhea. Rarely, excessive androgen may result

in clitoromegaly, deepening voice, or excessively muscular physique; when this occurs, evaluation should include causes of severe androgen excess (see Section I.A.4).

3. **PP** is present when significant pubertal development occurs, progresses, is associated with accelerated linear growth (Fig. 29-1), an advancement in skeletal age and biochemical evidence of a pubertal HPG axis. The etiology of gonadotropin-releasing hormone (GnRH)–stimulated or central precocious puberty (CPP) is the early onset of pituitary gonadotropin stimulation resulting from early reactivation of the HPG axis. CPP must be differentiated from other causes of early puberty that are not driven by the HPG axis (GnRH-independent or peripheral precocious puberty [PPP]) and from nonprogressive PP, in which there is early development but no progression. Table 29-1 outlines the etiologic categories of CPP.
    a. **GnRH-stimulated, CPP (pituitary gonadotropin stimulation)** may result from the following:
        i. Premature activation of the HPG axis resulting in the early onset of pubertal hormonal secretion without a demonstrable central nervous system (CNS) abnormality (also known as idiopathic CPP).
        ii. Redundant or excessive GnRH-releasing hypothalamic tissue, may result from a **hypothalamic hamartoma** (a congenital lesion—typically in the area of the tuber cinerium).

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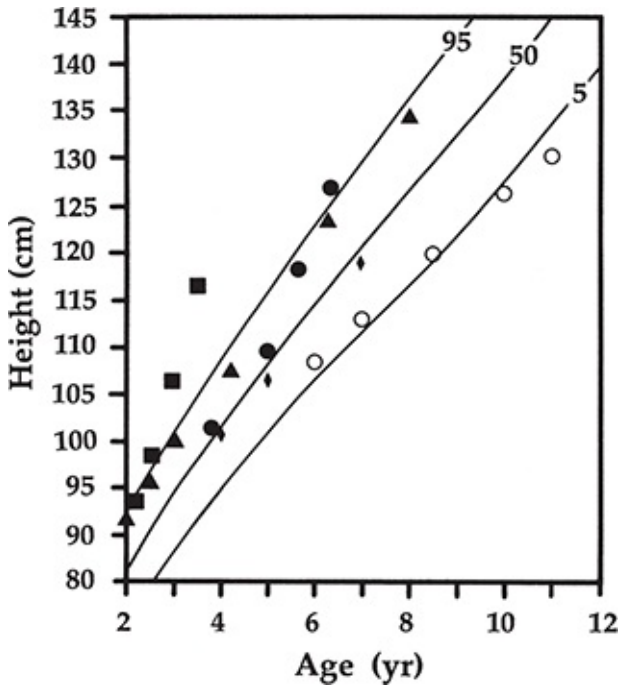

Figure 29-1. Height for age for five girls plotted against 5th, 50th, and 95th percentile standards of height for age from the National Center for Health Statistics. ■, heights of a child with mild 21-hydroxylase deficiency adrenal hyperplasia (note rapid growth acceleration from a young age); ▲, normal tall child growing consistently at the 90th percentile; ●, girl with idiopathic central precocious puberty with the onset of growth acceleration and pubertal changes at 5 years of age; ♦, child with premature adrenarche with no detectable alteration of growth rate; ○, child with Turner syndrome and growth deceleration.

iii. CNS lesions, including tumors, infections, and infiltrative conditions, affecting the balance between stimulatory and inhibitory influences on the HPG axis, with stimulation and upregulation of intermittent GnRH secretory bursts.

iv. Secondary to excessive sustained sex steroid exposure from sex steroid–producing tumors, congenital adrenal hyperplasia, or exogenous sources; such exposure during prepubertal years fosters early maturation of the HPG axis. Gonadarche (onset of gonadal pubertal hormone secretion) and adrenarche (onset of pubertal adrenal androgen secretion) are two independent events, which are unrelated physiologically, but are usually related temporally. Clinically significant amounts of androgen may not be secreted by the ovaries at the onset of gonadarche. Thus, CPP in girls may present with only gonadarche or estrogen-stimulated findings, such as breast and genital development, without sexual hair or other androgen stimulated findings.

In PP, as in normal pubertal development, the timing of menarche cannot be predicted. However, it is generally accepted that menarche is typically reached between 2 and 3 years after first evidence of thelarche. Initial menstrual cycles can be ovulatory, and therefore, the potential for fertility exists from menarche onward.

b. In **GnRH-independent PPP (precocious pseudopuberty),** clinical presentation is similar to centrally mediated puberty with breast development, sexual hair development, and accelerated linear growth.

i. Etiology. Because the cause is other than pituitary gonadotropin secretion, all forms are pathologic. The physical development results from gonadotropin or sex steroid exposure or production that is independent of the HPG axis. Causes include autonomous ovarian or adrenal hormone secretion, p. 361p. 362p. 362p. 363abnormal gonadotropin stimulation, and exogenous hormonal sources. Overall, endocrine disruptors, particularly chemicals in the environment with estrogen-like effects including lavender, have not been clearly shown to significantly affect pubertal onset and particularly tempo of change.

TABLE 29-1 Isosexual Precocious Pubertal Development

I. Pituitary gonadotropin secretion (central or true precocity)
Idiopathic (including sporadic and familial)
CNS abnormalities
Hypothalamic hamartomas (redundant or excessive normal tissue)
Space-occupying lesions (altering stimulatory–inhibitory effects)

- **a.** Astrocytomas
- **b.** Arachnoid cysts/suprasellar cysts
- **c.** Craniopharyngiomas
- **d.** Ectopic pinealomas
- **e.** Ependymomas
- **f.** Optic gliomas (with neurofibromatosis)
- **g.** Pituitary adenomas

h. Tumors associated with tuberous sclerosis

Resulting from cerebral damage due to:

a. Irradiation/chemotherapy

b. Surgery

c. Trauma

d. Encephalitis/meningitis/abscess

e. Myelomeningocele

Due to cerebral defects associated with CNS anomalies and other neurologic or mental defects

Coincident with hydrocephalus (may be reversible), brain abscess, or granulomas

Secondary to chronic exposure to sex steroids (tumors, untreated congenital adrenal hyperplasia)

II. Sexual steroid secretion effect independent of pituitary gonadotropin (peripheral precocious puberty and precocious pseudopuberty)[a]

Ovarian tumors (carcinoma, cystadenoma, gonadoblastoma, granulosa cell—may be associated with Peutz-Jeghers syndrome—, lipoid, luteoma, sex cord, or theca cell)

Adrenal adenomas or carcinomas (rarely secrete estrogens without androgen)

Exogenous sex steroids/gonadotropins[b]

McCune-Albright syndrome (G-protein–activating mutation)

Ectopic gonadotropin-producing tumor (virtually limited to males)

Ovarian cysts[b] (also associated with the normal prepubertal states, premature thelarche, central precocious puberty, and McCune-Albright syndrome)

Gonadotropin-independent puberty, full pubertal maturation, LH receptor–activating mutation

Gonadotropin-secreting pituitary adenoma

Occasional consequence of chronic primary hypothyroidism likely TSH occupation of FSH receptor[b]

III. Incomplete precocious puberty

Premature thelarche

Premature adrenarche

Premature pubarche may be the first manifestation of hyperandrogen states (CAH, PCOS)

Isolated menarche

CAH, congenital adrenal hyperplasia; CNS, central nervous system; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; TSH, thyroid-stimulating hormone.

[a]Vaginal foreign body or tumor (to be ruled out in patients presenting with vaginal discharge or bleeding).

[b]Limited and potentially reversible if of short duration or treated before secondary central precocious puberty occurs.

ii. PP associated with **McCune-Albright syndrome** arises because of ovarian activity resulting from an activating

mutation in the G-protein–linked cyclic adenosine monophosphate (cAMP) system. This postconception somatic mutation involves various cell lines and often involves the ovaries. The result is intermittent and autonomous ovarian estrogen secretion that stimulates abrupt pubertal changes commonly followed by rapidly falling estrogen levels and withdrawal uterine bleeding. Thus, this syndrome may present with menstrual bleeding despite minimal to no breast development.

a) Pubertal development, particularly breast development in girls and testicular growth in boys, may rarely develop with **chronic primary hypothyroidism**. This results from the promiscuous occupation and activation of follicle-stimulating hormone (FSH) receptors on ovarian granulosa cells by the abundant thyroid-stimulating hormone (TSH). The competition of the increased levels of TSH for these FSH receptors appears to stimulate FSH-mediated changes, including follicular growth with estrogen secretion as well as ovarian cyst formation and seminiferous tubule growth. In addition, the attendant **hyperprolactinemia resulting from increased TRH stimulation** as seen in severe hypothyroidism may play a role in breast growth.

b) Ovarian and adrenal sex steroid–secreting tumors are rare but may produce dramatic effects as a consequence of estrogen stimulation.

c) Exogenous estrogen in foods and cosmetics is regulated and is an unlikely but possible cause. Estrogen-containing medications require more than a single accidental exposure to cause physical pubertal changes.

d) Chorionic gonadotropin secretion of tumor origin will cause Leydig cell differentiation and testosterone secretion, resulting in PP in males. However, the luteinizing hormone **(LH) effect of human chorionic gonadotropin (hCG) alone does not result in pubertal changes in females, except at peripubertal ages**, because both LH and FSH are necessary for estrogen secretion.

iii. Physical changes. In PPP, as in CPP, pubertal changes

can progress rapidly. Withdrawal vaginal bleeding can occur, although ovulation is not expected. Endometrial sloughing can result from excessive estrogen stimulation, fluctuation of estrogen secretion, or a sudden decrease of estrogen effect. Although the bleeding pattern may be regular, it is more often erratic.

c. The sequence of normal pubertal events designated by Tanner staging is summarized in Table 29-2. In CPP, as in normal puberty, this tempo is variable. In PPP, the sequence and tempo are related to the magnitude of hormonal stimulation. CPP accounts for >90% of all cases of early puberty in girls, and most have no identifiable abnormality and are, therefore, considered idiopathic. With the availability of more refined imaging, particularly magnetic resonance imaging (MRI), aberrations associated with the CNS, including hypothalamic hamartomas, have become more readily demonstrable. CPP may be a consequence of childhood malignancies and/or treatment resulting from anterior pituitary hormone deficiencies.

4. Virilization in females occurs as the result of excessive androgen (hyperandrogenism).

a. Clinical findings include hirsutism, excessive acne, clitoromegaly, deepening of the voice, an accelerated growth rate or tall stature, excessive muscle development, and a masculine habitus. Although clitoral enlargement is usually the result of a virilizing process, it may rarely occur as a result of regional disease-specific abnormal tissue growth, such as may be seen in neurofibromatosis.

b. Laboratory findings. Hyperandrogenism is documented by elevated serum levels of testosterone, androstenedione, dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEA-S) for age. Skeletal maturity (bone age) is typically significantly advanced.

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TABLE 29-2 **Chronologic Sequence of Puberty and Approximate Range for Three Racial Groups**

	Approximate age range (yr)

Tanner stage of development and pubertal event	Black	Hispanic	White
Stage 1			
Prepubertal breasts, papilla elevation only, no pubic hair	Prepubertal		
Stage 2			
Breast budding, elevation of breast and papilla with increased areolar diameter	6.6–11.6	6.8–12.3	8.0–12.5
Pubic hair (long, slightly pigmented hair on labia)	6.7–11.7	7.4–12.7	8.0–12.7
Stage 3			
Further enlargement and elevation of breasts	6.8–12.5	9.5–13.3	10.8–13.3
Pubic hair spread over junction of mons pubis	8.0–12.7	9.7–13.6	8.0–13.6
Menarche	9.7–14.5	10.1–14.5	10.7–14.4
Stage 4			
Breasts: secondary mount projection of areola and papillae (does not always occur)	8.1–14.9	10.7–14.3	10.3–15.5
Adult-type pubic hair; incomplete distribution	7.6–14.3	10.7–15.8	10.6–14.8
Stage 5			
Breast development: mature	9.6–17.5	11.9–13.5	11.3–19.0
Adult quantity and distribution of pubic hair	10.2–18.4	13.5–19.3	12.5–19.7

c. Etiology. Causes of virilization in prepubertal and peripubertal girls may result from the milder non–salt-wasting forms of congenital adrenal hyperplasia, especially 21-hydroxylase deficiency. Mild unexplained virilization during late prepubertal years may herald significant ovarian hyperandrogenism. Other rare causes include androgen-producing tumors (including adrenal adenomas/carcinomas and ovarian arrhenoblastomas), choriocarcinomas, dysgerminomas, and teratomas. Hormone production and malignancy vary for these tumors.

B. Evaluation

Initial assessment of patients with signs of PP includes a history (searching for factors related to etiology) and a physical examination

(documenting growth, extent of sexual development, and identifying abnormal findings). A record of previous heights, such as an accurate growth chart, to identify growth acceleration is most useful.

1. A child presenting with **only breast development** or **only pubic hair** without growth acceleration (as shown by growth points plotted for the preceding years) usually needs careful clinical follow-up to monitor for progression and an increase in growth velocity. In addition, obtaining a skeletal age X-ray to document maturity and provide a reference for future progression should be considered.
   a. **History** should determine the age at which sexual development was first noticed and explore the possibility of exogenous sex steroid exposure, family pattern of pubertal onset, and the presence of neurologic, dermatologic (café-au-lait patches), or thyroid abnormalities.
   b. If previous growth history is not available in a relatively tall child with substantial breast development, a **skeletal age determination (bone-age radiograph)** can be done; if PP has caused growth acceleration, the bone age will be advanced.
   c. In children presenting with breast growth, a **plasma estradiol level** using a sensitive assay (Table 29-3) may help differentiate between the slightly elevated p. 364p. 365p. 365p. 366levels seen in isolated benign premature thelarche and the clearly elevated values seen (at times intermittently) in PP or paraneoplastic syndromes.

TABLE 29-3 **Approximate Range of Normal Hormone Level for Females at Various Ages and Pubertal Stages**

Hormone	Unit	Infancy (1–4 mo)[a]	Infancy (4–12 mo)	Childhood (1–6 yr)	Puberty (stages 2–4)	Adult (Stage 5)[b]
Serum						
Luteinizing hormone (LH)	mIU/mL	0.02–7.0	0.02–0.8	0.05–0.3	0.03–112.0	2–9
Follicle-stimulating hormone (FSH)	mIU/mL	0.2–14.0	0.2–4.0	1.0–4.0	1.0–11.0	2.0–11.0
Plasma						
Estradiol (E_2)	pg/mL	0.5–5.0	<1.5	<1.5	5–85	30–100
Dehydroepiandrosterone sulfate (DHEA-S)	μg/dL	5–100	5–55	5–55	35–260	75–260
Dehydroepiandrosterone	ng/dL	20–380	20–100	20–140	150–800	150–850
Androstenedione	ng/dL	U–280	<10–40	<10–20	<10–210	30–230
Testosterone (T)	ng/dL	U–10	U–10	U–10	5–35	10–55
Progesterone (P)	ng/dL	U–25	U–25	U–25	U–135	U–135
17-Hydroxyprogesterone (17-OHP)	ng/dL	10–85	10–85	3–90	10–70[a]	15–70

U indicates undetectable, below lower limits of assay.
[a]Preterm levels may vary.
[b]Follicular phase, if after menarche.

d. Patients with pubic hair secondary to adrenarche can be documented by showing an elevated level of plasma **DHEA-S** but normal testosterone and 17-hydroxyprogesterone (17-OHP) levels. Levels of both DHEA-S and DHEA rise significantly at the onset of adrenarche. The half-life of DHEA-S is much more prolonged than that of DHEA, so significant elevation of DHEA-S above prepubertal levels can often be detected before DHEA levels can. Both DHEA-S and DHEA are relatively mild androgens. During early adrenarche, both DHEA and DHEA-S levels are above prepubertal values and are within the normal pubertal ranges. Striking elevations of these hormones should lead to consideration of an adrenal sex steroid–secreting tumor, although because sulfatase enzymes are unique to the adrenal cortex, **tumors may be associated with low DHEA-S but elevated DHEA levels**.

e. If the bone age is advanced or if sexual development is not isolated to one physical dimension (such as only breast or only pubic hair), an evaluation should be undertaken. In these cases, PP is best diagnosed, using GnRH or GnRH analog (GnRHa) testing, hopefully before growth patterns and skeletal age become markedly advanced. A clearly pubertal gonadotropin response, particularly LH, indicates a pubertal hypothalamic-pituitary axis.

i. GnRH or GnRHa stimulation testing involves the intravenous/subcutaneous administration of GnRH or GnRHa with measurement of gonadotropins before and after the injection. GnRH is unavailable. GnRHa is now employed for diagnostic evaluation of PP; the subcutaneous

aqueous preparation of **leuprolide** acetate is given at a dose of 20 μg/kg (maximum dosage 1 000 μg). A child with CPP will show a rise of gonadotropins—particularly LH—after GnRH stimulation that is of greater magnitude than is seen in prepubertal children. Sampling of gonadotropins at 30 to 60 minutes after GnRHa administration is sufficient for diagnostic testing. The magnitude of the gonadotropin response varies considerably depending on the assays used, although responses among third-generation gonadotropin assays are similar. It is important to know prepubertal and pubertal responses for the gonadotropin assay used. Generally, **the rise of LH in the prepubertal female is approximately 2- to 4-fold above baseline, whereas the pubertal female will show at least an 8- to 10-fold elevation** above baseline LH. Normal prepubertal females also show a substantial rise of FSH in response to GnRHa (prepubertal males show this to a lesser degree), making the **FSH response to the GnRHa stimulation testing unnecessary** for evaluating CPP. Ratios of LH to FSH may be useful in differentiating a prepubertal from a pubertal response using basal or GnRHa-stimulated levels. Generally, a ratio <1 is consistent with a prepubertal state, whereas a ratio > 1 suggests puberty.

ii. **A basal level of LH** within the pubertal range may be adequate to make the diagnosis of CPP, but a pubertal response to GnRH/GnRHa stimulation remains definitive proof of central precocious puberty. Because gonadotropin response to GnRHa stimulation is the best evidence of a functional pubertal HPG axis, GnRHa stimulation should be undertaken when basal gonadotropin levels do not clearly indicate puberty in a girl with clinical pubertal progression.

2. If the findings of a child presenting with sexual hair suggest possible excessive virilization (e.g., clitoromegaly), a pathologic cause must be ruled out. If there is a persistent endogenous source of excessive androgen, plasma **DHEA-S, DHEA, androstenedione, 17-OHP,** or **testosterone** levels will be elevated. When plasma levels of any of these hormones are elevated, adrenal hyperplasia, adrenal tumors, ovarian tumors, and

other forms of hyperandrogenism must be sought. Mild forms of adrenal hyperplasia can present with minimal but progressive virilization.

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3. If a patient presents with the triad of findings indicative of PP (i.e., **breast and pubic hair development and growth acceleration**), the evaluation should confirm pubertal hormone levels and then determine whether this is gonadotropin-dependent (CPP) or gonadotropin-independent (PPP) sexual development.
   a. **History** should concentrate on growth patterns and rates (familial forms usually involve males but can affect both sexes), CNS symptoms or abnormalities (present or past), growth history, and possible exposure to exogenous hormones.
   b. **Physical examination** should document—in addition to anthropometric, neurologic, ophthalmologic, dermatologic, and general findings—sexual maturation (Tanner staging; see Table 29-2), degree of genital maturation, appearance of vaginal mucosa, clitoral and breast size, breast configuration, and pelvic ultrasound studies. A pink (vs. red-appearing), vaginal mucosa suggests cellular proliferation resulting from estrogen stimulation. Acne or skin pigmentation should be noted. The examination should also screen for the presence of a goiter or other physical markers of thyroid dysfunction.
   c. **Laboratory evaluation**
      i. To document PP and identify the etiologic category causing the early pubertal development, **hormone levels** can be documented (Table 29-3). Serum LH and FSH and plasma estradiol levels (using third-generation assays) should be measured and stratified into prepubertal, pubertal, or supraphysiologic. Plasma DHEA-S or androstenedione allows one to classify adrenal androgen production as preadrenarche, postadrenarche (pubertal), or supraphysiologic. Androstenedione levels are less useful for this purpose because this hormone has both ovarian and adrenal sources.
      ii. **Bone-age radiographs** are needed to record skeletal maturation in relation to age and are useful as baseline documentation for future comparison.

iii. A pubertal **basal level of LH** or a pubertal response to **GnRH/GnRHa stimulation testing** confirms CPP (Fig. 29-2), whereas lower levels or a minimal response indicate a noncentral etiology.

iv. **MRI of the brain** is indicated if there is evidence to suggest neurofibromatosis, the McCune-Albright syndrome, or neurologic or ophthalmologic deficits, and when pubertal onset begins at an especially young age (<6 years).

v. **In documented PP without known etiology, the MRI of the brain** should include coronal views of the sellar and hypothalamic areas to detect otherwise nonapparent CNS abnormalities, such as hamartomas or in the assessment of neurofibromatosis.

vi. **Abdominal–pelvic sonography** can be used to document ovarian, adrenal, and uterine size and symmetry. It is noteworthy that ovarian cysts may be present in the ovary in association with CPP, forms of PPP, and the prepubertal child.

vii. **Other workup** may be indicated based on the results of the physical and laboratory evaluation. More extensive neurologic assessment, thyroid function tests if **hypothyroidism** is a potential cause, and long-bone radiographs if the **McCune-Albright syndrome** is a possibility, may be indicated.

C. Management

1. **Premature thelarche** and **adrenarche** require only follow-up evaluation at 4- to 12-month intervals for 1 to 2 years to document any progression. Growth rates and, if excessive, bone age can be monitored.
2. **Management of PP** is aimed at stopping the untimely pubertal maturation, including menstruation, and reversing the consequences of the accelerated growth rate and skeletal maturation. Suppressive therapy is indicated to avoid and limit the compromise in adult height that may attend PP. This disproportionate effect explains why patients may be relatively tall in childhood and yet reach an adult height well below their genetic potential. The medical therapy is directed toward removing the excessive sex steroid stimulation, halting the progression (or allowing regression) of pubertal characteristics (including menses),

and reverting growth and skeletal maturation rates to prepubertal levels. Therapy involves the following:

a. Psychological preparation and reassurance.

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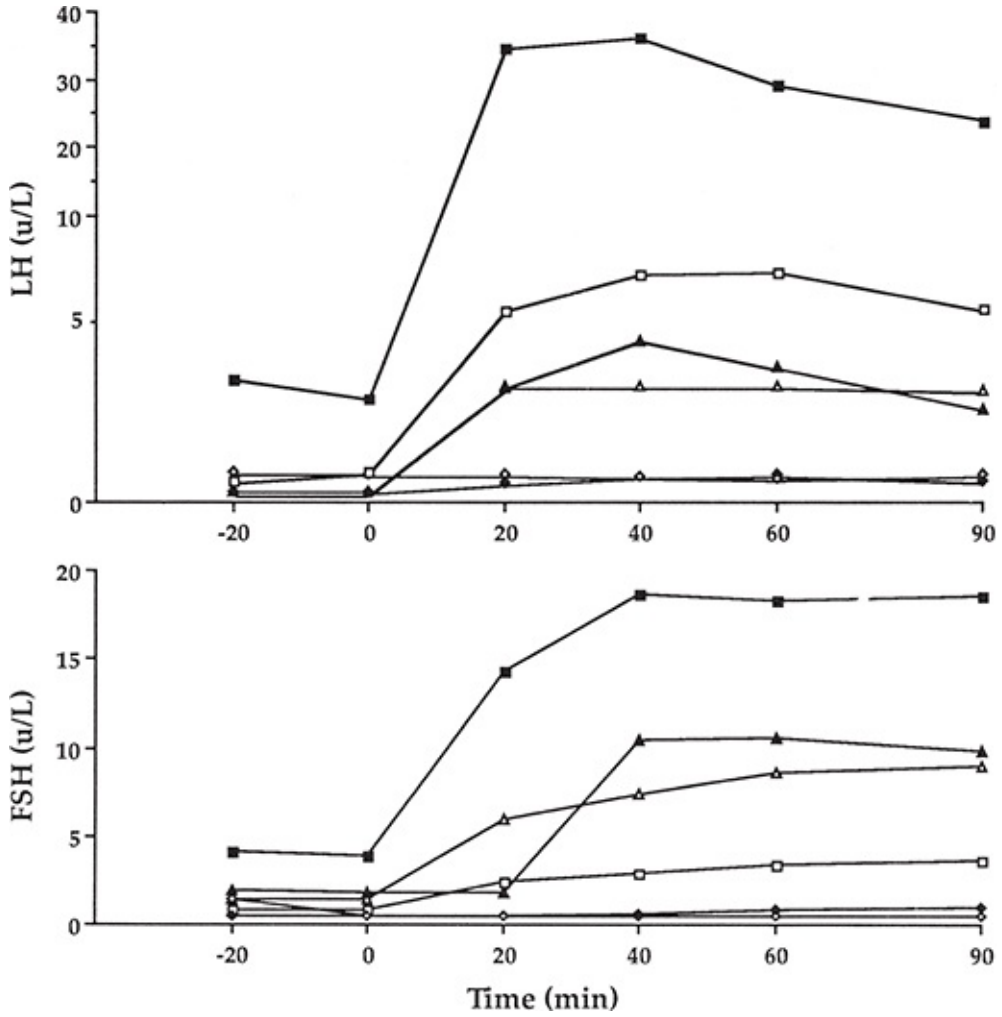

Figure 29-2. Gonadotropin-releasing hormone (GnRH) stimulation of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in six different clinical situations; 100 μg of GnRH was given as a bolus injection at time 0. ■, responses of LH and FSH in a 5-year-old with idiopathic central precocious puberty; ◊, lack of response in the same patient during suppressive GnRH analog therapy; ▲, response in a 7-year-old girl with premature thelarche; Δ, response of a normal prepubertal 6-year-old girl; □, minimal response in a 16-year-old hypogonadotropic girl; ♦, lack of response in a 17-year-old girl with hypogonadotropic hypogonadism secondary to a craniopharyngioma. Note scale for LH.

b. Treat or remove any **etiologic abnormality.** If exogenous hormones have been administered, they should be stopped. If

primary hypothyroidism is present, appropriate thyroid replacement therapy should be used to normalize TSH levels.

c. **If CPP** is the underlying cause, treatment is aimed at **suppressing** the episodic **release of gonadotropins**.
    i. **The long-acting GnRHa** are the **treatment of choice** for CPP. Preparations include depot forms (e.g., 4- and 12-week preparations of leuprolide acetate for depot injection, a 22.5 mg triptorelin 24 week injection, and a 50-mg subcutaneous histrelin implant that lasts for at least 1 year). Daily subcutaneous injections (including the original and generic preparations of leuprolide acetate with a starting dose of 20 mg/kg/day) are less commonly used and available. Doses may need to be titrated up, if needed, to achieve full suppression.

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a) The long-acting property of these analogs results in a persistently high level of GnRH at the pituitary, which, after a brief initial stimulatory phase, causes a downregulation of the cell-surface GnRH receptors on the pituitary gonadotrophs, resulting in unresponsiveness to GnRH. This induced pituitary nonresponsiveness prevents the release of LH and FSH. Accordingly, episodic gonadotropin secretion ceases, gonadotropins fall, ovarian estrogen production is suppressed, and pubertal development and rapid growth rates slow. Menstruation ceases, although there may be an episode of withdrawal bleeding within the first month of treatment if there has been significant estrogen-mediated endometrial growth.

b) Skeletal maturation rate will slow; however, this is often not apparent until after 6 months of suppression. Once a pubertal bone age is attained, there will be minimal progression thereafter until sex steroid exposure resumes. Growth rate will return to a prepubertal velocity (based on skeletal age).

c) Adequacy of suppressive therapy is **monitored** by random gonadotropin and sex steroid measurements, GnRH or GnRHa stimulation testing, growth rate, bone

age, and physical pubertal progression.

1) With therapy, sexual characteristics should cease and may regress; growth and skeletal maturation rates should slow to normal for age; and random hormone sampling levels should fall into the prepubertal range.
2) If it is unclear whether treatment is adequate, the definite test is GnRH or GnRHa stimulation testing on therapy with measurement of LH and FSH, which should document gonadotropin responses in the prepubertal range. A single sample 1 to 2 hours after the monthly depot injection also appears to be sufficient to document suppression. Estradiol levels likewise should also fall into the prepubertal range.

d) **Side effects** are unusual. None have been clearly shown to be due to the analog itself, although the vehicle may be implicated rarely in a variety of untoward local reactions, including local reactions with induration and sterile abscess formation that may develop into granulomas (with use of the depot injectable preparation and with difficulty inserting or removing the subcutaneous implant).

e) **After discontinuation of therapy,** pubertal hormone secretion resumes within months, followed by resumption of pubertal development. Growth and skeletal maturation resume, but in most cases, no appreciable growth spurt occurs. Following timely and successful GnRHa therapy, adult height will be greater than pretreatment height prediction and will be within range of target (genetically expected) height. Bone mineral density after therapy will be normal for age. Menses begin or resume at an appropriate age, and ovulation and normal rates of fertility have been documented. No long-term sequelae have been identified.

ii. **Medroxyprogesterone acetate** (Provera) can still be used in those rare situations in which the goal is merely to stop menstrual periods. It can be administered at doses ranging from 10 to 100 mg (usual dose is 20 to 30 mg)

daily orally (PO) or 100 to 200 mg intramuscularly (IM) every 2 weeks. Doses are generally titrated upward as needed. Side effects include diminished bone mineral density and those due to glucocorticoid properties with suppression of adrenocorticotropic hormone (ACTH) and cortisol secretion and evidence of a Cushingoid state.

3. **Treatment of hyperandrogenic states.** If the hyperandrogenic state is caused by an adrenal or ovarian tumor, treatment is directed toward eradicating the tumor. If it is caused by adrenal hyperplasia, appropriate treatment involves physiologic glucocorticoid and mineralocorticoid replacement therapy. With appropriate treatment, additional virilization will cease and may regress. Optimal treatment for a hyperandrogenic early pubertal girl who is at risk for progression to polycystic ovarian disease is not known.

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D. Miscellaneous considerations

1. **Ovarian cysts** have been associated with premature sexual development, as part of either CPP or PPP, or premature thelarche. Such ovarian cysts are also seen in normal prepubertal children.
   a. **Etiology.** Ovarian cysts may be an unusual outcome of the normal prepubertal recruitment and regression of ovarian follicles. Occasional follicles may continue to grow and secrete estradiol rather than following the usual pattern of limited growth and regression. Most cysts are thought to result from sporadic, albeit low-level, gonadotropin stimulation, which occurs in both normal and abnormal development. Therefore, the presence of ovarian cysts is neither indicative nor diagnostic of pathology. However, functional ovarian cysts are able to secrete sufficient estrogen to temporarily stimulate early pubertal changes.
   b. **Treatment.** In most instances, cysts regress within a matter of months, even in those with CPP. Functional cysts that cause pubertal changes should be monitored, but their identification should not be followed by immediate surgical resection unless there is an impending surgical emergency. If resection of a cyst is necessary, care should be taken to leave as much ovarian tissue as possible. Usually, a repeat pelvic sonogram within 2 to

3 months will verify cyst regression.

2. **The McCune-Albright syndrome** is an entity that classically includes **a triad** of autonomous endocrinopathies (most commonly **PP**), **polyostotic fibrous dysplasia**, and **café-au-lait skin** macules. However, this entity may occur with only one or two of these findings. In this syndrome, early puberty may present with vaginal bleeding in the absence of other features of pubertal development. This develops due to the significant rise of estrogen as during cyst rupture that is followed by a sudden fall in estrogen levels.
   a. **Associated disorders.** Other endocrinopathies that coexist include thyrotoxicosis, excess glucocorticoid production, and acromegaly.
   b. **Etiology.** The endocrinopathies that occur with this syndrome are the result of autonomous end-organ function without the stimulation of the tropic hormones, for example, ovarian function without gonadotropin stimulation. Each of the endocrine glands affected in this condition utilizes cAMP as the second messenger for the signal transduction pathway involving G proteins.
   c. **Treatment.** To date, there is no definitive therapy, and treatment is aimed toward blocking the effects of estrogen. Medroxyprogesterone, ketoconazole, aromatase inhibitors, and estrogen receptor antagonists have been tried and have varying efficacy. Because the etiology is independent of pubertal gonadotropin secretion, treatment with **GnRHa is inappropriate and ineffective** unless secondary CPP ensues. Aromatase inhibitors (including third-generation letrozole and anastrazole, in addition to testolactone) appear to be effective in reducing estrogen. There are limited data concerning the use of estrogen receptor antagonists (tamoxifen and fulvestrant) regarding effectiveness of blocking estrogen action in this syndrome, although available clinical studies show equal clinical effects using either drug approach. Medroxyprogesterone has been used the longest to treat the PP in this condition. Depo-Provera at 4 to 15 mg/kg IM monthly is one dosing regimen. Caution should be used in treating patients with severe bony lesions, because the lesions might be exacerbated as a result of the hypocalcemic effect of the drug.

3. **PP with primary hypothyroidism.** The occurrence of precocious puberty in patients with long-term primary hypothyroidism occurs rarely.
   a. **Etiology.** The pathophysiology of this disorder appears to involve the promiscuous occupation of the FSH receptor by the TSH molecule when TSH is in abundance. When the hypothyroidism is treated with thyroid hormone and TSH levels are suppressed into the physiologic range, TSH levels return to normal and premature sexual development regresses.
   b. **Clinical findings.** The sexual maturation occurring in this syndrome is consistent with a primary FSH-like effect, the most striking effect being breast development. Full **pubertal development does not occur**. Multicystic ovaries p. 370p. 371occur commonly. Skeletal age may be delayed rather than advanced, because of the thyroid hormone deficiency.
   c. **Treatment.** Appropriate treatment of the hypothyroidism is followed by regression of changes of puberty.
4. **Isolated vaginal bleeding** may occur in a prepubertal girl who has no evidence of significant estrogen stimulation, such as breast development, nor other secondary sexual characteristics. This may recur, and intermittent spotting may follow. When this occurs, it is important to evaluate for a functional ovarian cyst, infection, inflammation, foreign body, or sexual abuse or trauma. Indices of pubertal onset, including LH, FSH, and estradiol, are typically prepubertal. This, after pathology has been excluded, can be considered a benign, self-limiting condition.

II. DELAYED PUBERTY

A. General principles

The lack of onset of pubertal characteristics (breast or pubic hair development) by 13 years of age and the lack of menarche by 15 years of age represents a significant delay. In addition, a failure to reach menarche by 4 years after thelarche is a valid reason for investigation.

1. **Causes** of delayed or inadequate pubertal development are categorized as **hypogonadotropic** or **hypergonadotropic** states (Table 29-4).

2. **Hypogonadotropic states** may be **temporary** (delay in maturation or because of consequences of diseased or malnourished states) or **permanent** (congenital or acquired inability to synchronously secrete GnRH or gonadotropins).
   a. **Genetic etiology.** By convention, isolated hypogonadotropic hypogonadism without anosmia is called idiopathic hypothalamic hypogonadism (IHH), and IHH with anosmia is referred to as **Kallmann syndrome (KS)**. Because the etiologies of these problems have been elucidated, it is clear that there is considerable overlap between IHH with and without anosmia, with variation in the extent of or presence of anosmia. However, there is evidence of phenotype/genotype in KAL types 1 through 4. Types 1 and 2 have nonreproductive phenotypes, whereas KAL3 and KAL4 do not. These and other mutations are included in Table 29-4.

TABLE 29-4 Delayed or Inadequate Pubertal Development

I. Lack of physical pubertal development
Hypogonadotropic states
Temporary conditions resulting from:
Chronic malnutrition/malabsorption
Chronic systemic disease
1. Cardiac
2. Gastrointestinal (Crohn disease)
3. Hematologic (sickle cell)
4. Pulmonary (cystic fibrosis)
5. Chronic renal failure

Drug abuse
Emotional stress
Excessive physical stress/overexertion
Exogenous obesity
Malnutrition
Normal variant, constitutional delay of puberty
Psychiatric illness (anorexia nervosa)
Psychosocial dwarfism
Untreated endocrinopathies

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1. Diabetes mellitus

2. Glucocorticoid excess
3. Hypopituitarism
4. Hypothyroidism
5. Isolated growth hormone deficiency

Permanent hypothalamic or pituitary gonadotropin deficiency

Isolated gonadotropin deficiency (nonacquired)

1. Pituitary (no LH and FSH response to GnRH)
2. Hypothalamic (good LH and FSH response to GnRH)
3. Unclear, possibly hypothalamic (partial response to GnRH)

Associated with varying degrees of holoprosencephaly

1. Kallmann syndrome with anosmia or hyposmia
2. With central maxillary incisor
3. With cleft lip or cleft palate
4. Septo-optic dysplasia (optic nerve hypoplasia)

Associated with multiple pituitary hormone deficiencies

1. Panhypopituitarism (hypothalamic defects)

   Genetic mutations

   i. HESX1 (septo-optic dysplasia)
   ii. LHX3 (with hypothyroidism and hypoprolactinemia)
   iii. PROP1 with GH and TSH deficiency and hypoprolactinemia)
2. Pituitary dysgenesis
3. Space-occupying lesions (craniopharyngiomas, Rathke pouch cysts, hypothalamic tumors, pituitary adenomas)
4. Absence of corpus callosum
5. Following surgery
6. Following cranial irradiation
7. Following CNS chemotherapy
8. Following inflammation
9. Infiltrative or destructive processes (autoimmune, hemosiderosis)

Associated with syndromes involving hypothalamic function

1. Laurence-Moon-Biedl syndrome with retinitis pigmentosa, dwarfism, mental retardation (polydactyly, obesity)
2. Prader-Willi syndrome (neonatal hypotonia, mental retardation, short stature, hypogonadism, obesity)
3. Fröhlich syndrome (outdated term referring to hypogonadism and obesity resulting from a variety of causes)
4. Also, Alstrom, Börjeson-Forssman-Lehman, Carpenter, CHARGE, Gordon-Holmes spinocerebellar ataxia, multiple lentigines, Noonan and prosencephalon defects (also may include midfacial cleft, cleft lip or cleft palate, and central incisor)

Genetic mutations

KAL1 is related to anosmia and ANOSI and KAL1 mutations

KAL2 may be associated with cleft palate, agenesis of the corpus callosum, unilateral

hearing loss, and fusion of the fourth and fifth metacarpal bones, and considerable variability in the lack of sense of smell and mutations of the fibroblast growth factor-1 receptor (FGFR1) and FGF8, a critical ligand for FGFR1 in GnRH ontogeny associated with broad spectrum of pubertal development, hearing loss, and skeletal features including high arched palate, cleft lip/palate, severe osteoporosis, camptodactyly, and hyperlaxity of the digits.

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KAL3 is prokineticin receptor 2 (PROKR2) mutations and KAL4 Prokineticin 2 (PROK2) mutations and are not associated with nonreproductive phenotypes.

Additional mutations disrupting development and migration of GnRH neurons from the olfactory epithelium to hypothalamus include NELF, HS6ST1, CHD7, WDR11, and SEMA3A.

Genes that primarily interfere with the normal secretion of GnRH (*GNRH1*, *KISS1*, *KISS1R* (*GPR54*), *TAC3*, *TACR3*) and GNRHR that impacts action on the pituitary.

Additional mutations that cause both KS and IHH include HS6ST1, CHD7, WDR11, and SEMA3A.

Other mutations related to deficient gonadotropin secretion include FSH*β* (isolated FSH deficiency), PROP1 (pituitary deficiency), HESX1 (septo-optic dysplasia), DAX1, prohormone convertase deficiency, contiguous to Duchenne muscular dystrophy gene, leptin, and LeptinR

Hypergonadotropic states: no ovarian function

Congenital defects

Gonadal dysgenesis—Turner syndrome (45,X and mosaic forms)

Pure gonadal agenesis (46,XX or 46,XY)—Swyer syndrome

Mixed gonadal dysgenesis (45,X/46,XY)

Steroidogenic enzyme deficiencies

1. 17-Hydroxylase/17,20-desmolase
2. 17-Ketosteroid reductase
3. 3*β*-Hydroxysteroid dehydrogenase
4. P450 aromatase

Acquired defects: ovarian failure resulting from:

Autoimmune disease

Infection or inflammation

Infiltration (hemochromatosis, sickle cell)

Surgical resection

Irradiation

Chemotherapy

Bilateral ovarian torsion

Genetic mutation

FSH receptor (FSHR)

LH subunit gene mutation

II. Lack of menarche with otherwise apparent normal development

A. Hypogonadotropic states

Pubertal-aged onset of conditions (see Section I.A.1)

Lack of maturation of synchrony of hormonal stimulation

B. Hypergonadotropic states

Acquired defects (see Section I.A.2)

Follicular ovarian dysgenesis (resistant ovary syndrome)
Complete androgen insensitivity syndrome (46,XY)
Pregnancy
Polycystic ovarian disease

C. Physical defects

Absence of vagina or uterus
Obstruction of uterine–vaginal outflow tract

CNS, central nervous system; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

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b. Bone age. It may be impossible to tell whether the hypogonadotropism is temporary or permanent until the hypothalamus and pituitary have had ample opportunity to mature. As a general rule, skeletal maturation (bone age) is an excellent indicator of physiologic maturity and is, therefore, reflective of hypothalamic-pituitary maturation, so a bone age of 12.5 or 13 years in girls should be accompanied by pubertal or adult patterns of gonadotropin secretion. Thus, if levels are prepubertal in a patient who is otherwise healthy and has a bone age > 11 years, and if gonadotropin levels are not elevated, one can assume that permanent gonadotropin deficiency is likely.

c. Partial pubertal development. In a patient who presents with some pubertal development with little or no progression, it can be difficult to differentiate delay of development from a partial or acquired hypogonadotropic state. Patients with a prolonged period between the onset of puberty and menarche may be hypogonadal. If the delay is a result of ovarian failure, gonadotropins will be elevated (assuming age and skeletal age at or greater than that when puberty usually occurs). Low gonadotropin levels, however, may be a result of delay in progression of normal maturation or an inability to secrete adequate amounts of gonadotropin. Menarche in females who subsequently have normal fertility can normally be delayed up to 5 years beyond the onset of puberty; however, such a delay is of concern and may herald abnormalities. Although it may be normal for menses to be irregular, infrequent, or anovulatory for a period of time after menarche, menses should progressively

become more regular during the first 2 years after menarche.

3. **Hypergonadotropism** indicates primary gonadal failure and, once clearly documented, is almost always permanent. Because of the frequency of **Turner syndrome**, it remains the **most common cause of gonadal failure in females**. Etiologies are listed in Table 29-4. FSH receptor gene mutations have been identified as a cause of absent breast development and primary amenorrhea, whereas LH receptor mutations among 46,XY individuals result in essentially female genitalia.
   a. **Turner syndrome and Noonan syndrome** (see Chapter 14).
4. The approach to patients with lack of menarche (see Table 29-4) is initially the same as that to patients with delayed onset or progression of puberty.
   a. **Differential diagnosis.** If progression of puberty has been inadequate or incomplete in terms of physical characteristics, both hypogonadism and factors that impede gonadal function are possible (see Table 29-4). If physical development appears to be complete, the factors listed in Table 29-4 should be considered.
   b. **Complete androgen insensitivity.** This syndrome results from lack of androgen effect (because of deficiency or defect of androgen receptor or postreceptor mechanisms), so patients are not virilized in utero and do not masculinize at puberty. These patients are phenotypically females despite the presence of a 46,XY karyotype and normal testicular function. They may present with the complaint of primary amenorrhea, although most are diagnosable in infancy or childhood because of inguinal–labial gonads or inguinal hernias. Because of androgen receptor defects and the resulting lack of feedback, pubertal-aged patients have normal to elevated gonadotropins and significantly **elevated androgen levels. Estrogen levels are somewhat elevated for genetic males, and their unopposed effect results in feminization**. Patients present as phenotypic postpubertal females with ample breast development and little or no sexual hair. Because of the normal effect of testicular-derived Müllerian-inhibiting hormone in utero, the uterus is not present, and therefore, no menses occur.

B. Evaluation

1. A blood sample to determine **gonadotropin** status is ordered at the initial visit, even if other laboratory workup is not done. A single serum sample is adequate to document or exclude a hypergonadotropic state.
2. **History** should review the following:
   a. Rates of weight and height gain (see Fig. 29-1).

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   b. Evidence of current or previous illness, including various systemic diseases, especially subtle gastrointestinal disease (Crohn disease) or undiagnosed or inadequately treated endocrinopathies (hypothyroidism, adrenal insufficiency, and diabetes insipidus).
   c. Previous therapy, including surgery, irradiation, and chemotherapy. Gonadotropin levels elevated above the normal range may occur shortly after chemotherapy among oncology patients, with subsequent recovery.
   d. Family or pubertal history.
   e. Sense of smell.
3. **Physical examination** should document pubertal development. One should search for **stigmata of Turner syndrome (see Chapter 14).**
4. **Laboratory workup**
   a. **General approach. Gonadotropin (LH and FSH) determinations** in a blood sample will give values in the low range (consistent with the prepubertal state, hypogonadotropism, or early puberty), in the hypergonadotropic range (clearly elevated above normal adult ranges) or within the pubertal range. (This finding suggests that early hormonal puberty has occurred without physical changes.) It is most unusual to find borderline elevated levels, but when this occurs, GnRH or GnRHa stimulation testing is indicated to clarify the result. A hypergonadotropic response is markedly greater than in normal individuals (see Fig. 29-2).
   b. **Low gonadotropins.** If gonadotropin levels are low and there is a history of unusual emotional stress, ongoing excessive physical exertion, inadequate nutrition, or findings suggestive of a systemic condition, the workup should be directed toward diagnosing and correcting the primary abnormality to resolve

the hypogonadotropic state.

i. **A skeletal age** determination (bone-age radiograph) may reflect hypothalamic-pituitary maturation. If the **bone age** is less than the normal age of pubertal onset **(10 to 11 years),** this indicates biologic immaturity so that it is not yet possible to determine whether hypogonadotropism is transient or permanent. If the bone age is at or near the age of onset of puberty and there is no concomitant abnormality that could account for hypogonadotropism, a limited workup can be done to try to differentiate the cause. A girl who has had a bone age beyond 13 years for several years and who continues to show low gonadotropin levels likely has permanent hypogonadotropism.

ii. **GnRH or GnRHa stimulation testing** is seldom helpful in differentiating an etiology of pubertal delay providing little more information than basal LH and FSH levels. Although complete lack of response of LH and FSH levels suggests a complete pituitary defect, this is rare except in those who have had hypophysectomy or other destruction of the pituitary gland. A clear incremental rise of LH and FSH indicates the ability of the pituitary to respond when stimulated (see Fig. 29-2), but such a response does not discriminate between a permanent hypothalamic problem versus a transient one. Nevertheless, a response clearly well within the pubertal range is more suggestive of potential for normalcy than a minimal rise.

iii. If the bone age is well into the usual pubertal years or if the discrepancy between bone age and chronologic age is large (e.g., bone age 12 years, chronologic age 16 years), low gonadotropin levels are due either to a permanent defect or to one of the situations described in Table 29-4. Assessment of other pituitary hormones (growth hormone, TSH, ACTH, prolactin, and vasopressin) should be considered.

c. **Elevated gonadotropins.** If gonadotropins are elevated, a **karyotype** should be done to **rule out Turner syndrome**. Gonadal dysgenesis can occur with subtle to no stigmata of Turner syndrome. A 46,XY karyotype may be present in patients with a female phenotype with **46,XY sex reversal,** including the syndrome of pure **gonadal dysgenesis**, the

complete androgen insensitivity syndromes, as well as patients with enzyme deficiencies in sex steroid synthesis (see Section II.B.4.c.iii).

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i. If there is a clear explanation of primary hypogonadism (surgical resection and tumor therapy), no further workup is indicated.

ii. To assess autoimmune disease, **antiovarian antibodies** are indicated.

iii. **Enzyme deficiencies** are unlikely to present with pubertal delay. Most will also affect adrenal steroidogenesis and may have previously presented with evidence of adrenal abnormality. Because they represent a form of gonadal failure, hypergonadotropism will be present. If an enzyme deficiency needs to be ruled out, excessive steroid intermediates can be documented. Enzyme deficiencies that block estrogen synthesis include:

a) **StAR deficiency** (rare, most unlikely to present with pubertal delay, and likely to present during infancy with adrenal failure; low levels of all intermediate metabolites; both 46,XX and 46,XY individuals have female phenotype).

b) **17-Hydroxylase deficiency** (excessive pregnenolone and progesterone; 46,XY patients have a female phenotype, whereas 46,XY patients have genital ambiguity).

c) **17,20-Lyase deficiency** (excessive 17-hydroxyprogesterone OHP, 17- hydroxypregnenolone, and progesterone). These two enzymatic conversions are controlled by a single gene and enzyme (P450c17), although, in some instances, two clinical syndromes may be distinct.

d) **17-KS reductase, 3β-hydroxysteroid dehydrogenase, and P450 aromatase deficiency** will result in lack of or inadequate pubertal development in a 46,XX individual with a female or mildly ambiguous genital phenotype.

5. **Additional assessment for lack of menarche**

a. **Pelvic examination** and ultrasonography can be done to detect vaginal abnormality, absence of uterus, or abnormal ovarian size.
b. Karyotype is indicated if the uterus is absent, to rule out androgen insensitivity syndrome.
c. If LH is high and FSH is normal or moderately elevated, rule out pregnancy and androgen insensitivity syndrome and consider the diagnoses of partial ovarian failure and polycystic ovarian disease.
d. Progesterone stimulation can be done if estrogen effect is judged to be adequate by vaginal smear or estradiol levels and if the uterus is documented to be present. Although this test is done less frequently than before the ready availability of ultrasound studies, it is still used by administration of medroxyprogesterone acetate, 10 mg PO daily for 10 days. Bleeding 3 to 10 days after administration of the drug indicates an estrogen-primed endometrium; therefore, gonadotropin stimulation has been adequate to stimulate estrogen, suggesting that amenorrhea is a consequence of failure of ovulation and corpus luteum formation. Conversely, lack of bleeding suggests either gonadotropin deficiency or an inadequately developed endometrium. The latter can be ruled out by administration of estrogen plus progesterone with subsequent bleeding.

C. Treatment

1. Hypogonadotropic conditions resulting from ongoing physical, emotional, or systemic conditions are generally helped dramatically with replacement therapy.
2. Sex steroid treatment of apparently normal individuals with delayed puberty (see Sections II.C.4 to II.C.8) may be considered for psychosocial or psychosexual reasons.
3. Most patients with **Turner syndrome** are significantly short; although the cause is not understood, it is related to the loss of the *SHOX* gene.
   a. Although most of these patients are not growth hormone deficient, treatment with growth hormone increases adult height in most patients.
   b. In pubertal-aged girls, a very–low-dose estrogen plus growth hormone may produce more linear growth and a more timely pubertal development.

4. Current therapy for permanent hypogonadism, whether due to hypogonadotropism or primary gonadal failure, is the same: administration of sex steroids to produce and maintain sexual development. (Obviously, to produce ovulation in patients with potentially functional ovaries, therapy differs.) Because of altered feedback dynamics, it is generally not appropriate to monitor adequacy of therapy p. 376p. 377of hypergonadotropic individuals by attempting to document suppression of gonadotropins into the normal range.
5. **Therapy** can begin with daily oral estrogen: premarin (0.3 mg daily) or estradiol transdermal systems. Initial therapy begins using the lowest oral dose or partial transdermal preparation. Diethylstilbestrol is contraindicated, and ethinyl estradiol is not available. This regimen can be given daily and continually, although cyclic therapy with the addition of a progestin should be begun within 2 to 3 years or when breakthrough bleeding becomes problematic (see Section II.C.6). After this point, an estrogen–progestin cyclic combination preparation may be used. Therapy should be started when judged to be appropriate based on social and psychological factors and projected adult height, and after other hormonal deficiencies have been addressed.
6. Replacement therapy for hypogonadism in any patient with a uterus should eventually involve **cyclic estrogen and progesterone administration,** although an initial **period of not more than 1 year of daily estrogen treatment is appropriate**. Cyclic therapy should be begun earlier if breakthrough uterine bleeding occurs during daily estrogen therapy. Unopposed estrogen followed by cyclic treatment mimics natural pubertal stimulation and may more rapidly stimulate physical pubertal development.
7. A feasible **cyclic regimen** once breakthrough bleeding occurs or after 2 to 3 years of therapy or once pubertal development is complete can include a variety of regimens, usually using birth control preparations (BCPs), based primarily on the desired frequency of menses. If monthly periods are desired, preparations, including triphasic BCPs, can be used. If four periods or fewer per year are chosen, continuous preparations, such as Seasonale, Loestrin, or Prempro, can be used, interrupting for a week to allow

withdrawal bleeding

8. Patients with potentially normal ovaries might respond to ovulation induction, and those with dysfunctional ovaries but a normal uterus are candidates for **in vitro fertilization.**

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30 Ambiguous Genitalia

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Although ambiguous genitalia in a newborn is usually not an impending medical emergency, the inability to ascertain gender and name the infant creates much distress and requires prompt attention. The assessment should be done as part of a multidisciplinary team involving the family. The goal of the discussions with the family is to provide them with an understanding of the physiology and embryology of genital development as well as all currently available outcome data of similar patients. Clinicians need a forthright approach that will minimize anxiety while rapidly defining the child's internal and external genital anatomy and elucidating the basis for the ambiguity. Sex assignment can then be made concordant with the multiple factors agreed to have the greatest probability for the child to have a well-adjusted productive life. The karyotype and molecular basis of the child's disorder of sexual differentiation are relevant to the diagnosis. However, sex assignment may not concur with the karyotype depending on the molecular basis of the disorder.

I. MECHANISMS OF DIFFERENTIATION AND DEVELOPMENT

A. Fertilization. In the usual situations, an XX karyotype is associated with a female phenotype, whereas an XY karyotype is associated with the male differentiation. However, infants with genital ambiguity demonstrate that the course of sexual differentiation and development is clearly influenced by factors apart from the genes located on the sex chromosomes. Defects can occur at the level of the chromosome (mosaicism such as XX/XY), within one or more genes mapped to the sex chromosomes or autosomes, or may reflect environmental factors. Sexual differentiation does not begin until the gonadal ridges differentiate. These tissues begin as undifferentiated paired proliferation of coelomic epithelium and mesenchyme. The structural changes into an early gonad begin in the fourth postfertilization week with the appearance of the so-called sex cords. Primordial germ cells (the cells destined to become ova or sperm) then migrate from the yolk sac along the dorsal mesentery into these gonadal ridges (6 weeks).

B. Gonadal differentiation

1. The embryonic events of gonadal differentiation proceed independently within each gonad. Thus, gonadal histology can differ between sides. Even within a single gonadal ridge, cells representing both primordial testicular and ovarian cells can develop. One example is ovotesticular disorder of sexual differentiation in which both ovarian and testicular differentiation occur. Gonadal histology can range from ovary or testis to ovotestis.
2. In the normal XY male, a specific gene on the short arm of the Y chromosome, *SRY* (sex-determining region on Y), is the molecular switch that directs differentiation of the indifferent gonad, the sex cords, and surrounding tissues into a testis. Evidence acquired from an XX mouse transgenic for the *Sry* gene indicated that the *SRY* gene is the only gene on the Y chromosome required for testis determination. Mutations in the *SRY* gene are associated with 46,XY male to female sex reversal.
3. The *SRY* gene has been identified among those with male differentiation of genitalia who lack a cytogenetically demonstrable Y chromosome. In such individuals with **46,XX testicular disorders of sexual differentiation**, the presence of the p. 378p. 379*SRY* gene can often be confirmed by molecular techniques. Typically, the *SRY* gene has been translocated to the pseudoautosomal region of the X chromosome.
4. Multiple genes have roles both upstream and downstream from *SRY*. In addition to *SRY*, this complex regulatory cascade of sex-linked and autosomal genes includes *DAX1*, *SOX9*, *SF1*, and *DHH*. The protein products of these genes function as transcription factors. In humans, duplication of the *DAX1* gene and mutations involving the *SRY*, *SOX9*, *SF1*, and *WT1* genes are associated with XY male to female sex reversal. Duplication of *SOX9* was identified in a 46,XX infant with penile/scrotal hypospadias and palpable gonads. Duplication of the *WNT4* gene is associated with XY sex reversal.
5. Genes upstream from *SRY* may be involved in early development of the gonads and the urinary tract. Steroidogenic factor-1 (SF1) encoded by *NR5A1* is essential for gonadal, adrenal, and pituitary development. WT1 is necessary for normal urogenital tract development. Mutations of *WT1* are associated with Denys-Drash

and Fraser syndromes. Deletions of chromosome 9p are associated with XY sex reversal. Although no deleterious mutations have been identified in *DMRT1* which is located at chromosome 9, it remains a candidate gene for sex determination because it is expressed in the developing testis and is highly conserved.

6. Mutations of *SOX9* are associated with XY sex reversal in females and campomelic dwarfism. However, *SOX9* mutations have been identified in the absence of campomelic dwarfism.
7. Loss-of-function mutations of DAX1 encoded by *NROB1* are associated with adrenal hypoplasia and hypogonadotropic hypogonadism. *NROB1* maps to the dosage-sensitive sex reversal locus on the X chromosome. Duplications of this locus are associated with XY females.
8. WNT4 is a signaling molecule; it normally upregulates DAX1 expression. Duplication of WNT4 is associated with 46,XY male to female sex reversal and impaired testicular differentiation.
9. As germ cells penetrate the somatic cell matrix of the differentiating gonad, another regulatory step can occur. If the karyotype of the germ cell is different from that of the gonad (i.e., an XX germ cell migrating into a developing XY testis), the germ cell will usually not survive and a "sterile" gonad will result. In this model, variants may develop, however, such as a **testis containing only XX sperm**.

C. Gonadal development and function

1. Testicular organogenesis is rapid, and by the ninth week **testosterone** and **anti-Müllerian hormone (AMH)** are being produced by Leydig and Sertoli cells, respectively. The first evidence of testicular differentiation is the appearance of primitive Sertoli cells at 6 to 7 weeks' gestation in the human fetal testis. Subsequently, the testicular cords develop. The cords are the precursors of the seminiferous tubules that will contain Sertoli and germ cells.
2. Ovarian organogenesis occurs more slowly; a recognizable structure might not be present until weeks 17 to 20. Contrary to prior beliefs, specific genes, that is, *RSPO1* and *WNT4*, modulate ovarian development. Following histologic differentiation, the ovary, unlike the testis, may lose its integrity and may become a **streak gonad** if viable meiotic germ cells are not present or are not forming normal follicles. The ovaries of girls with Turner

syndrome initially develop follicles that undergo premature degeneration/atresia, resulting in a streak gonad. Thus, one X chromosome is sufficient for ovarian differentiation, but two X chromosomes are required for maintenance of germ cells and adult ovarian function. Two phases of testicular descent are recognized. INSL3, secreted by Leydig cells, mediates the transabdominal phase, whereas testosterone influences the inguinoscrotal phase of testicular descent. The effects of INSL3 are mediated by its receptor, LGR8.

D. Internal genital duct development

1. The internal genital ducts develop from two different sets of paired mesodermal duct-like structures. Both sets develop alongside each gonadal ridge. Different control mechanisms govern the differentiation of these ducts. The mesonephric (Wolffian) ducts are present and located in close proximity to the gonadal ridges

p. 379p. 380by 4 weeks, and the paramesonephric (Müllerian) ducts develop at 5 weeks in a more lateral position. Testosterone secreted by the ipsilateral testicular Leydig cells stimulates the duct cells to develop into the Wolffian-derived structures: epididymis, ductus deferens, seminal vesicle, and ejaculatory duct. This organization is obvious by 9 weeks and may be complete by 14 weeks. In the absence of locally secreted testosterone, the mesonephric/Wolffian duct passively regresses. Thus, Wolffian structures undergo further differentiation only if located on the side with a functional testis. If only one testis is present, the Wolffian structures regress on the side of the absent testis.

2. The **Sertoli cells** in the functional testis secrete the glycoprotein, AMH that also acts locally and not on the contralateral side to cause degeneration of the paramesonephric duct. When a testis is not present or when there is a lack of production or action of AMH, the paramesonephric duct develops into a fallopian tube and a hemiuterus, which normally fuses later with the contralateral structure, and includes the upper third of the vagina. Failure of testicular AMH secretion or mutations of the *AMH* gene or the *AMH* receptor gene are associated with the persistent Müllerian duct syndrome. Ovarian dysgenesis or exposure to excessive androgens such as in virilizing congenital adrenal hyperplasia

(CAH) does not impair development of the Müllerian duct derivatives in an XX fetus. Ovaries are located in the normal pelvic position in virilized 46,XX fetuses with CAH.

E. External genital development. The final step in fetal sexual differentiation involves two complex embryonic mechanisms: the development of the excretory system, both urogenital and alimentary, and the development of those elements of the external genitalia directed toward reproductive function and whose appearance ordinarily dictates sex assignment.

1. At about 3 weeks' gestation, the cloacal membrane, which closes the hindgut, is already present. An unpaired genital tubercle develops anteriorly, whereas two pairs of genital folds develop laterally. The cloacal membrane then divides into urogenital and anal membranes (6 weeks), and finally into an anterior urogenital groove and a posterior anorectal canal (8 weeks). The genital folds divide into medial labiourethral folds (surrounding the urogenital groove) and lateral labioscrotal swellings. These steps all occur before the fetus begins true sexual differentiation. Thus, these early embryonic changes are common to both sexes. Congenital anomalies, such as imperforate anus, exstrophy of the cloaca, penoscrotal transposition (in which the genital tubercle is below the genital folds), and agenesis of the phallus, all occur during this time. These anomalies represent an early embryonic field defect rather than being associated with impaired gonadal development or inappropriate sex hormone milieu.
2. Sexual divergence of the external genitalia occurs after 8 weeks' gestation.

   In the normal male fetus, circulating testosterone of testicular origin reaches the genital tubercle, where it is converted locally to **dihydrotestosterone (DHT)** by the 5α-reductase enzyme (type 2). DHT, acting through the androgen receptor (AR), causes rapid elongation of the tubercle. The urogenital groove is also pulled forward, the parallel mucosa folds fuse, and a penile urethra forms by 12 weeks. The genital swellings move caudally and fuse to develop into the scrotum. The final glandular urethra (to the tip of the phallus) does not occur until 4 months' gestation, when an invagination of penile ectoderm reaches the formed lumen. This process might not be directly related to testosterone synthesis or action, or it might reflect subtle defects in testosterone secretion,

DHT action, or the presence of increased quantities of antiandrogenic steroids such as some synthetic forms of progesterone. Based upon rodent models, a fetal masculinization programming window (MPW) seems to occur between 8 and 14 weeks' gestation in humans. The MPW is hypothesized to be necessary to masculinize all components of the reproductive tract and impacts later complete development. One indicator of androgen action, as a marker of the MPW, is the anogenital distance (AGD). Diminished AGD is associated with disorders of sex development (DSD) and other disorders, such as azoospermia, hypospadias, and cryptorchidism. Although p. 380p. 381it has been suggested as a clinical assessment indicator in DSD, the usefulness of this measurement is unclear beyond evidence of diminished androgen action. **Reduced AGD is an indication of diminished testosterone** exposure during early fetal life, whereas an anogenital ratio (distance from anus to base of clitoris to distance from anus to posterior fourchette) >0.5 suggests virilization for a female.

3. In a female fetus in whom circulating testosterone levels are normally low, the external genitalia, formed during the first 8 weeks of embryologic development, do not manifest significant further differentiation. The genital tubercle remains to form the clitoris. Both prenatally and postnatally, the clitoris has the potential to enlarge when exposed to elevated androgen concentrations. The urethral folds are pulled anteriorly, form the hood over the clitoris, and extend posteriorly to remain as the unfused labia minora. The genital swellings do not migrate but enlarge to form the labia majora, and the urogenital groove remains open to form the vaginal vestibule. The relative position of the urethral orifice becomes fixed by about 14 weeks, and exposure to androgen thereafter can neither shift the urethral folds anteriorly nor fuse the labia. Therefore, the timing of these events helps to determine when prenatal androgen exposure occurred during gestation. Virilization after 14 weeks may cause clitoromegaly alone, whereas exposure prior to 14 weeks can cause varying degrees of clitoromegaly, scrotalization of the labia majora, labial

fusion, and obliteration of the vaginal vestibule.

II. DIFFERENTIAL DIAGNOSIS OF AMBIGUOUS GENITALIA

The differential diagnosis of genital ambiguity begins with a medical history followed by a careful physical examination of the infant with particular attention to the anatomy of the internal and external genitalia. Some disorders such as Smith-Lemli-Opitz are associated with multiple congenital anomalies. In addition to the physical examination (which may change over time and, therefore, requires reexamination), radiologic examinations such as contrast retrograde urethrography, ultrasound, fistulography, and, if indicated, cystoscopy with contrast instillation may be helpful. During the physical examination, the symmetry and extent of virilization is assessed. The primordial labioscrotal folds may have developed as labia majora, a fully fused scrotum, or varying degrees of labial–scrotal fusion. The phallus may appear as a clitoris typical of a newborn female, as a penis with the urethral meatus at the tip, or as either an overdeveloped clitoris or underdeveloped penis with a single or two openings on the perineum. The phallus may be markedly enlarged but curved ventrally (chordee).

Varying degrees of fusion of the labiourethral folds may be present. The opening may be on the perineum, along the underside of the shaft of the phallus, or with full fusion with the meatus opening at the tip of the glans. It is important to realize that the point of the opening of the meatus does not predict the probability of successful surgical correction to bring the urethra to the tip if the surgical aim is to construct a penis. It also does not necessarily correlate with the extent of development of the underlying tissues, referred to as a ventral triangular defect. While the extent of this defect may be proportional to the chordee, the extent of the corpus spongiosum fusion cannot be accurately determined without surgical exploration.

In addition, the evaluation should include the appropriate hormonal determinations and chromosomal studies. When available, identification of genetic mutations is helpful to confirm the diagnosis and for genetic counseling/predictions for future pregnancies. In some instances, stimulation or suppression tests may be indicated during the neonatal period to assess adrenal and/or testicular steroidogenesis. Exploratory laparoscopy, laparotomy, and gonadal biopsy are necessary in some cases to reach a definitive diagnosis. Androgen responsiveness evidenced by phallic growth during a trial of androgen therapy is indicated before

considering a male gender assignment. A schematic approach to the infant with ambiguous genitalia is shown in Figure 30-1, and hormonal aberrations are summarized in Table 30-1. Some key elements of the physical examination are further discussed below.

Assessment for the presence or absence of a palpable inguinal or labioscrotal gonad(s) is crucial because virilized females do not have a palpable gonad, and incompletely virilized males may have one or both gonads palpable. Some disorders p. 381p. 382of gonadal differentiation present with a single palpable gonad and asymmetry of the external genitalia; greater scrotalization of the labioscrotal folds is usually observed on the side of the palpable gonad.

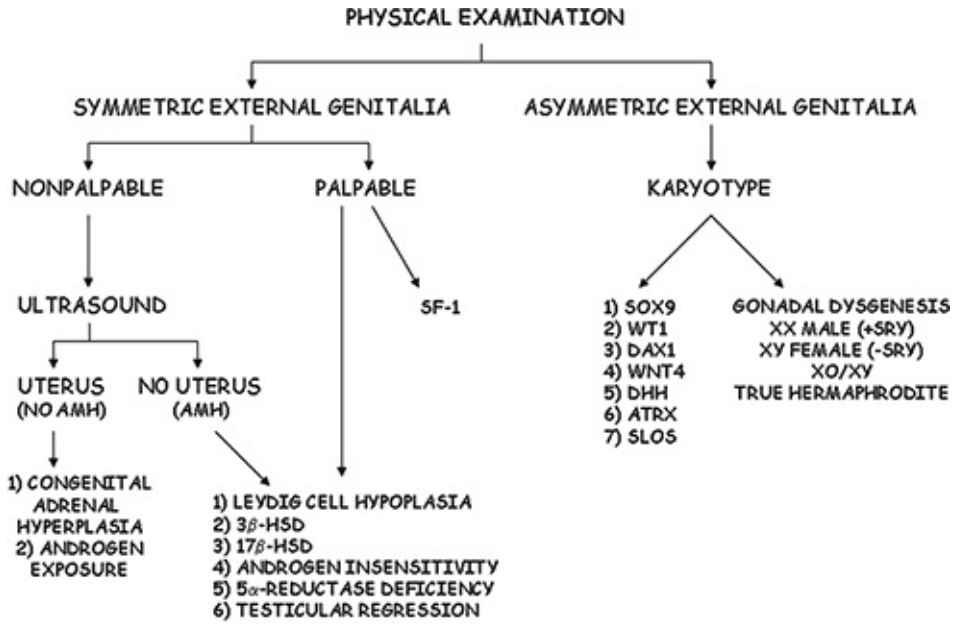

Figure 30-1. Schematic approach to the differential diagnosis of ambiguous genitalia in the infant. CAH, congenital adrenal hyperplasia; IVP, intravenous pyelogram; VCUG, voiding cystourethrogram. (From Lippe BM. Sexual differentiation and development. In: Hershman JM, ed. *Endocrine Pathophysiology: A Patient-Oriented Approach.* 2nd ed. Philadelphia: Lea & Febiger; 1988:118.)

A. No palpable gonads: suspect virilized female. If no gonads are palpable and an ultrasound shows the presence of a uterus, the most likely diagnosis is an XX female infant with virilizing CAH. Confirmatory tests include steroid hormone determinations and karyotype. Monitoring of electrolytes for hyponatremia and

hyperkalemia because of the possibility of salt loss must be done until mineralocorticoid deficiency is confirmed or excluded. Plasma renin levels are elevated and highly variable in the newborn, as are circulating adrenal steroid levels. The most common of the virilizing forms of CAH is 21-hydroxylase deficiency (with or without adrenal insufficiency and salt loss), which accounts for >95% of cases. Plasma 17α-hydroxyprogesterone (17-OHP) concentration after 48 hours or thereafter is a most valuable test. Typically, the 17-OHP value is >10 000 ng/dL. Genital development is normal in boys with 21-hydroxylase deficiency. 11β-Hydroxylase deficiency is a much less common (<5%) type of CAH and is associated with elevated 11-deoxycortisol concentrations (compound S). 3β-Hydroxysteroid dehydrogenase deficiency is a very rare (<1%) cause of virilizing CAH among 46,XX infants; this disorder of steroidogenesis is also associated with inadequate virilization in 46,XY infants. This disorder can be excluded by determining the dehydroepiandrosterone (DHEA) and 17-OH pregnenolone levels. A serum testosterone value should also be obtained to estimate conversion outside the adrenal cortex to this potent androgen; approximately 15% of androstenedione produced by the adrenal cortex is converted peripherally to testosterone. Other rare causes of prenatal virilization of a female fetus include maternal hyperandrogenism, P450 oxidoreductase deficiency, and aromatase deficiency. Maternal hyperandrogenism and placental aromatase deficiency are associated with virilization of the mother during the pregnancy. The genes coding 21-hydroxylase (*CYP21A2*), 11β-hydroxylase (*CYP11B1*), 3β-hydroxysteroid dehydrogenase (*HSD3B2*), P450 oxidoreductase (*POR*), and aromatase (*CYP19A1*) have been mapped and sequenced. Molecular p. 382p. 383genetic studies can be performed to characterize the molecular defect and verify the diagnosis. Subsequently, genetic testing can be performed in family members to enable more accurate genetic counseling of risks for recurrence.

TABLE 30-1 **Genetic and Hormonal Characteristics of Causes of Errors in Sexual Differentiation**

	Hormone

Disorder	Phenotype	findings	Genetic locus
Congenital lipoid CAH	46,XY sex reversal Adrenal insufficiency	↓ 17-PREG, 17-OHP, and cortisol	*StAR*
17*α*-Hydroxylase/17,20-lyase deficiency	46,XY sex reversal	↑ PREG, ↑ PROG, ↓ 17PREG, ↓ 17-OHP	*CYP17*
Smith-Lemli-Opitz syndrome	46,XY sex reversal polydactyly/syndactyly	↓ Cholesterol	*SLOS*
3*β*-Hydroxysteroid dehydrogenase deficiency	46,XY sex reversal Virilization of 46,XX fetus	↑ 17-PREG, ↓ 17-OHP	*HSD3B2*
21-Hydroxylase deficiency	Virilization of 46,XX fetus Adrenal insufficiency	↑ 17-OHP	*CYP21*
11*β*-Hydroxylase deficiency	Virilization of 46,XX fetus	↑ 11-Deoxycortisol	*CYP11B1*
5*α*-Reductase deficiency	Undervirilization of 46,XY fetus	↑ Testosterone, ↓ DHT	*SRD5A2*
Androgen insensitivity	Undervirilization of 46,XY fetus	↑ Testosterone, ↑ LH	*AR*
Leydig cell hypoplasia	Undervirilization of 46,XY fetus	↓ Testosterone, ↑ LH	*LHR*
17*β*-Hydroxysteroid dehydrogenase deficiency	Undervirilization of 46,XY fetus	↑ Androstenedione, ↓ testosterone	*HSD17B3*
Ambiguous genitalia	46,XY sex reversal Adrenal insufficiency	↓ Testosterone and LH	*SF1*
Ambiguous genitalia	46,XY sex reversal Hypogonadotropic hypogonadism	↓ Testosterone	*DAX1* duplication
Ambiguous genitalia and camptomelic dysplasia	46,XY sex reversal	↓ Testosterone	*SOX9*
Denys-Drash syndrome	46,XY sex reversal	↓ Testosterone	*WT1*
Fraser syndrome	46,XY sex reversal	↓ Testosterone	*WT1*
XY female	46,XY sex reversal	↓ Testosterone	*SRY* (loss-of-function mutation)
XX male	46,XX sex reversal	↓ or nl Testosterone	Translocation of *SRY* gene
X-linked *α*-thalassemia–mental retardation syndrome	46,XY sex reversal	↓ Testosterone	*ATRX*
Ambiguous genitalia and polyneuropathy	46,XY sex reversal	↓ Testosterone	*DHH*
Ambiguous genitalia	46,XY sex reversal	↓ Testosterone	Chromosome 9p deletion

Persistent Müllerian duct syndrome	46,XY with uterus or uterine remnants	(1) Low AMH (2) High AMH	(1) *AMH* (2) *AMHR2*

AMH, anti-Müllerian hormone; CAH, congenital adrenal hyperplasia; DHT, dihydrotestosterone; LH, luteinizing hormone; nl, normal; 17-OHP, 17-hydroxyprogesterone.

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B. Mineralocorticoid deficiency can lead to catastrophic salt loss. In the untreated patient with mineralocorticoid deficiency, adrenal insufficiency commonly occurs during the second week of life. Clinical features include hypotension, weight loss, vomiting, hyponatremia, and hyperkalemia. Once basal blood samples for electrolytes, steroid hormones, and renin measurements have been obtained, hydrocortisone and fludrocortisone acetate therapy can be initiated. If dehydration accompanied by severe hyperkalemia and hyponatremia occurs, intravenous (IV) fluid therapy can be instituted. Mineralocorticoid treatment with fludrocortisone acetate (Florinef Acetate), 0.1 to 0.4 mg daily, and glucocorticoid therapy at stress dosages of 25 to 50 mg hydrocortisone IV, intramuscularly (IM), or orally for 48 hours (depending on the degree of illness) should be initiated upon confirmation of diagnosis. Subsequently, the dosage should be gradually decreased to physiologic replacement for the neonatal period of 25 to 30 mg/m^2/day in the neonatal period, divided into 3 doses (at ~8-hour intervals). Within the subsequent months, the hydrocortisone dose can be decreased to 8 to 18 mg/m^2/day. Prednisone and dexamethasone can be considered as alternative glucocorticoid therapies. However, these synthetic steroids are extremely potent and may have deleterious effects on linear growth.

A greater mineralocorticoid dose for the neonate is typically required. During the first year of life, the dosage can usually be gradually decreased to 0.1 mg/day. Sodium polystyrene sulfonate (Kayexalate), 1 g/kg/dose, every 6 hours, may be needed to correct life-threatening hyperkalemia. After acute IV therapy, supplemental NaCl may be given orally (3 to 8 mEq/day) as needed to replenish Na stores and levels. Parents of affected children should learn when to administer stress doses and how to administer IM hydrocortisone (Solu-Cortef) for emergency situations. Patients with adrenal

insufficiency should wear Medic-Alert identification. All states and many countries have instituted newborn screening programs. These programs have decreased the morbidity and mortality secondary to undiagnosed 21-hydroxylase deficiency. The use of prenatal dexamethasone therapy to decrease virilization of affected female infants remains controversial.

C. If the diagnosis is not CAH and exposure to exogenous/maternal androgens has been excluded, **genitography** and **abdominal-pelvic ultrasound** can be helpful to visualize structures, including the upper vagina, cervix, and uterus, and the interrelationship of the urinary outflow tract and the vagina. Renal anomalies may be present in some undervirilized males and in some neonates with complex congenital anomalies. In the neonate, however, neither intra-abdominal testes nor ovaries are likely to be seen, so nonvisualization cannot verify the absence of a gonad. Because the adrenal glands are normally large prior to involution of the fetal zone during infancy, adrenal size estimations may not be helpful in the diagnosis of adrenal hyperplasia.

1. If the imaging studies, hormone determinations, and chromosomes fail to clarify the etiology of the genital ambiguity, **hormonal stimulation tests** with human chorionic gonadotropin (hCG) or adrenocorticotropic hormone (ACTH) may be useful before proceeding to surgical exploration and gonadal biopsy. In the immediate neonatal period, basal gonadotropin and sex steroid hormone concentrations may be sufficient, because of the intrinsic activity of the hypothalamic-pituitary-gonadal axis at this age. For those older than 3 to 4 months, stimulation testing may be helpful to:

a. Define a block in gonadal or adrenal hormone production by identifying precursor accumulation or product deficiency. For example, hCG stimulation may elicit increased androstenedione concentrations with low testosterone concentrations characteristic of 17β-hydroxysteroid dehydrogenase deficiency resulting from *HSD17B3* mutations.

b. Suggest the presence of a hormonally competent gonad that was not under maximum stimulation at the time the basal hormones were obtained.

c. The difficulty with stimulation tests is that precise protocols and defined normal responses have not been established for the

neonatal period and infancy. For p. 384p. 385example, protocols for hCG are similar to those employed in older children (e.g., 1 000 IU IM for 3 to 5 days, obtaining plasma steroids on day 4 or 6), with unclear criteria to judge a normal response. Similarly, ACTH, administered as cosyntropin (Cortrosyn), can be given (0.25 mg IV) with serum steroids obtained at 30 and/or 60 minutes. Results are then compared to the normal responses established for older children.

2. Mild virilization in the presence of a 46,XY karyotype suggests impaired testosterone secretion. The differential diagnosis includes dysgenetic testis, Denys-Drash syndrome, Fraser syndrome, testicular regression, or *DAX1* or *WNT4* gene duplications.

D. Asymmetry (gonad on one side only). Virilized external genitalia in 46,XX infants and undervirilized genitalia in 46,XY infants are generally symmetrical. When the genitalia are asymmetrical, with the labioscrotal folds being fuller on one side, particularly if a gonad is palpable on that side, mixed gonadal dysgenesis or ovotesticular disorder of sexual differentiation needs to be considered in the differential diagnosis. Normal ovaries do not usually herniate or descend into the lower labioscrotal fold. On the other hand, a testis or ovotestis with its associated gubernaculum can migrate from the pelvis and lodge anywhere along the normal path of testicular descent. The contralateral gonad may be a streak, ovary, dysgenetic testis, or another ovotestis. The phenotype of the persistent Müllerian duct syndrome also presents with asymmetry, although with an appearance more like a unilateral hernia. This may be either as "hernia uteri inguinalis"—the hernia sac containing a testis and Müllerian remnants—or as transverse testicular ectopia—the sac containing both testes. This situation generally presents with a hernia or cryptorchidism, not genital ambiguity even though there is asymmetry.

1. Proceed with genitogram and ultrasonography.
2. The chromosomal karyotype may show mosaicism, such as XX/XY, XX/XO, or XY/X0. However, up to 80% of **those diagnosed with ovotesticular DSD**, defined as the presence

of ovarian follicles and testicular tubules in the same patient (in either one or two gonads) have an XX karyotype.

3. Regardless of the karyotype, sex of rearing depends on clinical judgment that estimates the extent of in utero and neonatal central nervous system androgen exposure, potential for a functional testis or ovary, and whether the internal anatomy includes a reasonably developed uterus, as well as external genital anatomy. Surgical exploration to determine the full extent of the anatomy may provide insight into the underlying diagnosis. For example, patients with an ovotesticular disorder of sexual differentiation with one intact ovary and uterus have been fertile, and a female sex of rearing may be considered. Generally, the male ducts for sperm maturation and delivery are not fully formed, so such individuals cannot be expected to be fertile as males without assisted fertility techniques. Nevertheless, a male sex of rearing may be most appropriate for a patient with evidence of considerable androgen exposure before birth, particularly if there is considerable phallic development. Knowledge of the sex chromosome constitution remains relevant, but the knowledge of specific gene deletions/duplications provides critical information to help with decisions regarding gender of rearing. Thus, some with ovotesticular DSD with a XX karyotype may be best reared as males, whereas some XY patients with gonadal dysgenesis may best be reared as females.

E. Palpable gonads, with symmetrically or nonsymmetrical genitalia. In the presence of palpable testes, whether the genitalia are symmetrical or not, the most likely diagnosis is an undervirilized male due to defects in steroidogenesis, androgen sensitivity, or testicular dysgenesis. Rarely, ovotestes can descend into the scrotum. One rare cause of genital ambiguity in 46,XY infants is 3*β*-hydroxysteroid dehydrogenase deficiency resulting from mutations in the *HSD3B2* gene; affected infants are at risk for salt loss secondary to mineralocorticoid deficiency. Males with defects in testosterone synthesis can have a similar defect in the adrenal and exhibit salt loss (as discussed previously). Leydig cell hypoplasia is an autosomal recessive disorder secondary to mutations in the luteinizing hormone (LH) receptor p. 385p. 386(*LHCGR*) gene. Defects in testosterone biosynthesis are also autosomal recessive conditions.

Mutations in the *AR* gene mapped to the X chromosome cause androgen insensitivity; inheritance is X-linked. The most difficult condition to diagnose and treat is partial androgen insensitivity (PAIS). Inquiry regarding affected maternal relatives can be helpful.

1. Ultrasonography is indicated, because the varying degrees of Müllerian duct–derived development may be present, depending on the amount and timing of AMH secretion.
2. If microphallus alone is present, suspect congenital growth hormone deficiency, hypopituitarism, or a defect in testosterone synthesis or action. Males with hypopituitarism and microphallus often have hypoglycemia and should, therefore, be monitored closely. In addition, thyroid function should be evaluated to rule out central hypothyroidism. The hypothalamic-pituitary-adrenal axis should be evaluated to assess for ACTH deficiency. Elevated levels of LH, follicle-stimulating hormone, and testosterone in the neonatal period are consistent with PAIS but may not always be demonstrable. Testing must involve a trial of testosterone to demonstrate androgen responsiveness (penis growth). Assessment includes mutation analysis of the *AR* gene. It is important to realize that although over 200 AR mutations have been identified, not all genetic variants associated with defective receptor activity have been identified. Failure to identify a known mutation or polymorphism relating to a receptor defect does not exclude this diagnosis.
3. When anatomic malformations of the genitalia or rectum are present, the differential diagnoses include CHARGE syndrome, VATER syndrome, IMAGE syndrome, and penoscrotal transposition. These early defects in embryogenesis, involving the formation of the cloaca, anus, and other structures, are usually sporadic. The CHARGE syndrome includes *c*oloboma, *h*eart defect, *a*tresia choanae, *r*etarded growth and development, *g*enetic anomalies, *e*ar anomalies, and possibly hypopituitarism. The VATER syndrome often also includes *v*ertebral *a*nomalies, other bony anomalies, *t*racheo*e*sophageal fistula, and *r*enal problems. IMAGe syndrome is characterized by *i*ntrauterine growth retardation, *m*etaphyseal dysplasia, *a*drenal, *g*enital, hypoplasia (cryptorchidism, small penis) and hypercalciuria or hypercalcemia. Penoscrotal transposition can be isolated or associated with imperforate anus.

III. MANAGEMENT OF THE CHILD WITH AMBIGUOUS GENITALIA

Once a diagnosis has been made and a sex assigned, the management of the child and family includes the following approaches.

A. Consideration of genital surgery

1. A multidisciplinary team, involving an endocrinologist, urologist/pediatric surgeon, and psychologists, together with genetic, gynecologic, and social work representatives, is recommended to evaluate the infant and educate the parents regarding the likely diagnosis, current treatment options, and available outcome information. Such conversations are essential for the overall assessment and decision-making regarding therapies, particularly surgery. It is the right and responsibility of the parents to make care decisions, after thorough communication with experienced health care workers.
2. In the female, if clitoromegaly is severe, clitoroplasty may be considered. Importantly, parents need to be informed that there is considerable controversy concerning such surgery during infancy or early childhood. Arguments for early vaginal surgery include better outcome for those with a high urethral-vaginal (urogenital sinus) confluence because tissues in infancy heal more readily and the distance to the perineum is shorter. Some individuals, including those in patient advocacy groups, suggest that any such genital surgery be deferred until the child becomes mature enough to make his or her own decisions. However, this argument provides no guidance to determine when an individual is at the point to make this decision and also assumes that growing up with atypical genitalia does not impact gender development. Further, if the position of the urethra is high, surgery may be indicated to provide urinary outflow to minimize the risks p. 386p. 387of recurrent urinary tract infections. When there is agreement that surgery is indicated, the goal for the age of surgery has traditionally been prior to a time when the child herself would recognize the ambiguity. It is generally agreed that the use of vaginal dilators has no place during childhood.
3. In the male, penis construction is generally a staged procedure, depending on the degree of hypospadias or chordee. The Prader stage based upon the external fusion of the urethralabial folds (location of the external meatus) does not correlate with the

development of tissues including the corpus spongiosum, and hence surgical possibilities cannot be completely discussed until exploratory surgery can be done to assess the "ventral urethral triangle." This impacts the decision of parents in deciding upon surgery. Issues to be discussed are the unpredictability of outcome, the likelihood of multiple surgeries, the importance of being able to stand to urinate dressed or undressed, and risk of outcome that may not be considered satisfactory. If testes are absent, scrotal implants may be considered. Generally, because it is usually not a concern for the prepubertal boy, and because there is greater risk of complications with multiple procedures implanting increasing-sized prostheses, most opt for a single implant procedure, with adult-size prostheses placed in adolescence after scrotal maturity has begun.

B. Mechanisms for multidisciplinary care of the child and family

1. Medical as well as surgical management involves a plan for long-term management. This plan should be outlined with the parents in conjunction with educational sessions. The initial evaluation and conversation with the parents about their infant significantly impacts upon their long-term perspective for their child and their adherence with medical recommendations.
2. When conditions are inherited as autosomal recessive or X-linked traits, genetic counseling is indicated. In addition, the heterogeneity of clinical expression of some disorders (especially those of androgen action) might mandate examination or testing (or both) of family members.
3. The psychological impact of a disorder resulting in ambiguity, as well as a clinical condition requiring long-term medication or multiple surgical procedures, is significant for the family (and later for the child). The medical team needs to be aware of cultural, social, and parental concerns to ensure positive outcomes for these infants. Thus, initial counseling with subsequent reassessment of the need for further counseling is highly recommended. Most of the initial education regarding the diagnosis was provided to the parents when the patient was an infant. As the child ages, the child needs to be educated as well. Ideally, the parents should provide information to the child. However, it is important to recognize that some parents have difficulty sharing this information. In this

instance, the physician, parents, and patients can discuss the child's medical diagnosis and care.

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SECTION 5

Mineral Disorders

31

Disorders of Calciotropic Hormones in Adults

Sarah Nadeem, Vinita Singh, and Pauline M. Camacho

I. CALCIOTROPIC REGULATORY HORMONES AND FACTORS

Calcium and phosphorus homeostasis may be modulated in large part through three hormones that exert actions at the intestine, kidney, and bone: parathyroid hormone, vitamin D, and calcitonin, although the role of calcitonin in man remains less certain. Other calciotropic factors have been identified through their presence in several pathologic states and may have a role in modulating divalent ion metabolism under physiologic conditions. A partial list of these includes magnesium; parathyroid hormone–related peptide (PTHrP); various cytokines and growth factors such as interleukin (IL) 1, 2, and 6; transforming growth factors α and β; the superfamily of tumor necrosis factors, including RANK, RANK ligand (RANKL), and osteoprotegerin; platelet-derived growth factor; and the family of insulin-like growth factors and related binding proteins.

A. Parathyroid hormone

1. **Modulating factors.** Human PTH is an 84-amino-acid polypeptide **(intact PTH 1-84)** secreted by the parathyroid glands which is acutely modulated by by the level of ionized calcium perfusing the glands. PTH secretion is inversely related to the extracellular concentration of calcium. The level of calcium is "sensed" by a G-protein–coupled receptor in the cell surface

(calcium-sensing receptor [CSR]). Calcium ion acts as an agonist to the CSR. A rise in extracellular calcium concentration activates the CSR, which, through a series of intracellular events, suppresses the secretion of PTH. Long-term stimulation can suppress parathyroid cell proliferation. Serum calcium levels modulate transcription of the *PTH* gene. Extracellular and tissue levels of magnesium can also modulate PTH secretion, with both high levels and low levels or tissue depletion suppressing secretion. Calcitriol **(1,25-dihydroxycholecalciferol [1,25(OH)$_2$D$_3$]),** but not its precursor, 25-OHD$_3$, has been shown to modulate transcription activity of the *PTH* gene and production of the prohormone form of PTH. Finally, although serum phosphorus has been thought to have no direct effect on PTH secretion, studies have suggested that high levels of phosphate ion stimulate PTH synthesis independent of effects of the ion on 1,25(OH)$_2$D$_3$ production. Although the classic target organs for PTH are bone and kidneys, receptors for the hormone have been identified in a variety of other tissues, a fact that should be kept in mind when considering other possible actions of PTH.

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2. **Structure.** The *PTH* gene resides on chromosome 11 and codes for a precursor polypeptide, prepro-PTH, which undergoes sequential cleavage to form the mature secreted form of the hormone (PTH 1-84). PTH 1-84 is also metabolized in the parathyroid glands and at extracellular sites (e.g., liver, kidney, bone) forming **carboxy-terminal (C-terminal)** and **amino-terminal (N-terminal) fragments**. Both PTH 1-84 and the N-terminal fragment (containing at least the first 32 amino acids) are biologically active. Some studies in vitro have also demonstrated selective biologic activity for C-terminal peptides, although the physiologic significance of these observations remains to be established. C-terminal fragments are disposed off by glomerular filtration and subsequent degradation by the kidney. Under conditions of reduced renal function, disappearance of the C-terminal fragment is prolonged. Reduction of renal function has less effect on plasma clearance of the N-terminal fragment, which is filtered by the kidney and removed by peritubular uptake and

metabolism at sites of action. Radioimmunoassays have been developed to measure PTH 1-84 and both C-terminal and N-terminal fragments. Assays for PTH 1-84 are quite useful because the levels are not affected by underlying renal insufficiency. It has been previously demonstrated that the most used commercial intact PTH assay (Nichols Institute intact PTH) also measures nonintact hormone fragments.

3. **Action.** PTH acts at the bone to modulate osteoblastic activity directly and osteoclastic activity indirectly through coupled bone remodeling activity. Only the osteoblast has receptors for PTH. At the kidney, PTH modulates transtubular transport of phosphorus, calcium, bicarbonate, and magnesium ions. The major effect of PTH on the intestinal transport of calcium is indirect, for example, through its regulatory function on the formation of calcitriol from its precursor, 25-hydroxycholecalciferol [25(OH)D].

B. Vitamin D

1. Vitamins D_2 and D_3

a. Vitamin D is a general term that has been used to refer to the concerted activity of several different metabolites of cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). The metabolites are sterols whose production occurs in several different organs. Vitamin D_3 is synthesized in the epidermis, whereas vitamin D_2 comes from plants and yeasts and has been synthesized to fortify various foods and vitamin products. In general, **the biologic activity of vitamin D_2 and its metabolites is equal to that of vitamin D_3**. For purposes of diagnostic testing, separate measurements of vitamins D_3 and D_2 are preferred.

b. Vitamin D_3 is a **prohormone** produced in the epidermis from conversion of **7-dehydrocholesterol (7-DHC; provitamin D_3)** to **previtamin D_3,** reactions requiring absorption of ultraviolet radiation and thermally induced isomerization. It (vitamin D_3 + vitamin D_2) circulates in small amounts (1 to 2 ng/mL) bound to a single **vitamin D–binding protein**, which binds and transports all vitamin D sterols. A number of factors can influence the production of vitamin D_3 in the skin, including melanin pigmentation, age, season, and geographic

latitude. Because aging reduces epidermal levels of 7-DHC, inadequate production of vitamin D_3 contributes to depletion, particularly in elderly persons during the winter months. Prolonged use of sunscreens can contribute to development of vitamin D_3 deficiency. In contrast, vitamin D intoxication is not known to occur with excessive sun exposure in otherwise healthy individuals. Low circulating levels are also seen in the obese individuals. Obesity-associated vitamin D insufficiency is attributed to multiple factors.

2. **Calcidiol.** Vitamin D is metabolized in the liver by a **cytochrome P450 hydroxylase** to form 25(OH)D **(calcidiol)**. **Quantitatively, it is the major circulating vitamin D metabolite.** Clinically and diagnostically, measurement of plasma levels of 25(OH)D is used to indicate the "vitamin D status" of an individual (delineation of vitamin sufficiency, depletion, or intoxication) with the latter being attributable to excessive administration of vitamin D_2/D_3. Normal levels are now thought to range from 30 to 50 ng/mL. The metabolite is approximately p. 389p. 3901 in 10 to 1 in 100 as active as $1,25(OH)_2D$ (**calcitriol**). Synthetic $25(OH)D_3$ is available for clinical use in a 20-μg dose.
3. **Calcitriol.** Under physiologic conditions, 25(OH)D undergoes a second hydroxylation in the kidney to either $1,25(OH)_2D$ or $24,25(OH)_2D$, the former considered to be the hormonally active form of vitamin D.
   - **a.** A possible physiologic function for **$24,25(OH)_2D$** in humans is controversial. Its formation has also been regarded as a disposal pathway. It circulates at levels 100 times greater than that of calcitriol.
   - **b.** Enzymatic formation of calcitriol **25(OH)-1α-hydroxylase** is very tightly regulated, involving factors such as levels of PTH, dietary intake, extracellular concentrations of calcium and phosphorus, the level of calcitriol itself, and possibly (directly or indirectly) other hormones, including calcitonin, estrogen, insulin, and growth hormone. Calcitriol secretion is modulated

by PTH and extracellular and intracellular levels of phosphorus, calcium, and magnesium. Hypophosphatemia, hypocalcemia, and elevated levels of PTH stimulate secretion. In addition to the kidney, other tissues produce calcitriol under pathologic conditions. During pregnancy, the placenta can also produce the hormone.

c. Calcitriol is recognized as the most active natural metabolite stimulating active intestinal transport of calcium and phosphorus. In bone, calcitriol promotes formation of osteoclasts from stem cells, although mature **osteoclasts lack vitamin D** receptors. In contrast, mature **osteoblasts possess vitamin D** receptors and respond to calcitriol by producing a number of cytokines and other humoral factors. The latter then can modulate osteoclastic activity. Calcitriol promotes bone mineralization by maintaining extracellular divalent ion concentrations in a physiologic range that allows deposition of calcium hydroxyapatite in osteoid.

i. Hypercalcemia, the hallmark of vitamin D intoxication, may only occur if circulating 25(OH)D levels are consistently above 375 to 500 nmol/L.

ii. The Institute of Medicine report recommended that the tolerable UL for vitamin D should be 1 000 IU/day for children 0 to 6 m, 1 500 IU/day for 6 months to 1 year, 2 500 IU/day children 1 to 3 years, and 3 000 IU/day for children 4 to 8 years. For over 9 years and for all adults, they recommend the UL at 4 000 IU/day. Endo Society Guidelines state that a UL of 10 000 IU/day of vitamin D for adults is reasonable.

4. **Vitamin D receptors.** High-affinity nuclear receptors for calcitriol have been identified in a large number of target tissues for vitamin D. These include tissues other than intestine, bone, and kidney. Receptors have been identified in the pancreas, skeletal muscle, vascular smooth muscle, epidermal keratinocytes, hematopoietic cellular elements, and lymphocytes, as well as in other cells of the immune system. This indicates that vitamin D sterols have cellular functions other than regulation of extracellular divalent ion concentrations.

C. Calcitonin

1. **Action.** Calcitonin is a 32-amino-acid peptide produced primarily

by **parafollicular C cells** of the thyroid gland. Other neuroendocrine cells also have the capacity to produce calcitonin. **Like PTH, cellular secretion of calcitonin is modulated by a CSR**. However, secretion by the thyroid C cells is stimulated by a rise in extracellular calcium and inhibited by a fall in calcium. In addition, calcitonin secretion may also be modulated by several gastrointestinal hormones, including **gastrin**.

a. Calcitonin reduces bone resorption by inhibiting osteoclastic activity.

b. At the kidney, calcitonin reduces tubular reabsorption of both calcium and phosphorus, producing a modest increase in excretion of both ions. The former may contribute to the hypocalcemic effect of pharmacologic doses of calcitonin.

c. A homeostatic function of calcitonin may be to buffer calcium absorbed through the intestine. The net effect of the stimulation of calcitonin secretion (or exogenous administration) is a lowering of serum levels of both calcium and phosphorus.

d. In women, **estrogen** may also play a role in maintaining secretory capacity of calcitonin. There is some evidence that in estrogen-deficient states (natural p. 390p. 391or artificial menopause), the calcitonin level is decreased, thereby affecting the accelerated menopausal bone loss.

2. **Clinical application.** Calcitonin is the major tumor marker for **medullary carcinoma of the thyroid gland**. Basal, as well as pentagastrin- and calcium-stimulated calcitonin secretion, is utilized to assess tumor activity.

3. **Calcitonin gene–related peptide** is a 37-amino-acid peptide that is produced by alternative expression of the calcitonin gene. Secreted by neuroendocrine cells, it acts as a neurotransmitter and has vasodilatory action.

D. PTHrP (see Chapter 34)

1. PTHrP was originally discovered as a circulating factor responsible for the development of hypercalcemia in patients with various malignant disorders (humoral hypercalcemia of malignancy [HHCM]). Elevated circulating levels of PTHrP have been demonstrated in 50% to 80% of patients with malignancy-associated hypercalcemia. PTHrP is a much larger molecule than PTH and is synthesized in three different polypeptide isoforms.

2. **Action.** Both PTH and PTHrP have structural homology at only 8 of the first 13 amino acids of the amino terminus, which explains the similarity in some of their biologic activities. Both PTH and N-terminal fragments of PTH bind with high affinity to a common receptor **(PTH/PTHrP receptor)** and produce common physiologic actions. A unique cell receptor for PTHrP has not been identified, although specific receptors for some of its fragments apparently exist.

   Under normal physiologic circumstances, PTHrP probably circulates in much lower levels than PTH, although with present assays it is **not measurable in normal individuals**. A major role in the maintenance of normal divalent ion homeostasis has not been demonstrated. However, a large body of evidence indicates that **PTHrP** has important physiologic functions in growth regulation in developing fetal and adult tissues. These are local (autocrine and paracrine actions) rather than systemic actions of the hormone or its peptide fragments. PTHrP has been demonstrated in numerous tissues. With respect to the breast, PTHrP appears to have roles both in morphogenesis and in lactation. High concentrations of PTHrP have been shown in human milk. Other observations suggest that PTHrP functions in utero to modulate mineral homeostasis across the placenta and in the developing fetus. **Elevated levels of PTHrP** may be one cause of **hypercalcemia of infancy**.

E. Fibroblast growth factor-23. Fibroblast growth factor-23 (FGF23) is a systemic factor which in recent years has been found to be an important regulator of the serum phosphorus concentration and a factor in the pathogenesis of both hypophosphatemic and hyperphosphatemic disorders. The *FGF23* gene produces a 251-amino-acid peptide with a 24-amino-acid signal peptide. The protein appears to be produced primarily in bone and, unlike other members of the FGF family, it **functions as a hormone** rather than a local factor. **Elevations of serum FGF23 lower the serum phosphorus concentration and serum 1,25(OH)D_2.** FGF23 appears to be the causative factor in a number of hypophosphatemic disorders, including **autosomal dominant hypophosphatemic rickets/osteomalacia, tumor-induced rickets/osteomalacia, X-linked hypophosphatemic rickets/osteomalacia, and**

autosomal recessive hypophosphatemic rickets/osteomalacia. Familial hyperphosphatemic tumoral calcinosis is associated with low levels of full-length FGF23 in the circulation, further evidence for the importance of the protein in phosphorus homeostasis.

II. DISORDERS ASSOCIATED WITH HYPERCALCEMIA

A. Clinical features of hypercalcemia.

Gradually developing severe hypercalcemia in a younger individual may be surprisingly well tolerated with minimal symptoms, whereas mild-to-moderate hypercalcemia developing acutely may be associated with severe symptoms. Elderly patients are frequently sensitive to mild elevations in serum calcium. Most symptoms reflect disturbances in the renal, gastrointestinal, cardiovascular, neuromuscular, and central nervous systems (CNS).

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1. **Central nervous system.** Symptoms referable to hypercalcemia-induced disturbances in the neuromuscular system and CNS include weakness, fatigue, lassitude, anorexia, depression, and confusion, and, in severe cases, stupor and coma. Impairment in cognitive function is common, particularly in the elderly, even in cases of mild elevation in serum calcium. Agitated behavior, including frank psychosis, can occur with serum calcium levels >14 to 15 mg/dL.
2. **Cardiovascular system.** Possible disturbances in the cardiovascular system include hypertension, bradycardia, nonspecific cardiac arrhythmias (shortened QT interval on the electrocardiogram), and increased sensitivity to digitalis glycosides. If intravascular volume is not maintained, hypotension may occur.
3. **Renal.** Alterations in renal function include impaired urine-concentrating capacity, polyuria (with consequent polydipsia), reduced glomerular filtration rate (GFR), nephrocalcinosis, and nephrolithiasis. Depending on the primary disorder, urinary calcium excretion can vary from low to markedly elevated. Nephrocalcinosis and/or nephrolithiasis can occur particularly in conditions associated with chronic hypercalcemia.
4. **Gastrointestinal.** Gastrointestinal disturbances range from

gastroesopheal reflux with or without the presence of peptic ulcer disease, nausea, vomiting, and anorexia to constipation. **Acute pancreatitis** is an uncommon but serious presenting condition of **hypercalcemia**.

B. Causes of hypercalcemia. A differential diagnosis for hypercalcemia includes an extensive group of disorders (Table 31-1). A thorough medical history and a few readily available diagnostic tests usually can reduce the list of possible causes. The most common disorders include primary hyperparathyroidism (PHPT), malignancy, granulomatous diseases, and medications. A useful approach is to classify disorders according to the altered physiologic condition responsible for the development of hypercalcemia: **(a)** increased release of calcium from bone (increased resorption); **(b)** increased intestinal absorption of calcium; **(c)** a combination of increased intestinal calcium absorption and bone resorption; and **(d)** decreased urinary excretion of calcium.

In a few conditions, the mechanism of hypercalcemia remains poorly characterized.

1. **Primary hyperparathyroidism.** PHPT is the most common cause of hypercalcemia in an unselected clinical setting. Both sporadic and familial forms of the disorder occur, the latter being very uncommon to rare, with autosomal dominant inheritance demonstrated in most cases. Solitary **parathyroid adenomas**, single or multiple, are found in 80% to 85% of cases, and two parathyroid adenomas are found in 1% to 2% of patients. **Parathyroid hyperplasia** involving all glands occurs in 15% to 20% of patients. **Parathyroid carcinoma** is rare, occurring in <1% of cases. Benign **parathyroid cysts** are rarely associated with hypercalcemia, although the high levels of PTH can be demonstrated in aspirated cyst fluid.

   Hereditary forms of PHPT occur as both isolated parathyroid disorders or in association with other genetically determined conditions. **Multiple endocrine neoplasia type 1 (MEN1/Wermer syndrome)** is a distinct disorder in which PHPT is the most common feature (occurring in >95% of cases), but in which concomitant enteropancreatic and pituitary neoplasms may also occur with high frequency (frequency varying among different kindreds). The most common pancreatic lesions are **gastrin-producing tumor (Zollinger-Ellison syndrome)**

and **insulin-producing tumor.** The most commonly encountered pituitary tumor is **prolactinoma.** A variety of other substances may be produced by these respective tumors **(**pancreas —**glucagon, vasoactive intestinal polypeptide, pancreatic polypeptide;** pituitary—**growth hormone, adrenocorticotropic hormone)**, but these associated syndromes occur less commonly. **Adrenal hyperplasia** and **thyroid adenomas** have also been described in some kindreds. The development of MEN1 has been linked to the expression of an inactivating mutation of a tumor-suppressor gene **(*Menin/MEN1* gene)** that is localized to **chromosome 11q13**. The clinical expression of PHPT in MEN1 is similar to that of sporadic PHPT, but it tends to occur at younger ages and with equal frequency in both sexes. Although solitary parathyroid adenomas have been described in MEN1, it is usually characterized by the presence of multiglandular parathyroid hyperplasia. Parathyroid carcinoma has been reported but is rare in MEN1.

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TABLE 31-1 Classification of Causes of Hypercalcemia According to Pathogenesis

Increased Release of Calcium from Bone
Primary hyperparathyroidism
Exogenous PTH therapy
Malignancy
Humoral hypercalcemia of malignancy (tumor production of PTHrP)
Osteolytic bone metastases
Tumor-associated ectopic cytokine production
Ectopic tumor-produced PTH
Immobilization
Thyrotoxicosis
Vitamin A intoxication
Reset Parathyroid Calcium Sensor Receptor
Familial hypocalciuric hypercalcemia
Lithium
Increased Intestinal Absorption of Calcium
Autonomous hyperparathyroidism of diverse etiologies
Vitamin D intoxication
Chronic granulomatous disease [extrarenal $1,25(OH)_2D_3$ formation]

Malignancy [extrarenal $1,25(OH)_2D_3$ formation]	
Milk-alkali syndrome	
Decreased Renal Calcium Excretion	
Familial hypocalciuric hypercalcemia	
Acute renal failure	
Milk–alkali syndrome	
Decreased Uptake of Calcium by Bone	
Aluminum toxicity	
Pseudohypercalcemia	
Hyperalbuminemia	
Macroglobulinemia of Waldenström	
Myeloma	
Hyperlipidemia	
Miscellaneous Causes or Uncertain Pathogenesis	
Adrenal Insufficiency	Thiazide Diuretics
Pheochromocytoma	Theophylline, aminophylline
VIP-producing pancreatic tumors (VIPoma)	Estrogens and antiestrogens
Parenteral hyperalimentation	Tamoxifen
Hemodialysis (high-Ca dialycate)	Androgens
	Growth hormone

PTH, parathyroid hormone; PTHrP, parathyroid hormone–related peptide; VIP, vasoactive intestinal polypeptide.

Multiple endocrine neoplasia type 2a (MEN2a/Sipple syndrome) is a distinct disorder characterized by the expression of **medullary carcinoma of the thyroid** (~100% of cases), bilateral **pheochromocytomas** (up to 50% of cases), and parathyroid hyperplasia (50% to 70% of cases). Clinical PHPT tends to be mild in MEN2. The syndrome is caused by an **activating mutation of the RET proto-oncogene on chromosome 10**. Commercial genetic tests are available for identification of individuals at risk for both MEN1 and MEN2a.

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Other familial syndromes associated with PHPT include **hyperparathyroidism–jaw tumor syndrome (HJTS)** and **familial isolated PHPT**. HJTS is an autosomal dominant

disorder characterized by early-onset (childhood to adolescence), often severe, PHPT. Recurrent adenoma and parathyroid carcinoma have been described. The bone lesions associated with HJTS occur as punched-out cystic lesions in the mandible and maxilla, ranging from small asymptomatic cysts to large disfiguring masses. They differ from the classic "brown tumors" of PHPT in that they lack osteoclasts. Various types of renal tumors, including Wilms tumor and hamartomas, have been described in different kindreds. Mutations in the tumor-suppressor protein **parafibromin** are responsible for HJTS as well as some kindreds with familial isolated PHPT and parathyroid cancer.

a. Pathophysiology of PHPT. In individuals with parathyroid adenomas, the set point for calcium-induced suppression of PTH secretion is altered or "shifted" so that the level of hormone secreted is inappropriately increased for the level of calcium (e.g., a loss of feedback control). The calcium set point for PTH secretion (effected by the CSR) is an ionized calcium level of 4 mg/dL (1 mmol/L). In PHPT resulting from hyperplasia of the parathyroids, the calcium set point is normal, but the number of PTH secreting cells is increased. Activation of *PTH* gene expression also promotes cell growth. Separate studies have shown increased levels of *PRAD1* in up to 20% of tumors. The *MEN1* tumor-suppressor gene has also been identified in some sporadic adenomas.

With excess PTH, bone remodeling is increased, and there is increased release of calcium, contributing to the generation of hypercalcemia. At the kidney, the tubular threshold for phosphate reabsorption is lowered, augmenting phosphaturia and contributing to the development of hypophosphatemia. Tubular reabsorption of calcium is increased, but the net effect on urinary excretion of calcium is balanced by the increased filtered load of calcium as a function of the degree of hypercalcemia. Both excess PTH and hypophosphatemia stimulate calcitriol production and augmentation of intestinal absorption of calcium. Hypercalciuria and augmented intestinal absorption of calcium are present in 40% and 60% of patients, respectively.

b. Clinical features of PHPT (Table 31-2)

i. The disorder occurs at all ages, with a peak incidence

between 60 and 70 years of age. Currently, >50% of diagnosed patients are asymptomatic, with hypercalcemia discovered fortuitously.

ii. Severe metabolic bone disease **(osteitis fibrosa cystica)**, with development of bone cysts, brown tumors, and marrow space fibrosis, is now uncommon in PHPT. Severe skeletal disease is more likely to be found in patients with underlying renal insufficiency or familial disorders, such as HJTS. Regardless of the severity of the bone disorder, bone biopsy shows qualitative histologic features characteristic of PHPT in most cases. **Osteopenia** is now the most commonly observed skeletal abnormality in PHPT, **present in approximately 30% of cases**, depending on the method of assessment. Dual-energy x-ray absorptiometry (DXA) is very informative as a marker of cortical disease, so the with measurement of the distal 1/3 radius, a cortical site, in all patients with PHPT is extremely helpful. Other modalities, such as vertebral fracture assessment and trabecular bone score by DXA, and high-resolution peripheral quantitative computed tomography (CT) are emerging as important tools to help evaluate the trabecular compartment, particularly in many patients with asymptomatic PHPT. There is also evidence that **fracture rates at the forearm, hip, and spine are increased**.

iii. **Calcium nephrolithiasis** or **nephrocalcinosis** is present in 40% to 50% of patients with symptomatic PHPT. In contrast, <5% of calcium stone formers have PHPT. Renal stone disease has a reported peak incidence in the third and fourth decades.

iv. **Hypertension** has been reported in **30% to 50% of patients with PHPT**. It remains unclear whether this differs from the prevalence in the general p. 394p. 395population when corrected for age, sex, and race. It is also not known whether the incidence of hypertension in PHPT is greater than in other causes of hypercalcemia. **Acute elevation in serum calcium levels is**

associated with a rise in blood pressure in normal individuals.

TABLE 31-2 Spectrum of Clinical Features of Hyperparathyroidism According to Organ Systems

Central Nervous System
Fatigue, lassitude
Depression
Memory impairment
Dementia
Psychosis
Coma

Ocular
Cataracts
Band keratopathy

Gastrointestinal
Peptic ulcer disease
GERD, cholelithiasis
Pancreatitis
Constipation

Skeletal
Osteopenia
Osteoporosis
Fractures
Bone cysts
Brown tumors
Marrow fibrosis
Osteosclerosis

Neuromuscular and Articular
Myopathy
Gout
Pseudogout
Chondrocalcinosis
Erosive arthritis

Cardiovascular
Hypertension
Left ventricular hypertrophy
Shortened QT interval

Arterial stiffness Arrhythmias Vascular and cardiac calcifications **Renal** Polyuria Urine-concentrating defect Nephrolithiasis Renal tubular acidosis **Miscellaneous** Anemia Fever of unknown origin	
GERD, gastroesophageal reflux disease.	

c. Diagnosis. Clinical suspicion is a major consideration in the diagnosis of PHPT.

i. Hypercalcemia is present in the majority of patients. Determination of ionized calcium is a useful adjunct to confirming the presence of hypercalcemia. Some patients may have persistent normocalcemia **(normocalcemic PHPT)**, which can represent a transient phase in the natural history of the disorder. Rarely, the presence of vitamin D deficiency with osteomalacia masks hypercalcemia. Treatment with replacement doses of vitamin D will unmask PHPT in this setting **(vitamin D challenge test)**.

ii. PTH levels can be measured using a number of highly sensitive assays, the most useful being those that measure the **intact hormone** (PTH 1-84). They employ one- or two-site radioimmunoassay techniques, respectively. It is essential that total serum or ionized calcium be measured simultaneously with PTH. In most cases, this is sufficient for diagnosis.

iii. With the development of sensitive and clinically useful assays for PTH, measurement of cAMP excretion is seldom used as a diagnostic aid in PHPT.

iv. Urinary calcium excretion varies from normal to elevated in PHPT, depending on the level of serum calcium, filtered load of calcium by the kidney, intestinal absorption of calcium, dietary intake, and effect of PTH on tubular

reabsorption of calcium. Because most non-PHPT causes for hypercalcemia are associated with the presence of hypercalciuria, normal urinary calcium excretion in the presence of hypercalcemia is frequently of greater diagnostic value than the presence of increased urinary calcium. p. 395p. 396In PHPT, the degree of hypercalciuria correlates with elevated levels of $1,25(OH)_2D$.

v. **Hypophosphatemia** is present in approximately 50% of cases and is associated with a lowered **renal threshold for phosphorus reabsorption,** that is, the **tubular maximum for phosphorus reabsorption (TmP)** expressed as a function of GFR **(TmP/100 mL GFR)**.

vi. An elevated serum **chloride to phosphorus ratio** (normal > 32) occurs in 60% to 70% of patients with PHPT, indirectly reflecting the effect of PTH as lowering the tubular maximum for bicarbonate excretion (mild elevation in serum chloride and depression of serum bicarbonate).

vii. **Biochemical markers of bone remodeling** are typically increased in PHPT **(**e.g., **formation markers—osteocalcin** and **bone-specific alkaline phosphatase;** and **resorption markers—hydroxyproline, deoxypyridinoline, collagen *N*-telopeptide**, and **collagen C-telopeptide)**. These alterations may on occasion be helpful in distinguishing PHPT from other disorders associated with hypercalcemia.

d. Pre- and intraoperative parathyroid localization procedures

Successful treatment of PHPT involves localization and excision of the involved parathyroid gland. Ultrasound (US), Sestamibi scan (^{99m}Tc methoxyisobutylnitrile) (MIBI), and magnetic resonance imaging (MRI) are the most common modalities of preop localization. Success rates are approximately 90% to 95%.

Depending on the experience of the technologist, **ultrasonography localizes parathyroid enlargement in up to 80% of cases**. Recently, intraoperative ultrasonography

performed by surgeons has also proved successful in localizing abnormal parathyroid glands. MRI is similar to US in detecting parathyroid abnormalities, but its high cost is a drawback. CT imaging is also an effective but expensive technology.

^{99m}Tc-sestamibi scintigraphy has become widely used as a sensitive localization procedure (sensitivity ~ 80%) for parathyroids. Because all noninvasive localization procedures are associated with false-positive and false-negative results, **confirmation of findings with two procedures can offer greater confidence in test results**.

US is inexpensive, has good sensitivity (70% to 80%) and specificity (90%), and does not expose the patient to radiation. MIBI scan is relatively inexpensive, has better sensitivity and specificity scores (80% to 90% and 98%, respectively), and involves low radiation exposure. CT scanning has become more widely used with added sensitivity by employing three-dimensional technology and a fourth dimension (time).

The 2014 summary statement from the Fourth International Workshop on Management of Asymptomatic HPT mentions that US and Sestamibi scan are the most common modalities of preoperative localization, but does not recommend any one study over the other.

A meta-analysis published in *Head and Neck* in March 2015 concluded that ^{99m}Tc-MIBI SPECT/CT has high detection rate for hyperfunctioning parathyroid glands in patients with PHPT.

In one study published in 2015, comparison was made between four-dimensional CT (4-D CT), US, and Sestamibi scan. **4-D CT proved superior** in terms of sensitivity, specificity, positive predicative value, negative predicative value, and accuracy. The authors recommend 4-D CT as the imaging method of choice unless the patient is young and/or the level of radiation exposure is prohibitive.

In another study, MIBI parathyroid scintigraphy and ultrasound (US) had 85.3% and 72.5% sensitivity, respectively. These results show that MIBI parathyroid scintigraphy was superior to US in localizing enlarged parathyroid glands. The authors also reported that the overall sensitivity and the positive

predictive value of the combined techniques was 90.4% and 92.6%, respectively.

Therefore, the **most successful approach** for the localization would be concurrent application of **US and MIBI scan**. The concomitance of thyroid p. 396p. 397diseases affects the sensitivity of both US and MIBI scan in identifying enlarged parathyroid glands.

In a retrospective study published in November 2015 in *Clinical Endocrinology* by Y. Ebner et al., parathyroidectomy success rate was similar in patients with PHPT and MIBI-only or US-only positive localization studies compared with matched US/MIBI studies. The authors recommended that the positive results from one imaging technique, either MIBI or US, are sufficient to refer a patient for parathyroid surgery.

Parathyroid angiography, particularly when combined with selective venous sampling to identify a gradient in PTH levels, can localize hyperplastic glands or an adenoma in most cases (80% to 95%).

Intraoperative parathyroid localization is now common in many centers using ^{99m}Tc-sestamibi imaging. A hand-held *γ*-radiation detector **(γ probe)** can often rapidly locate an abnormal gland. When combined with intraoperative US, the detection of adenomas is approximately 90%. Intraoperative PTH levels can be measured following removal of suspicious lesions. **A decrease in >50% 10 minutes after removal of an abnormal gland nearly always indicates correction of HPT**. Patients with hyperplasia require multiple gland removal before PTH levels are appropriate.

e. Management

i. Surgical removal and angiographic ablation (selective infarction) of the parathyroid glands are the only definitive treatments for PHPT.

ii. Transcutaneous injection of adenomas with alcohol has been carried out in several centers using US. The procedure has been associated with a **high incidence**

of complications, such as injury to the recurrent laryngeal nerve.

iii. Patients who are poor surgical risks, who have had previous unsuccessful surgery, or who decline surgical intervention can benefit from medical treatment.

iv. Bisphosphonates, including **alendronate**, has been convincingly shown to preserve bone mineral density (BMD) in patients with PHPT. Maintenance of normal serum calcium levels with chronic bisphosphonate therapy has not been convincing, although acute decreases in high serum calcium levels are readily achieved with intravenous bisphonates. **Zoledronic acid is now becoming the preferred intravenous bisphosphonate** compared to pamidronate, given its increased potency and similar safety profile. The safety of long-term management of PHPT with bisphosphonates has not been established, but a meta-analysis has shown that increases in BMD in response to surgical intervention were comparable to those induced by antiresorptive therapies at least for the initial 2 years.

v. **Denosumab** is now approved for management of HCM refractory to bisphosphonate therapy. It has also been shown to be effective in the management of hypercalcemia in parathyroid carcinoma. In case reports, an increase in BMD was seen at 1 year from baseline, but the lowering of serum calcium was not sustained.

vi. **Calcimimetics** (cinacalcet) act as calcium sensor-receptor agonists, and administration of calcimet to patients with PHPT has been shown to reduce both serum calcium and PTH levels for up to 5 years. Despite this, it cannot be the first-line treatment because there is no evidence that it produces the same benefits as surgical cure, such as improvement in BMD. It is appropriate to consider its use if patients refuse surgery or have medical contraindications for surgery. As yet, this agent has only been approved by the US Food and Drug Administration (FDA) for secondary HPT in adult patients with chronic kidney disease on dialysis, hypercalcemia in adult patients with parathyroid carcinoma and hypercalcemia in adult patients with PHPT for whom parathyroidectomy would be indicated on the

basis of serum calcium levels, but who are unable to undergo parathyroidectomy.

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2. **Familial hypocalciuric hypercalcemia (FHH).** Also known as **familial benign hypercalcemia**, FHH is an uncommon disorder that **can be confused with PHPT**. It may represent **1% to 2% of cases of asymptomatic hypercalcemia**. The major clue to the diagnosis is a **family history of hypercalcemia**, sometimes in individuals who have undergone unsuccessful exploratory parathyroid surgery.
   - **a.** Inheritance is autosomal dominant and is **expressed very early in life**, with hypercalcemia sometimes detected within the first few days. Sporadic cases have also been described. In the majority of cases of FHH studied, the presence of an **inactivating (loss-of-function) mutation of the CSR** has been demonstrated. A number of different mutations have been identified in different kindreds and have been mapped to genes on the **long arm of chromosome 3**, as well as on both the **long and short arms of chromosome 19**. These CSR mutations cause a shift in the set point for suppression of PTH secretion, resulting in a higher threshold of serum calcium to suppress hormone secretion and the presence of mild-to-moderate hypercalcemia. The presence of the mutated CSR in the kidney produces a variable reduction in urinary calcium excretion, often to the level of hypocalciuria.
   - **b.** Biochemical features include varying degrees of reduced urinary calcium excretion (“hypocalciuria”), hypercalcemia, hypomagnesuria, and hypermagnesemia. Urinary calcium excretion is usually expressed as the **ratio of calcium clearance to creatinine (CCa/CCr)**, which is a more sensitive index of renal calcium excretion than total urinary calcium. The **CCa/CCr** in FHH is usually <.01, allowing discrimination from PHPT. Serum phosphorus levels are variable. PTH levels are normal to slightly elevated, as is urinary cAMP excretion. Levels of vitamin D metabolites are normal.
   - **c.** Patients with FHH lack the clinical features of PHPT or MEN syndrome. Serum calcium levels are generally mild to

moderately elevated, with clustering of similar levels of calcium in affected individuals in families. Acute and recurrent pancreatitis has been described in individuals and within kindreds that have higher degrees of hypercalcemia. **Response to parathyroid surgery in FHH is, however, invariably poor**, thus underscoring the need to distinguish the disorder from PHPT prior to undertaking surgical exploration. **The development of recurrent pancreatitis in FHH may necessitate total parathyroidectomy**. At surgery, the parathyroids can have the appearance of chief-cell hyperplasia **(pseudoadenomatous chief-cell hyperplasia)**.

d. Neonatal severe primary hyperparathyroidism (see Chapter 35).

3. Hypercalcemia of malignancy. HCM is the most common cause of hypercalcemia in hospitalized patients. The pathogenesis of HCM is multifactorial, varying among the different types of malignancy. Hypercalcemia occurs most commonly in patients with various squamous cell carcinomas, breast cancer, renal cell carcinoma, bladder carcinoma, multiple myeloma, and various lymphomas. It is **uncommon in certain malignancies, such as colon and prostate cancers**. As with other hypercalcemic disorders, dehydration, immobilization, and treatment with certain drugs (e.g., thiazide diuretics, lithium, vitamin D) can contribute to or potentiate development of HCM. Other **specific** causes include:

a. Direct invasion of bone (local osteolysis)

b. Tumor production of one or more circulating factors that augment osteoclastic resorption of bone (humoral HCM)

c. Ectopic production of $1,25(OH)_2D_3$

d. Concomitant malignancy

e. PHPT or granulomatous disorders

f. Treatment with antiestrogens (tamoxifen) leading to tumor flare hypercalcemia as described below.

i. Tumor-associated local osteolysis accounts for hypercalcemia in about 20% to 40% of cases.

a) Although direct resorption of bone by malignant cells has been hypothesized, most investigators do not believe this is the case.

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b) A number of locally produced **osteoclast-activating factors** that activate osteoclastic resorption of bone (e.g., by a paracrine pathway) have been identified. Such factors may be produced by or under the influence of malignant cells acting on in situ bone cell elements. They comprise, **PTHrP, prostaglandins** of the E series, and several cytokines, including **tumor necrosis factor-*α* (cachectin) and tumor necrosis factor-*β* (lymphotoxin), transforming growth factors *α* and *β***, and several **interleukins (IL-1*α*, IL-1*β*, and IL-6)**. The pathogenesis of bone lesions in multiple myeloma is particularly complex, because recent studies have identified **RANK ligand**, **macrophage inflammatory peptide 1*α*** and **IL-3** as likely mediators of bone resorption and a suppression of **osteoprotegerin** secretion as a contributory mechanism.

ii. **HHCM** refers to a condition in which a malignant tumor produces one or more circulating factors that cause hypercalcemia in the absence of evidence for skeletal metastasis. HHCM accounts for malignancy-associated hypercalcemia in 40% to 50% of cases. The term **pseudohyperparathyroidism** was originally used to describe this condition.

a) It is now recognized that **tumor production of a PTHrP is the major cause of HHCM (see Chapter 34)**. Elevated circulating levels of PTHrP have been reported for a number of malignancies, utilizing several different commercial assays.

b) PTHrP-mediated hypercalcemia is associated with low-to-undetectable PTH, hypophosphatemia due to a lowered TmP/GFR, increased urinary nephrogenous cAMP excretion, and relative hypercalciuria. However, in contrast to PHPT, the levels of $1,25(OH)_2D$ are low or reduced (Table 31-3).

iii. Tumors capable of producing a peptide that is

immunologically and physiologically identical to native PTH (e.g., **ectopic PHPT**) are rare. Patients whose ectopic PHPT meet such criteria include those with **squamous carcinoma of the lung, ovarian adenocarcinoma, thymoma,** **p. 399p. 400** **papillary carcinoma of the thyroid,** and **small-cell carcinomas of the lung and ovary**.

TABLE 31-3 **Comparison of Biochemical Features of Primary Hyperparathyroidism, Humoral Hypercalcemia of Malignancy (Ectopic PTHrP Syndrome), and Familial Hypocalciuric Hypercalcemia**

Feature	PHPT	HHCM	FHH
Serum Ca	I	I	I
PTH	I	D	N/sl.I
PTHrP	N	I	N
CSR set point	I/N[a]	N	I
Serum phosphorus	D/N	D	N/sl.D
TmP/GFR	D	D	N
Serum chloride	N/I	N/D	N
Urinary calcium	I/N	I	D
Urine NcAMP	I	I	N/sl.I
$1,25(OH)_2D_3$	I/N	D	N
Osteocalcin	I/N	D	N
Urine *N*-telopeptide collagen cross-links	I/N	I	N

CSR, calcium sensor receptor; D, decreased; I, increased; N, Normal; FHH, familial hypocalciuric hypercalcemia; GFR, glomerular filtration rate; HHCM, humoral hypercalcemia of malignancy; NcAMP, nephrogenous cyclic adenosine phosphate; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; PTHrP, parathyroid hormone–related peptide; sl.D, slightly decreased; sl.I, slightly increased.

[a]The CSR set point is normal in idiopathic parathyroid hyperplasia.

iv. Hypercalcemia caused by **extrarenal production of $1,25(OH)_2D$** affects patients with lymphoproliferative malignancies, including **Hodgkin disease, B-cell lymphomas, and Burkitt lymphoma**. The malignant lymphoid cell is the site of 1α-hydroxylase activity. In some cases of **T-cell lymphoma**, hypercalcemia may be attributed at least in part to tumor production of calcitriol;

however, in other cases, the **predominant factor appears to be ectopic production of PTHrP**.

v. Some squamous cell or poorly differentiated carcinomas have been reported to produce high levels of an E prostaglandin (PGE-M). Tumor production of **prostaglandin** E_2 has been described in some patients with renal carcinoma. Treatment with **aspirin** or **indomethacin (prostaglandin synthetase inhibitors)** has resulted in a concomitant reduction of high urinary levels of PGE-M and control of hypercalcemia. This does not appear to be a common mechanism for HCM and contrasts with prostaglandin-mediated local osteolysis.

vi. Treatment of some women with breast cancer with tamoxifen can produce a **hypercalcemic flare**. The mechanism is not well understood.

4. Granulomatous diseases (Table 31-4)

a. Hypercalcemia occurs in approximately 10% of patients with active pulmonary sarcoidosis; hypercalciuria is detected even more frequently, in up to 50% of cases. A correlation can be shown between the degree of severity of sarcoidosis or elevation in the levels of angiotensin-converting enzyme and degree of hypercalcemia.

i. Patients with sarcoidosis have been shown to have elevated circulating levels of $1,25(OH)_2D$. The cause has been shown to be ectopic production of $1,25(OH)_2D$ by granuloma macrophages containing a 25(OH)-vitamin D-1α-hydroxylase, similar to that in the kidney. Normal physiologic regulation of calcitriol formation is absent in granulomatous tissue. The increased sensitivity to vitamin D derived from dietary intake or solar exposure and classically described in sarcoidosis can be explained as p. 400p. 401rapid and unregulated conversion of precursors to the active metabolite. Circulating levels of calcitriol also correlate with disease severity.

TABLE 31-4 Tumors and Disorders Associated with Ectopic Production of $1,25(OH)_2D_3$

Malignant Disorders

B-cell lymphoma
Hodgkin disease
Myeloma (uncommon)
Lymphomatoid granulomatosis

Chronic Granulomatous Disorders

Infectious diseases

- Tuberculosis
- Histoplasmosis
- Coccidioidomycosis
- Candidiasis
- Cat-scratch fever
- Leprosy

Noninfectious conditions

- Sarcoidosis
- Foreign-body granulomata (silicon, paraffin, lipoid pneumonia)
- Berylliosis
- Eosinophilic granuloma
- Wegener granulomatosis

ii. **Treatment with steroids** is both rapid and highly effective in **controlling the hypercalcemia and hypercalciuria of sarcoidosis**. A **steroid suppression test** for hypercalcemia has been used to distinguish sarcoidosis from PHPT. This test is performed by administration of 150 mg of hydrocortisone (or 40 to 60 mg of prednisone) daily for 7 to 10 days. Serum calcium levels in patients with sarcoidosis invariably drop during treatment, usually within 3 days, whereas individuals with PHPT usually show no change. This test cannot identify the rare patient who has both disorders. Because patients with uncomplicated sarcoidosis have low levels of PTH, this measurement usually allows differentiation from PHPT.

iii. **Chloroquine, hydroxychloroquine,** and **ketoconazole** have also been shown to reduce $1,25(OH)_2D$ production and control both hypercalcemia and hypercalciuria in patients with sarcoidosis.

iv. In addition to the above-described measures, reduction in sun exposure, avoidance of excessive exogenous vitamin D

intake, and control of dietary calcium intake to not more than 1 000 mg/day are efficacious in the control of hypercalciuria and hypercalcemia.

b. Hypercalcemia has also been reported in a number of other granulomatous diseases (Table 31-4). Elevated serum levels of $1,25(OH)_2D$ have been documented in most of these conditions. The mechanism of ectopic production of calcitriol may be similar to that of sarcoidosis. However, other mechanisms for altered calcium homeostasis may be operative, because low levels of calcitriol in the presence of hypercalcemia have been described in isolated cases.

Treatment with steroids, hydration, and reduction of dietary calcium intake may be useful and effective in controlling hypercalciuria and hypercalcemia in various granulomatous disorders.

5. Vitamin D intoxication

a. Development of hypercalcemia because of accidental or intentional ingestion of high doses of vitamin D generally results from accumulation of high levels of 25(OH)D, but can also result from excessive dietary intake of calcium supplements or dairy products. This is a rare event. Vitamin D intoxication has also been described in individuals ingesting dairy products erroneously fortified with excessive amounts of vitamin D.

b. In this setting, hypercalcemia and hypercalciuria develop as an apparent consequence of the mass action effect of high levels of 25(OH)D acting at vitamin D receptors in the intestine and, possibly, skeletal sites. Because of the storage and slow release of 25(OH)D in muscle and adipose tissue, high circulating levels and the **potential for symptomatic vitamin D intoxication can persist for weeks to months after discontinuation of the medication**.

c. In comparison with the risks associated with vitamins D_3 and D_2, the potential for development of hypercalcemia during treatment is greater with more potent compounds, such as $25(OH)D_3$, $1,25(OH)_2D_3$, and the synthetic compounds **dihydrotachysterol** and **1α-hydroxyvitamin D_3** (both metabolized in the liver to their biologically active forms,

respectively, **25(OH)-dihydrotachysterol** and calcitriol). However, because these compounds are metabolized rapidly, the duration of hypercalcemia in comparison with vitamins D_3 and D_2 is shortened.

d. Management of vitamin D intoxication includes reduction of dietary calcium intake and discontinuation of the vitamin D preparation. In severe cases, the use of steroids (**prednisone, 40 to 60 mg/day**), which block intestinal and probably skeletal actions of vitamin D, may be required, sometimes for weeks or months.

6. Other endocrine causes of hypercalcemia

a. Hyperthyroidism. Hypercalcemia has been reported to occur in thyrotoxicosis in **15% to 50% of cases**. The mechanism appears to be thyroid hormone–mediated increased **osteoclastic bone resorption**. PTH and calcitriol levels are suppressed, and hypercalcemia is generally mild, possibly reflecting compensatory urinary calcium losses and reduced intestinal absorption of calcium.

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i. The diagnosis is usually not difficult unless hyperthyroidism is not recognized or is complicated by coexisting disorders, such as PHPT, in which case confirmation of hyperthyroidism as the cause of hypercalcemia occurs with effective treatment of the hyperthyroidism.

ii. A *β*-blocker (e.g., propranolol, 20 to 40 mg four times a day) may be effective treatment for hypercalcemia while awaiting response to antithyroid therapy in disorders, such as Graves disease or toxic multinodular goiter.

b. Pheochromocytoma (see Chapter 18). Hypercalcemia is frequently observed in patients with catecholamine-secreting adrenomedullary tumors. Although pheochromocytoma and PHPT occur together in MEN2a, hypercalcemia may also be found in the absence of intrinsic parathyroid disease. **Several mechanisms** are involved in the development of hypercalcemia. These include **catecholamine-induced volume contraction and hemoconcentration,**

epinephrine-induced PTH secretion, and, in some cases of malignant tumors, **secretion of PTHrP**. Rapid resolution of hypercalcemia usually follows removal of the tumor.

c. **Adrenal insufficiency** (see Chapter 24). Acute adrenal insufficiency **(Addisonian crisis)** can present with moderate-to-severe hypercalcemia. Few well-studied cases have been reported. Factors that probably contribute to the development of hypercalcemia include volume depletion with hemoconcentration and reduction in GFR, which facilitates increased tubular reabsorption of calcium, and increased skeletal release of calcium, possibly because of increased sensitivity to vitamin D. Correction of volume depletion and **treatment with corticosteroids rapidly correct hypercalcemia in this setting**. The disorder should be considered in hypercalcemic patients with AIDS because of the possible presence of concomitant infectious agents, such as ***Mycobacterium avium-intercellulare,*** which can cause adrenal insufficiency.

d. **Pancreatic islet cell tumors.** Hypercalcemia in patients with pancreatic islet cell tumors can occur as the result of several different abnormalities. These tumors may develop as part of MEN1 syndrome and occur in association with PHPT. In other cases, elevated circulating levels of PTHrP have been reported. However, the occurrence of hypercalcemia is particularly high in patients with tumors that secrete **vasoactive intestinal polypeptide (VIPomas)**. The mechanism of hypercalcemia in this condition has not been established.

7. **Miscellaneous causes of hypercalcemia**

a. **Milk–alkali syndrome.** Ingestion of excessive amounts of milk (or calcium supplements) and soluble alkali (absorbable antacid) can cause hypercalcemia. Treatment with vitamin D can further potentiate the syndrome, as can the presence of disorders in which augmented intestinal absorption of calcium is part of the pathophysiologic disturbance (e.g., PHPT). The usual implicated salts are sodium bicarbonate and calcium carbonate. Acute and chronic forms of milk–alkali syndrome are recognized.

i. **Chronic milk–alkali syndrome (Burnett syndrome)**

is associated with soft-tissue calcification in the kidneys and nephrocalcinosis. Progressive renal insufficiency can occur.

ii. Diagnosis of **acute milk–alkali syndrome**: hypercalcemia, frequently with slightly elevated serum phosphorus, mild azotemia, and metabolic alkalosis.

iii. Factors that contribute to the development of the disorder include increased intestinal absorption of calcium and decreased urinary excretion of calcium as a result of the reduction in GFR and increased tubular reabsorption of calcium in the presence of metabolic alkalosis.

iv. The incidence of the disorder has declined because of the availability of nonabsorbable antacids and the use of H_2 secretion–blocking agents, such as cimetidine and ranitidine. However, recent emphasis on the use of calcium carbonate as part of management regimens for osteoporosis has resulted in increased incidence.

v. **Treatment consists of discontinuation of calcium supplements** and alkali, and rehydration. This usually results in a rapid correction of p. 402p. 403hypercalcemia. Exclusion of coexisting PHPT (with peptic ulcer disease) in a setting consistent with development of milk–alkali syndrome may be required in some cases.

b. Drug-induced hypercalcemia. Treatment with a number of drugs can raise serum calcium levels and induce hypercalcemia de novo or by exacerbating the effects of other conditions or disorders in which hypercalcemia commonly occurs (Table 31-5). **The mechanism(s) of hypercalcemia associated with some of these drugs is currently not understood**.

i. **Vitamin D analogs.** The term **"vitamin D intoxication"** was previously used to describe a condition in which prolonged treatment with large doses of vitamin D_2 or D_3 or dihydrotachysterol was used in the management of a specific disorder (e.g., hypoparathyroidism). Formation of high levels of 25-hydroxy metabolites of these drugs

resulted in the development of hypercalcemia. Excessive commercial dairy fortification of cows' milk has also been demonstrated to produce vitamin D intoxication and hypercalcemia. With the availability of more potent vitamin D analogs, such as 25(OH)D3, 1*α*(OH)D3, and 1,25$(OH)_2D_3$, and their use in treatment in a variety of clinical settings, hypercalcemia is frequently encountered. The contributing factors to the development of hypercalcemia can be multiple but include hyperabsorption of calcium (in the presence of excessive calcium supplementation) and increased bone resorption. Treatment includes reduction in dose or discontinuation of the drug, reduction of dietary calcium intake, and treatment with glucocorticoids for variable periods.

ii. **Vitamin A analogs.** Treatment with doses of vitamin A > 50 000 IU/day can result in hypercalcemia. Hypercalcemia is also occasionally observed in patients being treated with ***cis*-retinoic acid** and **all-*trans*-retinoic acid.** The mechanism of increased serum calcium appears to be enhanced vitamin A–mediated osteoclastic bone resorption.

iii. **Thiazide diuretics.** Treatment with thiazide diuretics is frequently associated with mild hypercalcemia. The finding of more severe elevation in serum calcium usually indicates the presence of an underlying disorder of calcium metabolism (e.g., PHPT) or a bone disorder associated with high rates of bone remodeling, such as juvenile osteoporosis. The mechanism(s) of hypercalcemia includes increased renal tubular reabsorption of calcium and diuretic-induced volume depletion.

iv. **Lithium carbonate.** The use of lithium carbonate in the management of bipolar disorders is associated with a **rise in serum calcium in most patients and development of hypercalcemia in** approximately **5% of cases**. Enlargement of the parathyroids has been described, but the predominant **mechanism appears to be a reset in the CSR**. Increased

lithium-induced renal tubular reabsorption of calcium has also been described. Hypercalcemia is usually seen with higher doses of lithium carbonate. Reduction in dosage or discontinuation usually results in lower serum calcium levels. However, **surgically documented cases of PHPT in lithium-treated patients have been reported**. Whether or not the lithium caused the tumors is unclear, but either surgery or **cinacalcet** has been effective therapy.

TABLE 31-5 Medications Associated with Development of Hypercalcemia

Thiazide diuretics
Vitamin D analogs (vitamin D, calderol, calcitriol, DHT, topical calcipotriol)
Vitamin A and analogs (*cis*-retinoic acid, all-*trans*-retinoic acid)
Human PTH 1-34; recombinant human PTH 1-84
Lithium
Estrogen and antiestrogen (Tamoxifen)
Growth hormone
Aminophylline, theophylline
Foscarnet
8-Chloro-cAMP

cAMP, cyclic adenosine 3′,5′-monophosphate; DHT, dehydrotestosterone; PTH, parathyroid hormone.

C. General principles for management of hypercalcemia

1. Correction of dehydration and volume depletion.
2. Correction of electrolyte abnormalities (**frequently hypokalemia**).
3. Discontinuation or reduction in dosage of digitalis (hypercalcemia potentiates digitalis toxicity).
4. Discontinuation of treatment with medications that contribute to the development of hypercalcemia (e.g., vitamin D, vitamin A, estrogens, antiestrogens, thiazide diuretics, etc.).
5. Reduction of dietary intake of calcium in those disorders in which intestinal hyperabsorption of calcium can contribute to the development of hypercalcemia (e.g., vitamin D intoxication, milk–alkali syndrome).

6. Weight-bearing mobilization of patients confined to bed when possible. When the cause of disordered mineral homeostasis is known, it may be feasible to select a therapeutic agent or regimen that acts at the site of generation of hypercalcemia.

D. Management of hypercalcemia

1. Agents that decrease the release of calcium from bone or increase the uptake of calcium into bone

a. Calcitonin. Parenteral administration of calcitonin has been shown to be **effective in the acute management of hypercalcemia**. Salmon calcitonin is the only species of calcitonin available for use.

i. The mechanisms of action are rapid inhibition of osteoclastic activity and reduction in tubular reabsorption of calcium (e.g., increased urinary calcium excretion). **Onset of action** is rapid, with calcium lowering apparent within 2 to 4 hours of administration, but duration of action with a single dose is brief.

ii. Calcitonin is administered either by continuous infusion, or by intramuscular or subcutaneous injections at 6- to 12-hour intervals at a dose of 3 to 8 IU/kg. Frequently, a loss-of-response efficiency occurs after repeated dosing for longer than 3 to 4 days. There is evidence that this “escape” phenomenon may be blocked by glucocorticoid administration (prednisone, 30 to 60 mg/day). The latter may result in sustained reduction in calcium levels for several weeks. Nasal spray and rectal suppository preparations (not available in the United States) are generally not useful in the management of hypercalcemia.

iii. Calcitonin usually produces a modest reduction in serum calcium levels, but its **low toxicity** profile makes it a useful agent in the appropriate clinical setting. It may be particularly useful in the treatment of hypercalcemia associated with vitamin D intoxication. With the advent of intravenous bisphosphonate therapy, calcitonin use has dropped substantially.

b. Bisphosphonates

i. The bisphosphonates are structurally related to pyrophosphate, a natural metabolic product. These compounds bind to hydroxyapatite in bone matrix and

thereby provide sufficient tissue drug levels to **inhibit osteoclastic bone resorption**.

ii. Parenteral preparations for administration of both **pamidronate (Aredia)** and **zoledronic acid (Reclast)** are currently available in the United States. Because of its greater potency in lowering serum calcium and longer duration of action, **zoledronic acid is more frequently used** than etidronate for this indication. The only advantage of pamidronate is the lower cost of generic pamidronate. **Pamidronate** is generally infused as a **single dose (60 to 90 mg) over a 4-hour period**. Individualized treatment regimens p. 404p. 405with repeat dosing with pamidronate can achieve control of serum calcium for days to weeks. Side effects to parenteral therapy may include low-grade fever, myalgias, and leukopenia. Mild hypocalcemia and hypophosphatemia may occur in some cases, usually when multiple doses of drug have been administered. These alterations are usually mild and do not require corrective measures. **Zoledronic acid is infused as a single dose of 4 mg over 15 minutes.** Similar side effects to pamidronate may be encountered after zoledronic acid infusion. Patients should be given vitamin D_3 prior to use if there is evidence of vitamin D deficiency. Both pamidronate and zoledronic acid are **approved for use in HCM** by the FDA but have been used off-label in patients with other causes of hypercalcemia.

iii. **Oral bisphosphonate** preparations have generally **not been effective in the acute or long-term management of hypercalcemia**. However, both pamidronate and zoledronic acid have been used in the management of breast cancer, multiple myeloma, and other malignancies. In breast cancer, bisphosphonate therapy has been used to reduce the development of metastases, delay the development of hypercalcemia, control bone pain and possibly exert an anticancer effect on tumor cells in bone,

and delay progression of established metastatic lesions. Similarly, treatment with a bisphosphonate can delay or reduce the expression of skeletal complications in multiple myeloma and other malignancies.

c. **Denosumab.** Denosumab is a human monoclonal antibody with affinity for nuclear factor-κ ligand (RANKL). RANKL activates osteoclast precursors that leads to osteolysis and increase in calcium levels. Denosumab binds to RANKL and inhibits the formation, survival, and activity of the osteoclasts. It was **approved for the treatment of osteoporosis** in 2010 and 2014, and for the **treatment of hypercalcemia** refractory to bisphosphonates.

   Denosumab appears to be well tolerated apart from arthralgias and a risk of jaw osteonecrosis comparable to that of zoledronate. In trials evaluating the efficacy of denosumab in preventing skeletal-related events, rates of hypocalcemia were close to 10%, nearly double that of bisphosphonate therapy. No dose adjustment is needed for acute or chronic kidney disease because it is not metabolized by the kidneys. However, it should be cautiously used in patients with severe impairment (CrCl < 30 mL/minute) for augmented risk of hypocalcemia.

   Dose: SubQ: 120 mg every 4 weeks; during the first month, give an additional 120 mg on days 8 and 15.

d. **Cinacalcet. Cinacalcet** is a calcimimetic that interacts with the CSR on parathyroid cells, leading to the **downregulation of PTH** and thereby decreasing the calcium levels. It has been approved for the **treatment of hypercalcemia in parathyroid carcinoma and in patients with PHPT** who are unable to get parathyroidectomy.

   It can be started at a low dose of 30 mg two times a day (BID) and can be titrated up to 90 mg BID or four times a day dose to normalize the calcium levels. Major side effects include nausea, vomiting, diarrhea, constipation, or abdominal pain.

   (Pliamycin, gallium, and phosphate have fallen out of favor as treatment options with the availability of safer and more effective treatment modalities as above).

2. **Agents that increase urinary excretion of calcium**

a. **Loop diuretics and saline.** Intermittent infusion of normal saline with periodic doses of furosemide (or ethacrynic acid) to

maintain maximum natriuresis and calciuresis was widely used in the initial management of hypercalcemia before other effective agents were available. **Urinary calcium excretion is directly proportional to sodium excretion**. Therapy usually consists of administration of 4 to 8 L/24 hours, alternating saline and 5% dextrose, and water at a ratio of 3:1 to 4:1. The usual dose of furosemide is 80 to 120 mg every 2 to 6 hours. Administration of diuretics should be preceded by correction of volume depletion. Because urinary potassium and magnesium losses p. 405p. 406are large with this regimen, replacement requirements of these electrolytes are determined by careful monitoring of serum levels. Electrocardiographic and central venous pressure monitoring may be required in a setting of extremely aggressive therapy. Additional potential complications include volume overload as a result of insufficient diuresis and volume depletion as a result of excessive diuresis. Even in its most aggressive forms, this therapeutic approach usually produces only a modest drop in serum calcium levels, and **because of the success of bisphosphonate therapy, only hydration with saline of dehydrated patients is presently commonly used.**

b. Hemodialysis or peritoneal dialysis. In situations in which marked renal insufficiency or fulminant or incipient congestive heart failure is present or where life-threatening malignant hypercalcemia exists, hemodialysis or peritoneal dialysis can be considered. Dialysis using a calcium-free dialysate can rapidly lower serum calcium levels. Careful monitoring of cardiovascular parameters is required, because rapid lowering of calcium can result in hypotension, requiring volume expansion and administration of pressor agents.

3. Agents that reduce intestinal absorption of calcium. Enteral hyperabsorption of calcium contributes to the development and maintenance of hypercalcemia in a limited number of clinical settings.

a. In **disorders of vitamin D excess** [iatrogenic vitamin D intoxication or ectopic $1,25(OH)_2D_3$ production], **treatment with glucocorticoids** (prednisone, 30 to 60 mg/day) is highly

effective in reducing calcium absorption. **Steroids inhibit 1α-hydroxylase conversion of 25-hydroxyvitamin D (calcidiol) into 1,25-dihydroxyvitamin D (calcitriol)**, therefore lessening intestinal calcium absorption. Treatment involves intravenous hydrocortisone 200 to 400 mg/day for 3 to 5 days followed by oral prednisone 10 to 20 mg/day for an additional 7 days. The duration of response is uncertain but felt to be in the order of 1 week during which time malignancy-specific interventions are initiated. Side effects of such treatment include hyperglycemia and further immunosuppression.

b. Short-term **reduction of dietary intake of calcium** may be a useful maneuver in vitamin D–excess states as well as in the milk–alkali syndrome. **Treatment with cellulose phosphate**, which complexes with calcium in the intestine, has also been used to reduce effective net intestinal absorption of calcium.

c. Ketoconazole, an antifungal agent, has been shown to **reduce plasma levels of 1,25(OH)$_2$D$_3$** in normal individuals as well as in patients with sarcoidosis and PHPT.

III. HYPOCALCEMIC DISORDERS

A. Clinical features of hypocalcemia.

The signs and symptoms of hypocalcemia are a function of the level of serum calcium, age at onset and duration, levels of serum magnesium and potassium, and accompanying disturbances in acid–base homeostasis. To some extent, the clinical manifestations of hypocalcemia relate to the type of underlying disease process. Thus, the absence or deficiency of PTH per se can be responsible for some signs and symptoms of hypocalcemia in hypoparathyroidism. In contrast, **secondary HPT** can contribute to some symptoms present in patients with vitamin D deficiency or PTH-resistant disorders associated with hypocalcemia. Most frequently recognized clinical features of hypocalcemia involve the CNS and the neuromuscular, ocular, and ectodermal systems.

1. Increased neuromuscular irritability, resulting in muscle cramping (tetany), is a common feature of hypocalcemia. The classic sign of **tetany** is carpopedal spasm **(Trousseau sign). Chvostek sign** is evidence of increased irritability of the fifth cranial nerve. Other neuromuscular signs include paresthesias, laryngospasm,

bronchospasm, abdominal cramping, and generalized hyperreflexia. These can be induced or aggravated by hyperventilation, which causes a mild metabolic alkalosis. **CNS disturbances** include seizure equivalents **(hypocalcemic seizures)**, grand or petit mal seizures, syncope, impaired memory, psychosis, and disturbances of extrapyramidal system function, such as parkinsonism and p. 406p. 407choreoathetosis. Changes seen on the electroencephalogram are nonspecific. In general, these abnormalities improve or slowly revert to normal with correction of hypocalcemia.

2. The most common ocular manifestation of chronic hypocalcemia is the development of **cataracts**; calcium deposits can be found in subcapsular, anterior, or posterior zonular location. Both papilledema and **pseudotumor cerebri** can occur.
3. **Cardiovascular disturbances** include electrocardiographic abnormalities characterized by **prolongation of the QT interval** and by nonspecific T-wave changes. **Refractory congestive heart failure** with resistance to digitalis therapy has been reported in chronic hypocalcemia associated with hypoparathyroidism. Hypotension resistant to conventional doses of pressor agents or volume replacement has also been described.
4. Other features of chronic hypocalcemia resulting from hypoparathyroidism include **soft-tissue calcification** and exostoses. Periarticular deposition of calcium salts is common, with occasional presentation of chondrocalcinosis and pseudogout. Basal ganglion calcification is frequently present. The mechanism responsible for the ectopic calcification has yet to be determined.
5. **Macrocytic megaloblastic anemia** attributed to deficient binding of vitamin B_{12} to intrinsic factor in the presence of hypocalcemia has been reported. This abnormality (**abnormal Schilling test**) and the anemia are reversible with correction of the hypocalcemia.

B. Disorders of the parathyroid glands (Table 31-6)

1. **Surgical hypoparathyroidism.** Surgical damage to or removal of parathyroid tissue accounts for the majority of cases of loss of parathyroid function. **Partial or transient PTH insufficiency**

is also a common occurrence, the latter becoming apparent during periods of stress when symptomatic hypocalcemia develops. A spectrum of PTH insufficiency can be demonstrated by infusion of ethylenediaminetetraacetic acid or sodium citrate, both of which chelate calcium and stimulate PTH secretion.

2. **Idiopathic hypoparathyroidism.** This term encompasses several different disorders in which hypoparathyroidism occurs as an isolated condition or as part of a syndrome complex. The disorders may occur as both sporadic and familial conditions. Depending on the specific disorder, onset or clinical expression can occur during childhood or later in adult life. The diagnosis is established by demonstrating low or absent circulating levels of PTH and normal physiologic responses to exogenous administration of the hormone. Other biochemical features include hyperphosphatemia, reduced plasma levels of $1,25(OH)_2D$, but normal levels of 25(OH)D. Bone remodeling markers are generally reduced (osteocalcin and deoxypyridinoline) or normal (alkaline phosphatase). Urinary calcium excretion is low in the untreated state.
   a. **Autoimmune hypoparathyroidism** (vide infra) occurs both as part of autoimmune polyglandular syndrome (APS) type I and as an isolated autoimmune disorder. APS, also referred to as autoimmune polyglandular endocrinopathy–candidiasis–ectodermal dystrophy, is transmitted as an autosomal recessive condition linked to mutations of the autoimmune regulator gene (*AIRE*) located on chromosome 21q22.3. Circulating parathyroid antibodies have been reported to be detected in 40% of patients with APS. The most common associated conditions include Addison disease and mucocutaneous candidiasis. Parathyroid antibodies have been described in approximately 30% of patients with isolated hypoparathyroidism. Autoimmune hypoparathyroidism can be expressed clinically between early childhood and young adulthood. Less common associated features of APS include alopecia, steatorrhea, primary hypogonadism, primary hypothyroidism, chronic active hepatitis, pernicious anemia, and vitiligo.
   b. **Hypoparathyroidism resulting from defective PTH synthesis.** Hypoparathyroidism may also result from

defective PTH synthesis. Several types of **mutations in exon 2 of the *PTH* gene located on chromosome 11** have been described. **Autosomal dominant** forms of inheritance associated with p. 407p. 408other mutations have also been described. In one family, the entire exon 2 was found to be deleted. In these families, clinical disease was expressed very early, with low-to-undetectable circulating levels of PTH.

TABLE 31-6 Classification of Disorders of the Parathyroids (Structure or Function) Associated with Hypocalcemia

Disorders of Parathyroid Development (Agenesis)

Isolated hypoparathyroidism
DiGeorge syndrome (DiGeorge sequence)
Kenny-Caffey syndrome
Mitochondrial neuromyopathies
Long-chain hydroxyacyl-CoA dehydrogenase deficiency

Disorders Resulting from Destruction of the Parathyroids

Postsurgical hypoparathyroidism
Autoimmune hypoparathyroidism (polyglandular autoimmune deficiency)
Metastases to parathyroids
Granulomatous disease
Radiation
Metal overload disorders

- Iron—hemochromatosis, multiple transfusions
- Copper—Wilson disease
- Aluminum—chronic renal failure

PTH Resistance Disorders

Pseudohypoparathyroidism type Ia (Albright hereditary osteodystrophy)
Pseudohypoparathyroidism type Ib
Pseudohypoparathyroidism type II
Magnesium depletion
PTH antibodies (iatrogenic)
Isolated deficiency of $1,25(OH)_2D_3$

Disorders of Parathyroid Hormone Processing or Secretion

Calcium sensor-receptor–activating mutations
Defective prepro-PTH processing
Magnesium depletion

CoA, coenzyme A; PTH, parathyroid hormone.

c. **Hypoparathyroidism resulting from altered PTH regulation. Activating mutations (constitutive activation) of the CSR** produce a **functional hypoparathyroid state** (e.g., a decrease in the PTH secretion set point) characterized by the development of hypocalcemia, hypercalciuria, and low-to-absent circulating levels of PTH. Both sporadic cases and autosomal dominant inheritance have been identified.

3. **Developmental abnormalities of the parathyroids** (see Chapters 34 and 35).
4. **Other forms of hypoparathyroidism**
   a. Individuals with idiopathic **hemochromatosis** or secondary iron overload syndrome as a result of long-term treatment with blood transfusions (e.g., **thalassemia**) have been shown to develop hypoparathyroidism. Examination of parathyroid tissue in such cases reveals iron deposition and fibrotic destruction.
   b. Hypoparathyroidism has also been described in **Wilson disease**, presumably because of copper deposition in the parathyroids.
   c. In patients with chronic renal insufficiency, **aluminum deposition in the parathyroids** may result in impaired PTH secretion and thus partial-to-complete parathyroid insufficiency.
   d. Transient (and infrequently permanent) parathyroid insufficiency has been reported following ^{131}**iodine therapy** for hyperthyroidism. This should be p. 408p. 409distinguished from transient hypocalcemia as a consequence of "hungry bone syndrome" following thyroidectomy treatment for hyperthyroidism.
   e. Destruction of the parathyroids by **tumor metastases** (breast carcinoma) or **granulomatous disease** is an uncommon cause of hypoparathyroidism.
   f. **Hypermagnesemia** causes suppression of PTH secretion and, when sustained, is an unusual cause of hypoparathyroidism.

C. PTH resistance syndromes. The term

pseudohypoparathyroidism (PsHP) has been used to describe a group of disorders with biochemical and clinical features of hypoparathyroidism but with target-organ resistance to PTH as indicated by elevated levels of PTH. In the two major forms of this disorder (PsHP type Ia and PsHP type Ib), correction of hypocalcemia usually results in suppression of PTH levels but fails to correct target-organ resistance to the hormone.

1. **PsHP type Ia**
   - **a.** This classic disorder, originally described by Fuller Albright, is recognized by the characteristic biochemical features of hypoparathyroidism in association with characteristic developmental and somatic features (short stature, round facies, obesity, **brachydactyly, pseudowebbing of the neck, subcutaneous calcifications, and ossifications**). Mental retardation is a variable feature. The term **Albright hereditary osteodystrophy (AHO)** has been used to describe the characteristic phenotypic features associated with PsHP type Ia.
   - **b.** Individuals with PsHP type Ia share a sporadic or an inherited defect in the function of **stimulatory guanine nucleotide coupling protein (Gs protein)**. A number of different inactivating mutations have been identified in the ***GNASI* gene** (codes for α subunit of Gs protein [Gsα]) in patients with PsHP type Ia.
   - **c.** In addition to PTH resistance, patients with PsHP type Ia may express other hormone-resistance syndromes and neurosensory defects attributable to a generalized defect in deficiency of Gsα protein. Most common of these disorders are **thyroid-stimulating hormone resistance (hypothyroidism), glucagon resistance** (no clinical disorder), and **gonadotropin resistance (amenorrhea)**.
   - **d.** A **diagnosis** of PsHP type Ia is established by the presence of features of AHO, reduced Gsα protein activity (reduced by ~50% in red blood cell membranes), and evidence of target-organ resistance to exogenous PTH. Evidence for the latter is implied by the finding of **hypocalcemia and elevated circulating PTH** or a blunted rise in urinary excretion of nephrogenous cAMP coupled with a blunted or absent phosphaturic response to exogenous PTH **(PTH infusion test)**. Absent or blunted PTH stimulation of renal production of

$1,25(OH)_2D$ and a calcemic response (skeletal resistance) can also be demonstrated.

e. Hypocalcemia is intermittent in some patients, although PTH levels are usually persistently elevated. Urinary calcium excretion is low, reflecting the action of PTH on distal nephron reabsorption of filtered calcium. Despite normocalcemia, these patients manifest blunted renal responses to exogenous PTH.

f. The term **pseudopseudohypoparathyroidism (pseudo-PsHP)** has been used to describe a group of individuals who have the somatic features of AHO but who are normocalcemic and **lack evidence of PTH resistance**. Pseudo-PsHP is genetically related to PsHP in that both may occur in the same kindred and both demonstrate approximately 50% reduced Gs*α* protein activity in membrane isolates. Why individuals with pseudo-PsHP do not express hormone resistance is currently unexplained.

g. Inheritance of PsHP type Ia and pseudo-PsHP is by **autosomal dominant** transmission. There is strong evidence that maternal inheritance of Gs*α* protein deficiency results in PsHP type I, whereas paternal transmission results in pseudo-PsHP, implicating the possible occurrence of **genomic imprinting** of the *GNASI* gene.

2. **PsHP type Ib** is characterized by the occurrence of isolated PTH resistance, normal Gs*α* protein activity, and absence of the features of AHO. The biochemical expression of PTH resistance is identical to that of PsHP type Ia, a blunted or absent rise in urinary cAMP, and phosphaturic response to exogenous PTH. It p. 409p. 410is likely that the diagnosis of PsHP type Ib encompasses more than one disorder. An imprinting defect of the *GNASI* gene has been described.
3. **PsHP type Ic.** Patients with this disorder have features of AHO, multiple forms of hormone resistance analogous to PsHP type Ia, but normal Gs protein activity. It is possible that the defect is in Gs protein activity, although it is not demonstrable with current assays.
4. **PsHP type II.** This type of PTH resistance appears to be rare, and

several varieties have been reported. Affected individuals described lack the features of AHO. Administration of exogenous PTH produces a normal rise in urinary nephrogenous cAMP excretion but a blunted or absent phosphaturic response. Normalization of serum calcium can normalize the phosphaturic response to PTH. PsHP type II has been described in patients with osteomalacia secondary to vitamin D depletion.

5. **Other forms of PsHP.** Several other disorders with apparent resistance to both endogenous and exogenous PTH have been described.
   a. The term **pseudohypohyperparathyroidism** has also been applied to a disorder in which there appears to be renal resistance to PTH but a normal skeletal response. The latter is demonstrated by the presence of skeletal radiologic features of severe HPT (e.g., osteitis fibrosa, bone cysts, brown tumors).
   b. **Pseudoidiopathic hypoparathyroidism** refers to a disorder in which a structurally abnormal form of PTH is present. These individuals **fail to respond normally to their own PTH but respond in a normal manner to exogenous hormone.**
   c. A variant form of PsHP has been described in which skeletal resistance to exogenous PTH was attributed to a primary deficiency of $1,25(OH)_2D$ production. Short-term treatment with calcitriol restored skeletal responsiveness to exogenous PTH in a period too short to have allowed major healing of underlying metabolic bone disease.

D. Magnesium depletion. Magnesium depletion is a common cause of hypocalcemia in a public hospital setting.

1. Causes of development of magnesium depletion can be grouped into disorders of adequate dietary intake, excessive losses through the gastrointestinal tract, and excessive urinary excretion. In addition, magnesium deficiency and/or depletion may occur in several common endocrine and metabolic disorders. Gastrointestinal disorders or conditions associated with development of magnesium depletion include excessive loss of gastrointestinal fluids because of vomiting, nasogastric suction, diarrhea, malabsorption syndromes and steatorrhea of diverse etiologies, short-bowel syndrome because of surgical resection or

ileojejunal bypass procedures, and acute pancreatitis. Rare cases of sporadic or familial defective intestinal magnesium transport have been described. Long-term treatment with magnesuric diuretics (thiazides or furosemide) is a common cause of magnesium deficiency that can result in depletion. Other conditions associated with increased urinary magnesium losses include acute and chronic alcoholism, hyperalimentation, chronic metabolic acidosis, and magnesium wasting associated with chronic renal diseases, such as pyelonephritis and polycystic disease. Treatment with a number of medications can produce renal **magnesium wasting (magnesium wasting nephropathy)**. These include **aminoglycoside antibiotics (gentamicin, tobramycin, and amikacin)**, other anti-infection agents **(amphotericin B and pentamidine)**, the anticancer agent ***cis*-platinum,** and the immunosuppressive agent **cyclosporin**. Ingestion of **Nexium** has also been reported to cause hypomagnesemia. Rare causes of magnesium depletion, including **familial or sporadic isolated magnesium wasting nephropathy**, have also been reported. Magnesium depletion is encountered frequently in patients with **poorly controlled diabetes mellitus**. Contributing factors include glycosuria-associated osmotic diuresis and enhanced urinary magnesium losses, metabolic acidosis, and relative malnutrition. Hypomagnesemia and magnesium depletion are frequently seen in patients with primary aldosteronism. The latter is attributed to both volume expansion and direct effects of aldosterone on magnesium excretion. Hypercalciuria is associated with decreased renal reabsorption p. 410p. 411of magnesium. Patients with vitamin D–managed hypoparathyroidism may develop magnesium depletion in the face of marked persistent hypercalciuria. Rapid skeletal remineralization (hungry bone syndrome), following successful parathyroid surgery or, on rare occasion, thyroid surgery for Graves disease or other causes of thyrotoxicosis, can result in hypomagnesemia and clinical features of magnesium depletion.

2. The **mechanism of hypocalcemia in magnesium depletion** states is multifactorial.
   - **a.** Impaired PTH secretion
   - **b.** Target-organ resistance to PTH in both the kidney and the

skeleton

3. In the untreated state, circulating levels of PTH are either low or reduced relative to the degree of magnesium depletion and hypocalcemia. Plasma levels of $1,25(OH)_2D$ are frequently low, and there may be resistance to the action of vitamin D at the intestine.
4. A diagnosis of magnesium depletion is clinically accepted with the demonstration of a low serum magnesium level (<1 mEq/L) and low urinary magnesium (<1 mEq/day, unless a renal magnesium wasting state exists) in an appropriate setting.
5. Replacement therapy with magnesium salts results in a rapid rise in circulating levels of PTH, within minutes to hours, initially reaching levels several times normal. However, restoration of the serum calcium levels to normal may require several days.

E. Diagnosis of hypoparathyroid and pseudohypoparathyroid disorders

1. The **diagnosis of idiopathic hypoparathyroidism** is generally one of exclusion. Demonstration of little to no PTH in the presence of hypocalcemia, frequently with hyperphosphatemia and with no evidence for magnesium depletion, strongly supports this diagnosis.
2. Magnesium depletion can develop in individuals with hypoparathyroidism, potentially complicating the diagnostic evaluation. Such individuals can manifest PTH resistance or fail to respond normally to vitamin D treatment on the basis of magnesium depletion; this is reversed with correction of the magnesium deficit.
3. Demonstration of normal responsiveness to exogenous PTH through a standardized **PTH infusion test** excludes the diagnosis of some forms of PsHP, with the exception of the rare individual who has an abnormal circulating form of endogenous PTH (e.g., idiopathic hypoparathyroidism). The PTH infusion test is usually performed with a 5- to 10-minute infusion of 200 U of synthetic PTH 1-34 (human). The normal response is usually >10- to 20-fold increase in urinary cAMP and a doubling of the urinary fractional excretion of phosphorus.
4. Resistance to the action of PTH in stimulating renal formation of $1,25(OH)_2D$ has been demonstrated by measuring levels of

calcitriol first on a control day and again the morning after administration of two separate doses of 200 U of PTH 1-34 injected intramuscularly at 12 and 24 hours before sampling. A normal response is an increase in calcitriol of approximately 50% or a rise from subnormal to normal levels.

5. Demonstration of low tissue levels (red cells) of Gs protein activity in the presence of secondary HPT with or without the presence of hypocalcemia supports the diagnosis of PsHP type Ia. If calcium and PTH levels are normalized as a consequence of vitamin D treatment, a PTH infusion test might be required to distinguish PsHP type Ia from pseudo-PsHP, because Gs protein activity is also reduced in the latter condition.
6. Individuals with PsHP types Ib and Ic also have abnormal responses to PTH infusion, but normal levels of Gs protein activity. Patients with PsHP type Ic thus far described have features of AHO.
7. Patients with PsHP type II in response to a PTH infusion test show a dissociation of the urinary cAMP response (normal) and the phosphaturic response (blunted). In some cases, this is observed only under conditions of hypocalcemia, because normalization of calcium by vitamin therapy or calcium infusion can also normalize the phosphaturic response to PTH. Thus, it might not be possible to make a diagnosis of PsHP type II in a treated patient.

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IV. DISORDERS OF VITAMIN D METABOLISM

Hypocalcemia may be present in a number of primary and secondary disorders of vitamin D metabolism. In this setting, hypocalcemia develops as a consequence of both selective malabsorption of calcium (and possibly phosphorus and magnesium) and emergence of vitamin D deficiency bone disease (e.g., **rickets** or **osteomalacia**). The latter is associated with acquired resistance to the calcemic actions of PTH. In addition, synergistic actions of vitamin D in promoting bone resorptive processes can be blunted or absent. In these disorders, the development of hypocalcemia is associated with secondary HPT. Vitamin D deficiency bone disease is invariably associated with hypophosphatemia (in contrast to hypoparathyroidism or PTH-resistant disorders).

A. Disorders of 25(OH)D metabolism. Nutritional vitamin D

deficiency is now a common condition throughout the world, particularly in elderly patients. Measurement of plasma levels of 25(OH)D can define clinical and physiologic **vitamin D status**. Alterations in 25(OH)D metabolism occur primarily as a consequence of hepatic or hepatobiliary disease, treatment with drugs that alter hepatic vitamin D metabolism, gastrointestinal disorders associated with malabsorption or disruption of enterohepatic circulation of vitamin D, and protein wasting disorders associated with massive loss of protein-bound vitamin D. It should be emphasized that although 25(OH)D is low in these conditions, circulating levels of $1,25(OH)_2D$ can be low, normal, or elevated. Thus, **normal to elevated levels of $1,25(OH)_2D$ do not exclude a diagnosis of vitamin D deficiency**.

1. **Hepatic and hepatobiliary disease.** Circulating levels of 25(OH)D can be low in a number of parenchymal hepatic diseases because of impaired formation from vitamin D_3 or D_2. Disorders include alcoholic hepatitis, chronic active hepatitis, lupoid hepatitis, and alcoholic cirrhosis. However, clinically significant disease does not commonly occur unless severe malnutrition is present. A significant correlation has been described between circulating levels of 25(OH)D and results of the aminopyrine breath test, which provides a measure of hepatocellular function. In contrast, cholestatic hepatic disease, particularly biliary cirrhosis, is associated with a high incidence of metabolic bone disease, a significant component of which is osteomalacia. However, in these disorders, resistance to treatment with conventional doses of vitamin D has been reported, suggesting that factors other than vitamin D deficiency are involved in the associated bone disease.
2. **Gastrointestinal disorders.** Both intestinal malabsorption of fat-soluble vitamins and disruption of the enterohepatic circulation of vitamin D metabolites, particularly 25(OH)D, contribute to the development of vitamin D deficiency. Examples of conditions in which this occurs include primary small intestinal disease (regional enteritis and ulcerative enteritis) and surgical procedures such as total and subtotal gastrectomy and intestinal bypass surgery for weight reduction in the morbidly obese.
3. **Protein wasting disorders.** Vitamin D metabolites circulate predominantly in a protein-bound state. Disorders associated with

protein wasting, such as various enteropathies and conditions in which the nephrotic syndrome develops, frequently manifest low plasma levels of 25(OH)D.

4. **Drug-induced alteration of 25(OH)D metabolism.** Anticonvulsant agents, such as phenobarbital and phenytoin (Dilantin), have been shown **to increase hepatic conversion of 25(OH)D to inactive metabolites**. This results in low circulating levels of 25(OH)D and can cause rickets or osteomalacia in patients on long-term treatment. Adequate direct sunlight exposure or modestly increased vitamin D intake (1 000 to 3 000 U/day) is usually effective in preventing development of or managing the condition.

B. Disorders of $1,25(OH)_2D$ metabolism

1. Circulating levels of **$1,25(OH)_2D$ are increased** in approximately 50% of patients with PHPT, correlating closely with the degree of hypercalciuria and the prevalence of nephrolithiasis. In contrast, in patients with **hypoparathyroidism** and various forms of PsHP, levels of **$1,25(OH)_2D$ are decreased** in association with decreased intestinal absorption of calcium, providing a basis for hormone replacement therapy in these conditions. Similarly, in chronic renal insufficiency, p. 412p. 413an inverse correlation can be shown between renal function (creatinine clearance) and circulating levels of calcitriol. This observation, along with the knowledge that the kidney is the sole site of physiologic production of calcitriol (except for the placenta during pregnancy), has provided considerable understanding of a number of pathophysiologic features of renal osteodystrophy.
2. **Tumor-induced osteomalacia.** Although it is uncommon, tumor-induced osteomalacia (TIO), also referred to as **oncogenic osteomalacia**, is being recognized with increasing frequency. This paraneoplastic syndrome was initially recognized by the association of a malignant or benign tumor and the presence of clinical, biochemical, and radiologic features of osteomalacia or, in some cases, rickets. Surgical cure, when possible, was followed by improvement or resolution of osteomalacia/rickets. Initial cases,

mesenchymal in origin, involved ossifying and nonossifying mesenchymomas, hemangiomas, and giant-cell tumors of bone. Subsequently, a much greater diversity of tumor type has been recognized, including prostate carcinoma, breast carcinoma, small- and oat-cell carcinomas, multiple myeloma, and hematogenous malignancies, such as chronic lymphocytic leukemia.

a. Clinical features of TIO may initially be subtle and nonspecific but generally evolve to include bone pain, muscle weakness, recurrent pathologic fractures, and pseudofractures. Biochemical abnormalities include hypophosphatemia, and serum calcium levels that vary from normal to overt hypocalcemia, PTH levels varying with the serum calcium, and elevated levels of alkaline phosphatase. Serum levels of 25(OH)D are normal, whereas levels of $1,25(OH)_2D$ are either low or inappropriately reduced for the degree of hypophosphatemia. Urinary phosphate wasting is present with a reduced threshold for phosphorus reabsorption (TmP/GFR). Aminoaciduria may be present in some cases.

b. Studies of the **pathogenesis** of TIO have demonstrated that the tumors produce FGF23 and that high levels are found in the circulation.

c. Complete surgical removal of the tumor reduces high levels of FGF23 and invariably results in a cure. Prior to surgery, affected individuals are characteristically resistant to treatment with pharmacologic doses of vitamin D or dihydrotachysterol. However, for patients who are not cured by surgery, treatment with phosphorus supplements and near-physiologic doses of $1,25(OH)_2D_3$ (1 to 3 μg/day) may result in clinical improvement of bone pain with healing of osteomalacia.

V. MANAGEMENT OF HYPOCALCEMIC DISORDERS

Administration of oral calcium supplements, active vitamin D or vitamin D analogs, and magnesium supplementation is central to the management of hypocalcemic disorders. In treating hypoparathyroid disorders, the goal is to correct symptomatic hypocalcemia without inducing the development of hypercalcemia. Hypercalciuria may develop, which can be managed by thiazide diuretics. Phosphate binders and a low phosphate diet are also used if needed to control hyperphosphatemia. In general, the

therapeutic endpoint is to maintain serum calcium levels slightly below normal (no lower than 0.5 mg/dL below normal) in the range of 8.5 to 9.5 mg/dL, with urinary calcium levels below approximately 400 mg/day (Table 31-7).

A. Oral calcium supplements administered alone (3 to 7 g/day of elemental calcium) in multiple divided doses can be effective in correcting even moderately severe hypocalcemia unless a malabsorption syndrome is present. Choice of the form of calcium supplement is often a matter of personal preference (Table 31-8).

B. Doses of various forms of vitamin D analogs required to correct hypocalcemia vary with the underlying disorder.

1. In disorders associated with underlying skeletal mineralization defects (e.g., osteomalacia), a higher dose of vitamin D might be tolerated or required early in the course of therapy. With progressive remineralization, dose reduction might be required to prevent development of hypercalcemia.

2. With the use of more potent forms of vitamin D, such as **$1,25(OH)_2D_3$, the requirement for calcium supplementation is reduced**. Some individuals who ingest diets that are high in calcium content might not require additional

p. 413p. 414p. 414p. 415calcium. In contrast, treatment with vitamin D_2 or D_3 usually requires concomitant administration of larger amounts of calcium supplements.

TABLE 31-7 Dietary Reference Intakes for Calcium and Vitamin D

Life stage group	Calcium			Vitamin D		
	Estimated average requirement (mg/d)	Recommended dietary allowance (mg/d)	Upper level intake (mg/d)	Estimated average requirement (IU/d)	Recommended dietary allowance (IU/d)	Upper level intake (IU/d)
Infants 0–6 mo	*a*	*a*	1 000	*b*	*b*	1 000
Infants 6–12 mo	*a*	*a*	1 500	*b*	*b*	1 500
1–3 yr old	500	700	2 500	400	600	2 500
4–8 yr old	800	1 000	2 500	400	600	3 000
9–13 yr old	1 100	1 300	3 000	400	600	4 000
14–18 yr old	1 100	1 300	3 000	400	600	4 000
19–30 yr old	800	1 000	2 500	400	600	4 000
31–50 yr old	800	1 000	2 500	400	600	4 000
51–70 yr old males	800	1 000	2 000	400	600	4 000
51–70 yr old females	1 000	1 200	2 000	400	600	4 000
>70 yr old	1 000	1 200	2 000	400	800	4 000
14–18 yr old, pregnant/ lactating	1 100	1 300	3 000	400	600	4 000
19–50 yr old, pregnant/ lactating	800	1 000	2 500	400	600	4 000

[a]For infants, adequate intake is 200 mg/day for 0 to 6 months of age and 260 mg/day for 6 to 12 months of age.
[b]For infants, adequate intake is 400 IU/day for 0 to 6 months of age and 400 IU/day for 6 to 12 months of age.

TABLE 31-8 Oral and Parenteral Calcium Preparations Available for Management of Acute and Chronic Hypocalcemic Disorders

Calcium salt	Percent elemental calcium	Calcium content
Oral Preparations		
Calcium carbonate	40	400 mg/1 g (1 g/5 mL)
Calcium glubionate	7	64 mg/1 g (1.8 g/5 mL)
Calcium gluconate	9	90 mg/1 g
Calcium lactate	13	130 mg/1 g
Calcium citrate	21	211 mg/1 g
Tricalcium phosphate	39	390 mg/1 g
Intravenous Preparations		
Calcium chloride	36	360 mg/1 g (1 g/10 mL)
Calcium gluconate	9	90 mg/1 g (1 g/10 mL)

3. Similarly, simultaneous adjustment of calcium intake and doses of $1,25(OH)_2D_3$ can be difficult because of the extreme potency of this form of vitamin D. Thus, either calcium intake or the dose of calcitriol should be adjusted.

The major considerations involved in choosing a particular form of vitamin D include potency, time of onset and offset of action, and

the interval for returning serum calcium levels to normal, either on an inpatient or an outpatient basis. These properties, as applicable to treatment with various forms of vitamin D sterols or their analogs, are summarized in Table 31-9.

C. 1-84 recombinant human parathyroid hormone (rhPTH; Natpara) was approved by the FDA in January 2015 for the treatment of hypocalcemia patients with hypoparathyroidism whose hypocalcemia cannot be managed with calcium supplementation and active forms of vitamin D, and in whom the potential benefits outweigh p. 415p. 416the potential risk of osteosarcoma (Table 31-10). rhPTH 1-84 carries a black box warning that bone cancer (osteosarcoma) has been observed in rat studies with its use. It is unknown whether rhPTH 1-84 causes osteosarcoma in humans, but because of a potential risk of osteosarcoma, it is only available through a restricted program under a Risk Evaluation and Mitigation Strategy.

TABLE 31-9 Commercially Available Vitamin D Preparations

Compound	Trade name	Potency relative to vitamin D_3	Onset of action (d)	Offset of action
Vitamin D_3 (cholecalciferol)	Delta D_3	1	10–14	Weeks to months
Vitamin D_2 (ergocalciferol)	Drisdol	1	10–14	Weeks to months
Dihydrotachysterol	Hytakerol	5–10	4–7	7–21 d
Calcifediol (25-hydroxyvitamin D_3)	Calderol	10–15	7–10	Weeks
Alfacalcidiol[a,b] (1α-hydroxyvitamin D_3)	One-alpha	1 000	1–2	2–3 d
Calcitriol (1,25-dihydroxyvitamin D_3)	Rocaltrol, Calcijex+	1 000	1–2	2–3 d

[a]Not approved for clinical use in the United States.
[b]Available for parenteral administration.

TABLE 31-10 Indications for Considering the Use of rhPTH 1–84 in Hypoparathyroidism

1. Inadequate control of the serum calcium concentration (this could be due to intercurrent illness, compliance, absorption, or intrinsic changes in requirements that are beyond facile correction with calcium and active vitamin D)
2. Oral calcium/vitamin D medications required to control the serum calcium or symptoms that exceed 2.5 g of calcium or >1.5 μg of active vitamin D or >3.0 μg of the 1-α vitamin D analog.
3. Hypercalciuria, renal stones, nephrocalcinosis, stone risk, or reduced creatinine clearance or eGFR (<60 mL/min)
4. Hyperphosphatemia and/or calcium-phosphate product that exceeds 55 mg^2dL^2 (4.4 $mmol^2L^2$)
5. A gastrointestinal tract disorder that is associated with malabsorption
6. Reduced quality of life

rhPTH, recombinant human parathyroid hormone; eGFR, estimated glomerular filtration rate.
From Brandi ML, Bilezikian JP, Shoback D, et al. Management of hypoparathyroidism: Summary Statement and Guidelines. *J Clin Endocrinol Metab* 2016;101(6):2273–2283.

A trial was designed to determine whether rhPTH 1-84 can be used as a substitute for, or be used to help reduce the amount of, active forms of vitamin D or oral calcium taken by participants. Results showed 42% of rhPTH 1-84 treated participants achieved normal blood calcium levels on reduced doses of calcium supplements and active forms of vitamin D, compared to 3% of placebo-treated participants.

rhPTH 1-84 at doses of 50 μg titratable to 75 μg, or 100 μg/day, administered subcutaneously in the outpatient setting, was shown to be an efficacious and well-tolerated PTH replacement therapy for patients with hypoparathyroidism. The most common side effects observed in Natpara-treated participants were paresthesias, low and high blood calcium, headache, and nausea.

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32 Hypercalcemic Crisis

Catherine A. Sullivan and Devin Steenkamp

I. BACKGROUND

Elevation in serum calcium concentration (defined as an albumin corrected calcium greater than 10.5 mg/dL or 2.6 mmol/L) is a common metabolic disorder in endocrinology and general medicine. **Hypercalcemic crisis**, however, is an unusual presentation of hypercalcemia, encountered with decreasing frequency in modern clinical practice. Although there is no formal definition of hypercalcemic crisis, the diagnosis should be considered when the albumin corrected serum **calcium is greater than 14 mg/dL** associated with features of multi-organ dysfunction directly resulting from the underlying hypercalcemia. Approximately 40% of serum calcium is bound to albumin; therefore, in low albumin states, there can be a falsely low estimate of serum calcium levels if this is not accounted for. Calcium is bound to albumin in a ratio of 0.8 mg/dL calcium per 1 g/dL albumin in serum. A corrected calcium level in the setting of low albumin can be calculated as follows: measured total calcium in mg/dL + [0.8 × (4.0 - albumin in g/dL)] with 4.0 g/dL used as a normal albumin level. Hypercalcemic crisis should also be considered in symptomatic patients with relatively modest hypercalcemia with associated complications or in those with markedly asymptomatic hypercalcemia.

II. ETIOLOGY

There are multiple causes for elevated serum calcium, as listed in Table 32-1. Often, hypercalcemic crisis develops in patients with underlying mild elevations in calcium who then develop a condition exacerbating their primary disease. Acute illness, volume depletion, immobilization, as well as the use of certain medications may cause a transition from moderate to severe hypercalcemia. Infarction of a parathyroid adenoma has also been associated with hypercalcemic crisis. Increased physiologic bone turnover, as seen during puberty and in Paget disease, also increases the risk for transition into crisis. The presence of concomitant conditions that can each independently cause hypercalcemia may also result in crisis,

as in cases of coexisting primary hyperparathyroidism and humoral hypercalcemia of malignancy. A broad differential diagnosis is, therefore, imperative when determining the cause of hypercalcemia. Both parathyroid hormone (PTH)- and non–PTH-mediated causes of hypercalcemia have been implicated in the pathogenesis of hypercalcemic crisis.

A. Primary hyperparathyroidism is the **most common cause** of hypercalcemia in the outpatient setting and also the most common cause of hypercalcemic crisis. An elevated serum PTH level or inappropriately normal for the degree of hypercalcemia. (In hypercalcemia from primary hyperparathyroidism, serum PTH levels may be elevated or can be in the normal range. The vast majority of patients with primary hyperparathyroidism have a single benign parathyroid adenoma, irrespective of the degree of hypercalcemia. Ectopically located adenomas are often described in patients with crisis, which may bring about challenges in diagnosis and management. Parathyroid hyperplasia, multiple adenomas, and parathyroid carcinoma are less common causes of primary hyperparathyroidism. Parathyroid carcinoma accounts for less than 1% of all cases of primary hyperparathyroidism, but more commonly results in hypercalcemic crisis. Clues to suggest parathyroid carcinoma include an extremely elevated PTH (often greater than three times the upper limit of normal), a palpable neck mass, recurrent laryngeal nerve paralysis, and markedly elevated serum calcium levels.

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TABLE 32-1 Causes of Hypercalcemia

Conditions with an elevated or inappropriately normal PTH level:

1. Primary hyperparathyroidism
   - **a.** Parathyroid adenoma
   - **b.** Multiglandular hyperplasia (MEN1 or MEN2a syndromes)
   - **c.** Parathyroid carcinoma
2. Familial hypocalciuric hypercalcemia
3. Tertiary hyperparathyroidism
4. Inherited conditions: MEN1, MEN2a, familial isolated hyperparathyroidism, hyperparathyroidism jaw tumor syndrome
5. Ectopic PTH production[a]

6. Medication
    i. Lithium[b]

Conditions with a suppressed PTH:

1. Malignancy
    a. Parathyroid hormone-related protein-associated hypercalcemia (humoral hypercalcemia of malignancy)
    b. Ectopic production of 1,25 dihydroxyvitamin D (via extrarenal 1α-hydroxylase)
    c. Osteolytic bone metastasis
    d. Multiple myeloma (via osteolytic peptides)
    e. Cytokine-mediated local osteolysis
2. Granulomatous disease
    a. Tuberculosis
    b. Sarcoidosis
    c. Endemic mycosis (histoplasmosis, coccidiodomycosis)
    d. Leprosy
    e. Crohn disease
    f. Berylliosis
    g. Foreign body granulomas[c]
3. Medications
    a. Thiazides
    b. Estrogens
    c. Vitamin D excess
    d. Vitamin A excess
    e. SGLT-2 inhibitors[d]
4. Endocrine disorders
    a. Thyrotoxicosis
    b. Adrenal insufficiency
    c. Pheochromocytoma
    d. VIPoma
5. Miscellaneous causes
    a. Immobilization
    b. Recovery phase of acute tubular necrosis following rhabdomyolysis[c]

MEN, multiple endocrine neoplasia; PTH, parathyroid hormone; SGLT2, sodium-glucose cotransporter-2.

[a]Ectopic PTH production has been described in the following tumors/malignancies: ovarian, pancreatic neuroendocrine, medullary thyroid, papillary thyroid, lung, thymoma, melanoma, esophageal, gastric, breast, hepatocellular, and small intestine leiomyosarcoma.

[b]Lithium use can result in an increased calcium sensor set point as well as parathyroid

adenoma or hyperplasia.
[c]Reported in case reports of hypercalcemic crisis.
[d]Exact mechanism unknown, thought to be due to diuresis with reduced renal calcium excretion.

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B. Hypercalcemia of malignancy, encountered in up to 20% to 30% of malignancies, is often the cause of hypercalcemia encountered in the hospital setting. Typically, the underlying cancer diagnosis is established when patients present with elevated serum calcium levels. Squamous cell lung cancer and other epithelial tumors are most often implicated. Other malignancies, including ovarian cancer, multiple myeloma, lymphoma, renal, and breast cancers, have also been directly implicated in hypercalcemic crisis. Most malignancy-related cases are caused by elevations in serum parathyroid hormone-related peptide (PTH-rP), a condition also known as humoral hypercalcemia of malignancy (see Chapter 34). PTH-rP, oversecreted by some tumor cells, has a similar amino acid sequence as PTH and interacts at the PTH receptor in bone and the kidneys. This results in a subsequent increase in serum calcium levels because of increased bone resorption and decreased renal calcium excretion. Humoral hypercalcemia of malignancy has been described most commonly in squamous cell tumors (including the head and neck, esophagus, cervix, lung, and pancreas), renal cell carcinoma (including clear cell), bladder carcinoma, breast carcinoma, ovarian carcinoma, endometrial carcinoma, and HTLV-1–related lymphomas. Osteolytic bone metastases, extrarenal 1α-hydroxylase activity with 1,25-dihydroxyvitamin D excess (reported in certain lymphomas), ectopic PTH production, and calcium release from osteolytic peptides are other potential mechanisms of malignancy-induced hypercalcemia.

III. CLINICAL PRESENTATION

Hypercalcemia often does not become overtly symptomatic until serum calcium levels rise to greater than 12 mg/dL. The gastrointestinal, renal, neurologic, and musculoskeletal systems are most commonly affected. Owing to the variety of clinical manifestations reported in hypercalcemia and overlap with other medical conditions, the correct diagnosis may be

delayed. Mild hypercalcemia is often discovered incidentally through laboratory tests obtained for unrelated reasons. Patients with hypercalcemic crisis can be distinguished from those without crisis by the presence of more than one organ system abnormality, as listed in Table 32-2. Common presenting features of hypercalcemic crisis include pancreatitis, severe abdominal pain, psychosis, agitation, dehydration, and cardiac arrhythmias.

TABLE 32-2 Clinical Manifestations of Hypercalcemia

Gastrointestinal
Constipation, nausea, anorexia, vomiting, abdominal pain (may mimic acute abdomen[a]), pancreatitis[a]
Renal
Nephrogenic diabetes insipidus with dehydration, polyuria, polydipsia, acute renal injury, nephrocalcinosis, renal stones, renal vasoconstriction
Neurologic
Weakness, fatigue, confusion, poor concentration, personality changes, lethargy, coma, psychosis[a], agitation[a]
Cardiovascular
Bradyarrhythmias[a], heart block[a], shortened QT and QTc intervals, ventricular arrhythmias[a], vascular calcification, hypertension
Bone
Pain, arthralgias, osteopenia or osteoporosis (in the setting of hyperparathyroidism), osteitis fibrosis cystic
[a]More common in hypercalcemic crisis.

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IV. DIAGNOSIS AND WORKUP

Evaluation of hypercalcemic crisis should begin with assessment for the presence of primary hyperparathyroidism. Initial laboratory tests should include serum calcium, creatinine, albumin, phosphorous, and parathyroid hormone levels. If the initial evaluation does not support the diagnosis of primary hyperparathyroidism, or if there is diagnostic uncertainty, further studies may be indicated depending on the clinical situation. These additional studies would include, but are not limited to, serum thyroid-stimulating hormone level if there is concern for thyroid dysfunction, serum electrophoresis and urinary Bence-Jones proteins as part of the

evaluation for multiple myeloma, bone markers (such as alkaline phosphatase), PTH-rP, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D levels.

If primary hyperparathyroidism is confirmed based on the biochemical results, imaging should be carried out to localize the adenoma to guide further treatment. Various imaging modalities have respective strengths and weaknesses, and the choice of which initial imaging modality to select should be dictated by local expertise and availability of technology. An initial approach that has high sensitivity and specificity, without the risk of exposure to ionizing radiation, is a thorough neck ultrasound. Ultrasound-guided needle aspiration with analysis of the aspirate for PTH may provide biochemical confirmation of the imaging findings. (PTH levels from a parathyroid adenoma aspirate are run on a typical PTH assay, typically diluted in 1 mL saline. However, if hypercalcemia due to parathyroid carcinoma is suspected, FNA is not recommended due to potential risk for hemorrhage and tumor seeding along the needle track.) Additional benefits of ultrasound include relatively low cost, safety, and availability in the local practitioner's office. Disadvantages include limited visualization of ectopic parathyroid gland locations and dependence on operator experience. Up to 80% of neck parathyroid adenomas are detected by experienced ultrasonographers. In the event of a nondiagnostic neck ultrasound, a nuclear scintigraphy parathyroid scan, including images of the mediastinum and chest, is often the next best test to identify the possibility of an ectopic adenoma (which are typically located in the tracheoesophageal groove, mediastinum, or thymus). If both ultrasonography and scintigraphy are nondiagnostic, a contrast-enhanced four-dimensional computed tomography scan of the head, neck, and upper chest may be helpful, but may not be an option for patients with advanced renal disease. If an adenoma is not identified with imaging, but the diagnosis has been biochemically established, patients should be referred for exploratory parathyroid surgery by an experienced parathyroid surgeon. Unless there is consideration of atypical or multigland disease, the widespread availability of preoperative localization imaging affords many patients the benefit of avoiding bilateral neck exploration, which carries a higher risk of postoperative complications.

V. Treatment

The approach for patients presenting with crisis is similar to that for

patients with less severe hypercalcemia and often requires a multidisciplinary approach. The goals of treatment include correcting hypovolemia, lowering serum calcium (commonly initiated through increasing urinary calcium excretion), and decreasing bone calcium resorption. Prolonged immobilization may exacerbate hypercalcemia through increased bone turnover, and should be avoided. In addition, certain medications, such as thiazide diuretics, which promote renal calcium reabsorption, should be discontinued. The underlying cause of hypercalcemia further directs treatment strategy. In the majority of patients with primary hyperparathyroidism, definitive therapy that results in cure in most individuals is surgical parathyroidectomy. Long-term outcomes with combined modern medical and surgical management are excellent. Figure 32-1 outlines key concepts and steps in a proposed treatment algorithm.

A. Medical therapy

Initial medical management of hypercalcemic crisis focuses on intravenous (IV) hydration to expand intravascular volume and promote calciuresis. IV volume expansion increases glomerular filtration rate to promote calcium filtration at the glomerulus, inhibits calcium reabsorption at the proximal nephron, and increases distal calcium excretion. Initial treatment often requires 3 to 4 L of normal saline administered p. 421p. 422within the first 24 hours with bolus administration as indicated for severe volume depletion or circulatory compromise. Urine output should be strictly monitored with a goal of at least 2 L output daily, or approximately 100 to 150 cc of urine output per hour. A reduction in serum calcium by 1.6 to 2.4 mg/dL can be anticipated with isotonic fluid infusion alone. Loop diuretics, such as IV furosemide (40 to 80 mg/dose, given every 6 to 8 hours as needed), are often beneficial once patients are volume replete to manage the consequences of possible volume overload from fluid resuscitation and to further promote calciuresis by blocking calcium reabsorption in the ascending limb of the loop of Henle. Electrolytes, particularly potassium, should be closely monitored when using these agents, given the risk of hypokalemia. It is important to note that loop diuretics may have deleterious effects unless IV expansion is prioritized and should be used to augment renal calciuresis as needed.

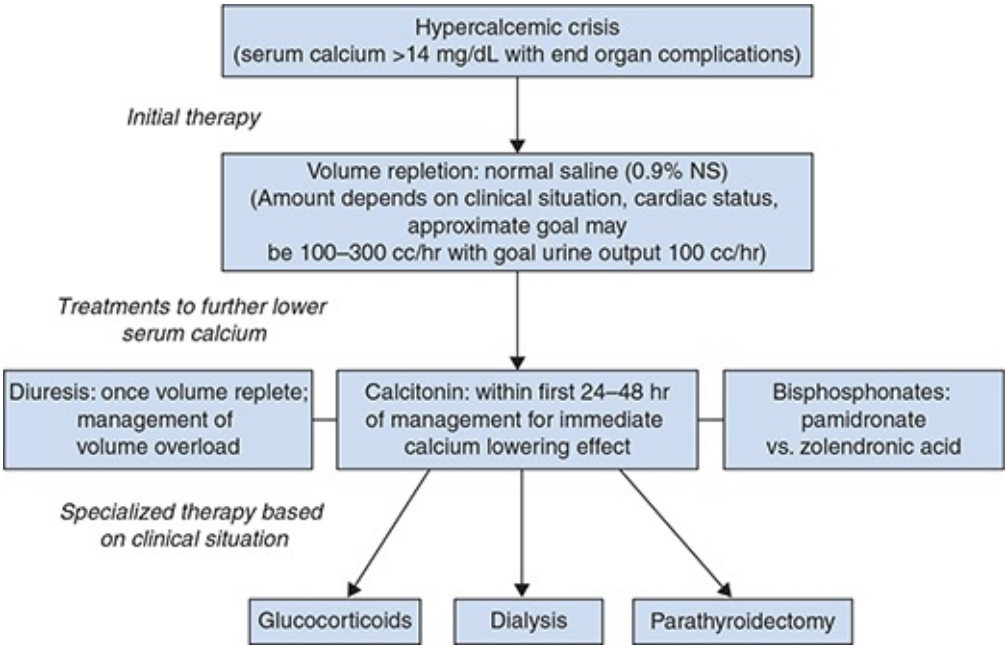

Figure 32-1. Algorithm for management of hypercalcemia NS, normal saline.

Once acute management with IV hydration has been initiated, **IV bisphosphonates** should be introduced, because these are the **most potent agents** available for medical management of hypercalcemic crisis. They lower serum calcium by blocking osteoclast-mediated bone resorption, decreasing osteoclast progenitor cell production, and inducing osteoclast apoptosis. IV preparations are preferred because of limited bioavailability of oral formulations, the relative increased potency of IV formulations, and the frequent presence of concomitant coexisting gastrointestinal symptoms, which limits oral intake in many patients. **Pamidronate and zoledronic acid** are approved in the United States for the treatment of hypercalcemia of malignancy. Although they are frequently utilized in the treatment of severe hypercalcemia due to other causes, their efficacy and safety in these settings is less established, and, as a result, they **are not approved** by the Food and Drug Administration in the United States for use in **non–cancer-related hypercalcemia**. Pamidronate is administered as a one time, 60 to 90 mg IV infusion over at least 2 hours. Calcium levels are expected to decline within 48 hours of administration, with a maximal effect in approximately 6 days and an overall duration of effect of approximately 30 days. Zoledronic acid (administered as 4 mg for the initial treatment and 8 mg for relapse) may be preferred over pamidronate because it may result in a slightly faster calcium

reduction, can be given as a one time, rapid infusion over 15 minutes, and may be p. 422p. 423superior in restoring normocalcemia. In head-to-head clinical trials, zoledronic acid has been reported to be superior in restoring normocalcemia in hypercalcemia of malignancy (86% to 88% for zoledronate vs. 70% for pamidronate). For both of these agents, repeat dosing can be considered at no sooner than 7 days, with need depending on the clinical situation of etiology of hypercalcemia. Renal function needs to be monitored prior to and following administration of these agents. In patients with a creatinine clearance less than 30 mL/minute, pamidronate should be administered over an extended infusion time of 4 to 6 hours, and decreased doses should be considered. Zoledronic acid is not recommended for patients with a creatinine clearance less than 30 mL/minute. However, in cases of severe hypercalcemia, one should consider the risks versus benefits of therapy.

Because it takes approximately 48 hours for bisphosphonate therapy to take effect, **calcitonin** may be used as an adjuvant rapid-acting treatment to ameliorate hypercalcemia. Calcitonin reduces osteoclast-mediated bone resorption and increases calciuresis via downregulation of calcitonin receptors in bone and the kidneys. Used alone, it has only a modest effect, with approximately 1 mg/dL reduction in calcium levels. It is administered subcutaneously or intramuscularly in a range of 4 to 8 IU/kg every 12 hours. Although it has the benefit of rapid onset of action (12 to 24 hours), it must be used in conjunction with other therapies as a result of the development of tachyphylaxis, which is typically seen within 48 hours of initiation of therapy.

Hypercalcemia may be responsive to **glucocorticoid therapy** if it is secondary to lymphoma (via antineoplastic effects) or granulomatous disease (by inhibition of 1α-hydroxylase CYP27B1 in activated macrophages). Glucocorticoid therapy also lowers serum calcium by decreasing bone resorption and intestinal calcium absorption and by slightly increasing renal calcium excretion. Typical doses required are 1 to 2 mg/kg prednisone daily for 3 to 5 days or 200 to 300 mg hydrocortisone daily for the same duration. Effect is not immediate, however, and is typically seen after 4 to 10 days of treatment.

Other therapies have been reported to be effective in select cases

of severe hypercalcemia, including Infliximab in Crohn's disease and sarcoidosis. **Denosumab**, a monoclonal antibody with affinity for the receptor activator of NF-κB ligand (RANKL) to inhibit osteoclast formation, has been used in refractory cases of hypercalcemic crisis due to parathyroid carcinoma, without needing to adjust for renal dysfunction. **Cinacalcet**, a calcimimetic agent, may also have modest benefit in patients with crisis due to parathyroid carcinoma.

Older agents, such as mithramycin, IV phosphate, and gallium nitrate, have been effectively employed in the management of hypercalcemic crisis prior to the widespread availability and potency of bisphosphonates. These agents are no longer commonly used because of side effects and limited efficacy compared to current therapies, but may be considered if bisphosphonates are ineffective or contraindicated. Dialysis against a low calcium or calcium-free dialysate to help reduce serum calcium levels may be valuable in select patients with severe renal dysfunction or failure, complications from volume overload precluding use of IV hydration, or when medical therapies are not effective or contraindicated.

B. Surgery

Medical treatment of primary hyperparathyroidism with crisis should be regarded as a temporary measure to "bridge" patients toward definitive curative parathyroidectomy, ideally performed by an experienced endocrine surgeon. Timing of surgery is not always straightforward and is often dependent on the availability of clinical expertise, diagnostic studies, and patients' clinical status. Recent case series favor early surgery after a period of medical optimization, rather than emergency surgery; however, exact timing has not been established. Intraoperative and postsurgical PTH levels can be expected to normalize rapidly, whereas calcium levels improve more slowly over days to weeks. Resolution of the complex metabolic changes due to hypercalcemia may take months, and many of the skeletal manifestations, such as osteitis fibrosa cystica, may improve only slightly. Postoperatively, symptomatic hypocalcemia (with or without tetany) may develop if this is not anticipated, and p. 423p. 424postsurgical calcium levels are not closely monitored as a result of development of the "hungry bone syndrome."

This entity may occur from subsequent relative hypoparathyroidism and transient suppression of the remaining parathyroid glands, leading to a reduction in bone turnover and marked increased calcium influx into bone.

VI. CONCLUSION

Hypercalcemic crisis is an increasingly rare manifestation of decompensated calcium homeostasis with subsequent multi-organ dysfunction, most often attributed to primary hyperparathyroidism. Medical therapy to optimize organ function should be prioritized with aggressive saline volume expansion and IV bisphosphonate administration as first-line therapy as a bridging measure toward definitive surgery by an experienced endocrine surgeon. Long-term outcomes with combined medical and surgical management are excellent.

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33 Metabolic Bone Disease

Rod Marianne Arceo-Mendoza, Arshi Basit, and Pauline M. Camacho

I. INTRODUCTION

A. Bone physiology. Bone is a specialized support structure subject to constant change. A constant regulatory balance is maintained between formation and resorption (breakdown). Bone is composed of three major elements: cells, matrix, and minerals. Bone cells make up 3% of the bone volume and constitute three major types: osteoblasts, osteocytes, and osteoclasts. **Osteoblasts** are mononucleated bone-forming cells originating from the mesenchymal stem cells (osteoprogenitor cells). They are responsible for producing protein matrix for bone mineral deposition and are rich in alkaline phosphatase. **Osteocytes**, derivatives of mature osteoblasts, are the most abundant cells in the bone, behaving as mechanosensors in bone formation and resorption. **Osteoclasts**, derived from the cells of monocyte macrophage series, are large, multinucleated cells responsible for bone resorption. The cellular content in an adult human skeleton is higher in trabecular bone (e.g., vertebrae) as compared to the cortical bone (e.g., hip).

B. Basis of metabolic bone disorders. There are several external regulatory factors controlling the chemical composition, mass, and mechanical properties of bone.

Factors disrupting normal bone homeostasis include:

1. Decreased calcium and phosphate intake or absorption
2. Decrease in vitamin D absorption or activation
3. Decreased production of estrogen, testosterone, or growth hormone
4. Increased endogenous production of parathyroid hormone (PTH), thyroid hormone, cortisol, or other nonregulatory hormones
5. Increased levels of inflammatory cytokines
6. Chronic treatment with supraphysiologic doses of glucocorticoids or thyroid hormones, or standard doses of some drugs (e.g., anticonvulsants, chemotherapeutic agents)
7. Decreased physical activity leading to reduced osteoblastic bone

formation

8. Age-related decline in osteoblast generation from mesenchymal stem cells
9. Congenital disorders of bone collagen formation

II. DIAGNOSTIC TESTS

A. Serum determinations.

A morning fasting blood sample of serum total calcium, ionized calcium, phosphate, intact PTH (iPTH), and biochemical markers of bone turnover, such as serum C-telopeptide, is preferable because of considerable diurnal and/or postprandial variations. 25 OH vitamin D is measured to assess vitamin D sufficiency.

B. Urinary determinations

24-hour urine calcium measurement should be performed that helps effectively identify hypercalciuria or malabsorption when results are outside the normal range (100 to 300 mg/day or 1.5 to 4 mg/kg/24 hours). Both disorders are associated with higher rates of bone loss. Patients may not show adequate response to osteoporosis therapy when calcium deficient. Spot urine calcium does not detect malabsorption because it can wrongfully diagnose hypocalciuria in an incomplete collection. 24-hour urine creatinine should also be measured simultaneously to assure completeness of collection. 24-hour urine sodium should also be measured. High sodium intake, measured as urinary sodium excretion, alters calcium metabolism by increasing urinary calcium excretion.

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Calcium excretion is diminished by thiazide diuretics by as much as 50 to 150 mg/day because of increased reabsorption. Furosemide may increase calcium excretion.

1. **N-Telopeptide (NTx)** excretion, an indicator of bone loss (resorption) activity, should be determined. Normal values vary with age and sex, but in general, values >65 nm BCE/mmol indicate increased bone loss activity, and values <35 nm BCE/mmol indicate satisfactory suppression of bone resorption.

C. Radiologic detection of decreased bone mass

1. **Standard radiographs**

   Dual-beam X-ray–based photon absorptiometry (DXA) is a reliable and sensitive method of detecting and quantitating bone

loss in the spine, hip, and forearm, detecting ≥15% change in bone mass. Radiation exposure to the patient is very small.

2. Quantitative computed tomography (qCT) is a type of computed tomography (CT) with similar accuracy in detecting bone mineral density (BMD) of the spine and hip. However, it is **not recommended for screening**, primarily because the application of T-scores to predict the risk of fracture has not been well validated.

III. DECREASED BONE MASS

A. Definition.

Decreased bone mass is the deterioration of bone tissue clinically and disruption of bone architecture radiographically, relative to normal values for sex and race, compromising bone strength and an increased risk for fracture. Osteoporosis has no clinical manifestations until there is a fracture. In comparison, pain is common in osteomalacia in the absence of fractures or other bone deformities.

B.

Three main types have been identified: **osteoporosis**, characterized by decreased bone formation paralleled by increased bone resorption with microarchitectural disruption and skeletal fragility; **osteomalacia**, a defect of bone mineralization with accumulation of unmineralized bony matrix, caused by deficiency in calcium, vitamin D, and/or phosphate; and **osteitis fibrosa**, a complication of hyperparathyroidism characterized by fibrous degeneration of bone caused by increased bone resorption leading to soft and deformed bones.

C. Evaluation

1. **Radiographs.** Vertebral compression fractures may first be visualized in a standard lateral radiograph of the spine, usually indicative of osteoporosis. Pseudofractures in bones like the pelvis, femurs, tibias, and fibulas may be seen in patients with osteomalacia.
2. **DXA or qCT bone mass measurements** are the appropriate techniques for precise quantitation of bone mass.
   a. DXA BMD measurement of the spine and hip is the most commonly used method. Individual BMD measurements are commonly expressed in terms of a **T-score**, calculated by subtracting the mean BMD of a young-adult reference population from the patient's BMD and dividing by the standard deviation (SD) of young-adult population. The **Z-score**

indicates difference in SD comparing an individual's BMD with an age-matched population. The T-score is the most useful and most commonly used indicator of BMD status in postmenopausal women. However, Z-scores are recommended for premenopausal women, with a Z-score −2.0 or lower defined as "below the expected range for age" and usually suggestive of the presence of causes of secondary osteoporosis.

b. The commonly used World Health Organization criteria for **severity of bone loss** as measured by DXA are as follows:

i. T-score that is 2.5 SD or more below the young-adult mean BMD is defined as **osteoporosis**, provided that other causes of low BMD have been ruled out. (T-score less than or equal to −2.5 SD)

ii. T-score that is 1SD to 2.5 SD below the young-adult mean is termed as **osteopenia** (T-score less than −1 and greater than −2.5 SD)

iii. Normal bone density is defined as a value within 1 SD of the mean value in the young-adult reference population. (T-score greater than or equal to −1 SD)

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The term "osteoporosis" as used in BMD measurement reports does not imply a histologic diagnosis of osteoporosis but merely indicates the degree of bone loss as measured by DXA. For every 1-SD decrease in age-adjusted BMD, the relative risk (RR) of fracture increases 1.6- to 2.6-fold. According to the **2016 American Association of Clinical Endocrinologists (AACE)/ American College of Endocrinology (ACE) Guidelines for Postmenopausal Osteoporosis**, while osteoporosis has traditionally been diagnosed based on low bone density in the absence of fracture, it may also be diagnosed in patients with osteopenia and increased fracture risk using the Fracture Risk Assessment Tool (FRAX) (www.shef.ac.uk/FRAX) country-specific thresholds. FRAX, developed in 2008, is an algorithm that allows estimation of fracture probability from an individual's set of risk factors. FRAX estimates the 10-year likelihood of the hip and major osteoporotic fractures.

D. When to measure DXA bone density

1. **All women aged 65 years and older and men over 70 years of age.**

   The US Preventive Services Task Force recommends BMD testing for all women aged ≥65 and younger women whose fracture risk is equal to or greater than that of a 65-year-old white woman who has no additional risk factors.

   By 60 years of age, 50% of the white women have osteopenia or osteoporosis. White women experience hip fractures twice as common as men; however, there is not much sex difference in the same fractures among African Americans and Asians. There is not much ethnic or racial variability in vertebral fractures worldwide.

2. **Younger postmenopausal women or younger men**
   - **a.** With a history of fracture(s) without major trauma
   - **b.** Starting or taking long-term systemic glucocorticoid therapy
   - **c.** With radiographic osteopenia
   - **d.** With clinical risk factors for osteoporosis (low body weight, cigarette smoking, family history of spine or hip fractures, early menopause, or secondary osteoporosis)

E. Risk factors for osteoporotic fractures include:

1. Age ≥ 65 years in women and ≥70 years in men
2. Low body weight (<57.6 kg [127 lb])
3. Family history of osteoporosis or fractures in first-degree relatives
4. Lifestyle risk factors, including smoking, excessive alcohol intake (>3 drinks daily), chronic low calcium intake, and low level of physical activity
5. Increased fall risk because of advanced age, frailty, or peripheral neuropathy
6. Vertebral deformity on standard radiographs suggesting decreased bone mass (height loss or kyphosis)
7. Endocrine disorders like hyperparathyroidism, hyperthyroidism, premature menopause, Cushing disease, hypogonadism, or vitamin D deficiency
8. Gonadal hormonal ablation therapy, including aromatase inhibitors for breast cancer and androgen deprivation therapy for prostate cancer
9. Some drugs associated with low bone mass (anticonvulsants, chemotherapeutic agents, transplant medications, high-dose

heparin, proton pump inhibitors, selective serotonin reuptake inhibitors, aromatase inhibitors, supraphysiologic doses of thyroid hormone, or glucocorticoid therapy)

10. Risk factors included in FRAX are as follows:
    a. Country of residence
    b. Ethnicity
    c. Age
    d. Sex
    e. Weight (in kg) and height (in cm) used to calculate body mass index
    f. Family history (history of hip fracture in the patient's mother or father)
    g. Personal history of fragility fracture, including radiographic vertebral fracture
    h. Glucocorticoid use
    i. Confirmed diagnosis of rheumatoid arthritis
    j. Smoking (current)
    k. Alcohol use (>3 units daily)
    l. Secondary osteoporosis

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F. Biochemical studies. A workup for secondary osteoporosis should be included in the initial evaluation and includes a complete blood count, complete metabolic panel for calcium, phosphate, liver and kidney function, thyroid-stimulating hormone level, serum 25-hydroxyvitamin D [25(OH)D] level, and 24-hour urine calcium, sodium, and creatinine levels. The urine collections should be performed after vitamin D is repleted and patient has been on a reasonable calcium intake of 1 000 to 1 200 mg/day for at least 2 weeks. Additional tests include PTH levels, gonadal hormone measurements, serum and urine protein electrophoresis, erythrocyte sedimentation rate, tryptase levels to rule out mastocytosis, bone turnover markers, celiac panel, 24-hour urine free cortisol, and transiliac bone biopsy (if there is low trauma fracture and negative evaluation).

IV. SPECIFIC DISORDERS ASSOCIATED WITH DECREASED BONE MASS

A. Osteoporosis. Osteoporosis is characterized by decrease in bone

mass and disruption of bone microarchitecture, leading to decreased bone strength. Trabecular integrity is disrupted early in osteoporosis and improves soon after treatment because of its high cellular content. In addition, decrease bone formation rate (as occurs in glucocorticoid and age-related osteoporosis) can lead to inadequate repair of the multiple microscopic subclinical bone "microfractures."

Increased fracture risk particularly involves the spine, hips, wrists, humerus, and pelvis. Individuals with T-scores of less than −2.5 have the highest risk of fracture. Hip fractures are associated with a 10% to 20% or greater one-year mortality.

B. Postmenopausal and age-related osteoporosis

More than 80% of osteoporosis in women, and 50% in men, is primarily the result of (a) inherited low bone mass combined with (b) aging-related decreases in bone formation and increased bone resorption. This is often referred to as "primary" osteoporosis. The process can be further accelerated by a decline in gonadal hormonal levels, especially menopause in women.

1. Pathogenesis

- **a.** Estrogen deficiency
- **b.** Aging
- **c.** Gender
- **d.** Ethnic factors

2. Diagnosis

- **a.** T-score −2.5 or below in the lumbar spine, femoral neck, total, and/or 33% (one third) radius
- **b.** Low trauma spine or hip fracture (regardless of BMD)
- **c.** Osteopenia or low bone mass (T-score between −1 and −2.5) **with** a fragility fracture of proximal humerus, pelvis, or, possibly, distal forearm
- **d.** Low bone mass or osteopenia and high FRAX fracture probability based on country-specific thresholds.

  Exclusion of other metabolic bone disorders, such as osteomalacia, as well as endocrine disorders (exogenous or endogenous glucocorticoid excess, hyperparathyroidism, hyperthyroidism, and vitamin D deficiency) and other causes of secondary osteoporosis is essential. **Multiple myeloma** may present as generalized osteopenia, and should always be considered.

3. Treatment

a. **Nonpharmacologic therapy.** Several lifestyle modifications can be done to achieve peak adult bone mass, preserve the structural integrity of the skeleton, and prevent falls and fractures.
   i. **Calcium.** The recommended calcium intake (including diet, supplementation, or both) for adults ≥ 50 years of age is **1 200 mg/day**. Calcium supplementation has shown to increase BMD slightly, and also a 15% reduction in total fracture risk, with 30% reduction in hip fractures (National Osteoporosis Foundation meta-analysis). Calcium carbonate provides 40% elemental calcium, is less expensive, requires less frequent dosing, however, may cause gastrointestinal (GI) side effects of constipation and bloating. It is best absorbed when taken with food. Calcium citrate, p. 428p. 429on the other hand, is not dependent on gastric acid for its absorption; and is less likely to cause the GI side effects.
   ii. **Vitamin D** is essential for calcium absorption, improves muscle strength and balance, and reduces fall risk. Optimum vitamin D **increases response to bisphosphonate** therapy, increases BMD, and prevents fractures. Sufficient 25(OH)D level is recommended to be ≥**30 ng/dL** per AACE and Endocrine Society guidelines. The upper limit of normal has been inconclusive and controversial, with 50 ng/dL as being the safe margin. Those deficient (<20 ng/mL) or insufficient (20 to 29 ng/mL) in 25(OH)D may be **treated with 50 000 IU of vitamin D_2 or vitamin D_3 once a week, or 5 000 IU vitamin D_2 or D_3 daily for 8 to 12 weeks** to achieve serum vitamin >30 ng/mL. Many scientific organizations recommend daily intake of 1 000 IU of vitamin D for adults ≥ 50 years of age and 4 000 IU/day as the safe upper limit.
   iii. **Exercise.** Regular weight-bearing exercises are encouraged throughout life. These exercises help slow down bone loss.
   iv. **Avoidance of smoking, excessive alcohol intake, and minimizing caffeine intake.** Current smoking

increases fracture risk as compared to previous smokers, possibly related to increased endogenous estrogen metabolism or direct effects of cadmium on bone metabolism. Excessive alcohol (>3 drinks/day) predisposes to falls, calcium deficiency, and chronic liver disease, which, in turn, predisposes to vitamin D deficiency. Caffeine intake should be minimized to <1 to 2 servings (8 to 12 oz/serving)/day. It decreases the intestinal calcium absorption and increases urinary calcium excretion.

v. Specific treatment

a) Treatment indications according to the 2016 AACE/ACE Postmenopausal Osteoporosis Guidelines:

1) Those with osteopenia or low bone mass and a history of fragility fracture of the hip or spine.

2) Those with a T-score of −2.5 or lower in the spine, femoral neck, total hip, and/or 33% radius.

3) Those with a T-score between −2.0 and −2.5 in the spine, femoral neck, total hip, or 33% radius, if the FRAX 10-year probability for major osteoporotic fracture in ≥20% or the 10-year probability of the hip fracture is >3% (in the United States).

4) Long-term glucocorticoids (5 mg prednisone/day for 3 months or longer should have baseline BMD and may be started on preventive treatment for osteoporosis).

5) Similarly, premature menopause (from surgery, irradiation, or chemotherapy) should also have baseline BMD performed and may be started on hormonal replacement therapy if no contraindications. **When estrogen is contraindicated, treatment with bisphosphonates** or other antiresorptive agents can be considered.

6) Evaluating the response to treatment

(a) Serial BMD measurements, every 1 to 2 years is appropriate in patients on treatment or with a baseline evaluation near a fracture intervention threshold.

(b) Biochemical markers of bone turnover

can be used for assessing patient fracture risk, medication compliance, drug absorption, and efficacy of treatment. They are **not used for diagnosing osteoporosis**. Recently, the National Bone Health Alliance and American Association for Clinical Chemistry have established the preferred **resorption marker as serum C-terminal telopeptide (S-CTX) and the preferred formation marker as serum carboxy-terminal propeptide of type 1 collagen**. Elevated S-CTX represents high bone turnover, and may represent malabsorption or poor compliance in patients on antiresorptive therapy. Significant reduction in bone turnover markers with p. 429p. 430antiresorptive therapy is associated with fracture reduction, and significant increases suggest good response to anabolic therapy. For S-CTX, an approximately 30% decline is predictive of improvement in BMD and fracture. For urinary excretion of NTx, a 50% decline is similarly predictive.

7) **Treatment regimens.** Most currently approved medications for osteoporosis are antiresorptive medications that increase bone mass and the strength by reducing osteoclastic bone resorption (bisphosphonates, denosumab, selective estrogen-receptor modulators [SERMs], estrogen, calcitonin), with the exception of **teriparatide and abaloparatide which stimulates bone formation directly**.

Bisphosphonates and denosumab have proven to be effective first-line therapy in the spine, hip, and nonvertebral fracture risk reduction.

(a) Bisphosphonates

Bisphosphonates are chemical analogs of

pyrophosphate that are adsorbed onto bone surfaces and **inhibit bone resorption** by blocking osteoclastic activity. These agents have been proven to reduce fracture risk in vertebral, nonvertebral, and hip areas. Both AACE and American Society for Bone and Mineral Research (ASBMR) recommend treatment duration of 10 years for an oral bisphosphonate or 6 years for intravenous (IV) zoledronic acid for higher risk patients. Beyond 10 years, risk–benefit ratio remains unknown. For moderate-risk patients, a drug holiday can be considered after 5 years of stability on oral bisphosphonate or 3 years of IV zoledronic acid. If the patient experiences a fracture or significant BMD loss or if bone turnover markers are rising to pretreatment levels during the drug holiday, therapy should likely be resumed.

(1) Oral bisphosphonates. Of the three available oral bisphosphonates (alendronate, risedronate, and ibandronate), alendronate and risedronate are most commonly used, and have evidence for broad-spectrum antifracture efficacy.

Alendronate (Fosamax) is typically dosed 70 mg once weekly, and **risedronate (Actonel)** can be given either as 35 mg once a week or 70 mg/day for 2 consecutive days/month. **Ibandronate** is available in both oral and IV formulation. The oral formulation (Boniva), given 150 mg once a month, is generally used as a second-line agent, and has shown to decrease vertebral but not hip or nonvertebral fracture incidence.

Oral bisphosphonates should be taken on an empty stomach, usually first time in the morning, swallowed with a full glass of water sitting upright (to prevent esophageal

irritation), and wait for about 30 to 45 minutes before ingestion of other medications, food, or beverages other than water (to ensure optimum absorption).

Primary side effect of oral bisphosphonates is GI irritation, usually gastric upset or bloating. Severe esophagitis, ulcerations, and bleeding have occasionally been reported. Oral bisphosphonates are contraindicated in patients with esophageal abnormalities that delay esophageal emptying (e.g., stricture, achalasia, or dysmotility), in patients unable to stand or sit upright for at least 30 minutes, patients having evidence of GI malabsorption (e.g., gastric bypass procedures, celiac disease, Crohn disease, infiltrative disorders, etc.), drug hypersensitivity, or hypocalcemia.

(2) IV bisphosphonates. IV zoledronic acid has been approved in postmenopausal women, men with osteoporosis, and both men and women on chronic glucocorticoid therapy. Zoledronic acid reduces the incidence of osteoporotic vertebral fractures

p. 430p. 431by 70%, hip fractures by 41%, and nonvertebral fractures by 25% over 3 years. It is administered as **5 mg** infusion over 15 minutes **once a year**. HORIZON study extension looked into extending the duration of therapy from the three annual IV infusions to additional 3 years in postmenopausal women. Patients receiving IV zoledronic acid for 6 years had fewer morphometric spine fractures as compared to placebo (RR = 0.51, 95% confidence interval [95% CI] 0.26–0.95; *P* = 0.035). Common side effects include transient mild fever in approximately 15% of

patients, a 1-day flulike syndrome in 7%, and arthralgia in 6% after the first infusion.

IV **ibandronate**, a second-line agent, given as a 30-second, 3 mg infusion every 3 months, has shown an increase in spine BMD similar to that produced by oral ibandronate.

Note: Prior to administration of any bisphosphonate therapy for osteoporosis, it is **essential** to ensure that 25(OH)D is replete (>30 ng/mL) and that there is adequate supplementation of calcium, 1 000 to 1 200 mg/day, in order to reduce the risk of hypocalcemia.

(b) Denosumab (Prolia) is a human monoclonal antibody that prevents receptor activator of nuclear factor κB ligand (RANKL) from binding to its receptor, RANK, thereby reducing the differentiation of precursor cells into mature osteoclasts and decreasing function and survival of activated osteoclasts. It is approved by the Food and Drug Administration (FDA) for treatment of osteoporosis in postmenopausal women and men. It is also indicated in treating bone loss in women with breast cancer on aromatase inhibitor therapies, and in men receiving gonadotropin-reducing hormone treatment for prostate cancer who are at high risk for fracture. Denosumab decreases vertebral fracture incidence by 68%, hip fractures by approximately 40%, and nonvertebral fractures by approximately 20% over 3 years. **60 mg subcutaneous injection every 6 months** is the recommended dose for osteoporosis. Calcium and vitamin D deficiency, and secondary hyperparathyroidism should be corrected prior to initiation of therapy to avoid precipitating hypocalcemia. Stopping therapy after 2 years decreased BMD and increases bone turnover

markers by 12 months of discontinuation, thus "drug holiday" is not recommended.

8) **Rare adverse events from prolonged antiresorptive therapy**

   (a) **Osteonecrosis of the jaw (ONJ)** is a rare, severe, nonhealing, suppurative inflammatory process occurring in the exposed bone of the maxillofacial region, often following tooth extraction or implants. It has been reported first in patients with advanced cancer receiving high-dose bisphosphonate (10 times higher doses of zoledronic acid annually than osteoporosis treatment) and high-dose denosumab therapy (12 times higher doses than osteoporosis treatment), usually in combination with chemotherapeutic agents. Incidence appears to be 1% to 2% in these patients. However, in contrast, incidence of ONJ is much lower, 1 in 10 000 to 1 in 100 000 patient-years in those treated with oral or IV bisphosphonates for treatment of osteoporosis.

   The etiology of ONJ remains uncertain, but may represent impaired bone healing, leading to local infection as a result of "overlap" suppressive effect of very high doses of bisphosphonates/denosumab on osteoblastic bone formation in addition to inhibition of bone resorption. There is no evidence to suggest discontinuation or interrupting therapy with bisphosphonates or p. 431p. 432denosumab will change outcomes or reduce risk of ONJ in patients requiring invasive dental procedures. Temporary discontinuation of bisphosphonates in patients undergoing these procedures could be considered, but the reduction in ONJ risk with this practice has not been studied. There are published **reports of**

patients treated with teriparatide to accelerate healing of ONJ.

(b) **Suppression of bone formation leading to atypical bone fractures** have been reported with long-term bisphosphonate therapy (>5 years duration) but rarely with high doses used in advanced cancer. Similar fractures were noted with denosumab therapy. These fractures are typically located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. **They are usually associated with minimal or no trauma**. Atypical fractures may present with prodromal groin or thigh pain (70%), bilateral fractures and bilateral radiographic abnormalities (28%), and delayed healing (26%). Interrupt the therapy until appropriate imaging studies are performed. The exact etiology is unknown; however, patients sustaining these fractures are hypothesized to have very low bone turnover. Similarly, **teriparatide has been used for patients who develop atypical fractures** with good results (i.e., acceleration of healing).

9) **Other agents for osteoporosis**

(a) **Teriparatide (Forteo).** Teriparatide is a recombinant human PTH (1-34), an agent capable of directly **stimulating osteoblast bone-forming** activity ("anabolic" agent). It has been FDA approved for initial treatment of **postmenopausal osteoporotic women**, at high risk of fractures or who have failed or were intolerant to previous osteoporotic therapy. It has also been approved for **glucocorticoid-induced osteoporosis**. It is administered as a daily subcutaneous injection of 20 μg. It is important to check calcium, 25(OH)D, and PTH levels before treatment with this drug.

It has shown to reduce the risk of vertebral and nonvertebral fractures in postmenopausal

osteoporosis; however, its protection against hip fracture is unknown. Side effects are mild and transient, including nausea, orthostatic hypotension (usually within the first few doses), leg cramps and asymptomatic, mild and transient hypercalcemia, and responsive to discontinuation of calcium supplements. **Teriparatide is contraindicated in any form of hyperparathyroidism, Paget disease of the bone, history of bone cancer or radiation exposure**, or an unexplained elevation of alkaline phosphatase level of skeletal origin.

(b) Treatment is limited to 2 years. Though fracture reduction may persist for 1 to 2 years, the bone density declines quickly during the following year, after discontinuation of teriparatide. It is essential to **institute an antiresorptive agent (bisphosphonate or denosumab) immediately at the end of teriparatide treatment** in order to preserve the increase in BMD. Teriparatide when combined with denosumab showed greater increase in BMD than either agent alone.

In a randomized controlled trial published in 2014 Denosumab and Teriparatide Administrator Randomized Controlled Trial (DATA study), Leder et al. concluded that 2 years of **concomitant teriparatide and denosumab therapy** in postmenopausal women with osteoporosis **increases BMD more than therapy with either medication alone**.

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(c) Abaloparatide (Tymlos). Abaloparatide is a synthetic analog of PTHrP (PTHrP 1–34) which like teriparatide, belongs to a class of anti-osteoporosis drugs called “anabolic agents.” Abaloparatide was approved by the US Food and

Drug Administration in April 2017. It is administered as a daily subcutaneous injection of 80 mcg into the periumbilical region of the abdomen.

Abaloparatide has shown to increase spine and hip bond and reduce the risk of vertebral and nonvertebral fractures. In an 18-month, phase III trail, double blind RCT (The Abaloparatide Comparator Trial in Vertebral Endpoints/ ACTIVE trail), vertebral and nonvertebral fractures occurred less frequently in the abaloparatide group compared with placebo. Improvement in bone density and fracture risk reduction is similar in the abaloparatide and teriparatide groups. The incidence of hypercalcemia was lower with abaloparatide.

(d) Estrogen replacement therapy. FDA has approved the use of estrogen therapy in postmenopausal women at significant risk for osteoporosis and in whom nonestrogen medications may not be considered appropriate. Estrogen should always be **prescribed with progestin** in women with an intact uterus to protect against endometrial stimulation. Conjugated equine estrogens (0.45 mg) combined with SERMs like bazedoxifene (20 mg) have been approved by the FDA for prevention of postmenopausal osteoporosis. Fracture risk reduction at the spine, hip, and nonvertebral sites with 0.625 mg daily conjugated equine estrogen, with or without medroxyprogesterone acetate, were observed in postmenopausal women. Considerable controversy remains regarding the adverse cardiovascular effects, breast cancer, and other extraskeletal effects of estrogen. Menopausal symptoms can be relieved by estrogen, with recommendations to use the lowest tolerated dose for the shortest time possible. If clinically

required, estrogen or a combination of estrogen/progestin can also be used along with other medications for osteoporosis.

SERMs have differential effects on key target organs. **Raloxifene** (Evista) has been FDA approved for the prevention and treatment of postmenopausal osteoporosis as well as **reducing the risk of breast cancer**. Raloxifene, 60 mg daily, has shown to **reduce the risk of vertebral fractures**. **Effects on nonvertebral and hip fractures have not been demonstrated**. Side effects include hot flushes, leg cramps, and threefold increased **risk of venous thromboembolism**. Skeletal benefits are lost 1 to 2 years following discontinuation of therapy.

Calcitonin has also been approved for postmenopausal osteoporosis treatment. Two dose formulations, **injectable** (100 IU daily subcutaneously or intramuscularly), and **nasal spray** (200 IU, 1 spray daily) are available. Nasal spray reduced the risk of new vertebral fracture in postmenopausal women at the specific dose of 200 IU daily; no effect was noted in reducing hip or nonvertebral fracture. Minor increase in spine BMD has been reported. No antifracture efficacy shown with the injectable form of calcitonin. Side effects of nasal calcitonin are largely limited to occasional nasal irritation.

Strontium ranelate has been approved for use in osteoporosis in other countries, but **not in the United States**. Although this has been shown to significantly reduce fractures, recent concerns with cardiovascular safety have been raised in Europe.

Vitamin D and calcium, as described above, also contribute in increasing spine and hip BMD

and decreasing fracture risk, but p. 433p. 434the effects of both agents on fracture risk reduction are quite mild. They should be supplemented along with other osteoporotic treatments.

10) **Duration of treatment.** The optimum duration of treatment remains undefined. Recently published ASBMR algorithm for management of long-term bisphosphonate treatment recommends patients at high risk initially (T-score ≤ −2.5) and who remain at high-risk receive treatment for a longer duration, 10 years with an oral bisphosphonate or 6 years for IV zoledronic acid. Beyond 10 years, the risk–benefit ratio remains undetermined. On the other hand, a lower risk patient may benefit with 5 years of oral bisphosphonate or 3 years of IV zoledronic acid, followed by a drug holiday. AACE/ACE Postmenopausal Osteoporosis Guidelines recommend 5 years of oral bisphosphonates and 3 years of IV zoledronic acid for moderate-risk patients and those with no prior fractures. For patients with prior fractures and higher fracture risk, up to 10 years of oral bisphosphonates and 6 years of IV zoledronic acid are recommended. Resuming therapy thereafter depends on recurrence of fracture, BMD loss, or rising bone turnover markers to pretreatment levels. **Teriparatide, or a weaker antiresorptive agent such as raloxifene, should be considered during the drug holiday** in high-risk patients. Calcium, vitamin D, weight-bearing exercise, and other lifestyle modifications should be continued lifelong.

V. MALE OSTEOPOROSIS

A. Incidence and etiologies. With the increasing longevity of the population, the incidence of osteoporosis in men is rising. In all, one in four men over 50 years of age will develop at least one osteoporosis-

related fracture in a lifetime. Men have increased bone mass in early life, larger bone size, smaller decline in BMD, and a more gradual decrease in gonadal hormones with aging as opposed to the more abrupt decline in menopause. This accounts for a less severe decrease in bone strength. Hip fractures, of all the osteoporotic fractures, contribute to the greatest morbidity and mortality in men. Every year, 80 000 men fracture their hip; 1 in 3 will die in the first year after the hip fracture, another one third tend to fracture again. The overall causes of osteoporosis in men and women are similar. Secondary causes of osteoporosis are more common in men, particularly glucocorticoid therapy, hypogonadism, alcoholism, renal disease, and GI/hepatic disorders.

B. Prevention. General measures for prevention of osteoporosis in men are described previously for women in Section IV. B3 and include good calcium and vitamin D intake, regular physical exercise, and avoiding smoking and excessive alcohol intake.

C. Treatment approaches include measures described previously and the management of any concurrent medical disorders that could correlate to bone loss. If there is evidence of hypogonadism, testosterone replacement therapy may increase bone mass to some extent; if not, testosterone is of little benefit. **Bisphosphonates** are more effective in this disorder and have been shown to increase BMD and reduce fracture incidence in men with osteoporosis of various causes.

VI. SECONDARY OSTEOPOROSIS

A. Glucocorticoid excess

1. **Pathogenesis.** Supraphysiologic levels of glucocorticoids produce bone loss by two mechanisms**: (a)** suppressing bone formation by inhibiting osteoblast generation from mesenchymal stem cell precursors and inducing osteoblast apoptosis; **(b)** increasing bone resorption by enhancing osteoclast generation. Bone quality is decreased as a result of a low bone formation and repair rate; **(c)** some indirect effects of glucocorticoids include a decrease in calcium resorption, suppression of gonadotropins and growth hormones, and alteration of PTH pulsatility.

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2. **Exogenous (iatrogenic)** glucocorticoid excess is the most common secondary cause of osteoporosis, affecting **up to 40% of**

people receiving glucocorticoids. The severity of bone loss occurs early in the course of use, most significantly in the first 6 months, with 12% in the first year, and then averaging 2% to 3% a year. Bone loss also correlates roughly with the total glucocorticoid dose and duration of therapy, and can be aggravated by decreased physical activity often associated with underlying disease. According to the International Osteoporosis Foundation, pharmacologic therapy is recommended in patients taking ≥7.5 mg/day of prednisone or its equivalent for an anticipated duration of ≥3 months.

a. **Diagnosis** is based on the clinical situation and the exclusion of other causes of bone loss. Primarily, BMD T-score and FRAX with country-specific thresholds are required for treatment.

b. **Management**

   i. Glucocorticoid dose reduction should be considered. Promote weight-bearing exercises for at least 20 to 30 minutes/day. Cease smoking and excessive alcohol intake. Appropriate calcium and vitamin D intake should be maintained.

   ii. After the initiation of glucocorticoid therapy, there is often an initial **hypercalciuric phase**, lasting 6 to 12 months presumably as a result of severe depression of osteoblast function with urinary "spillover" of unassimilated calcium. Hydrochlorothiazide, 25 to 50 mg/day, plus potassium supplements should be given as needed to reduce urinary calcium levels to normal.

   iii. When urinary calcium excretion falls to normal or subnormal levels after 6 to 12 months, patients should be supplemented with vitamin D to maintain serum 25(OH)D in the normal range (30 to 50 ng/mL) and calcium, 1 000 to 1 200 mg/day. In patients who are unable to meet the required amount from nutritional sources, supplementation may be necessary.

3. **Bisphosphonate therapy** is the first-line therapy for the treatment of glucocorticoid-induced osteoporosis.

   a. **Alendronate**, risedronate, and zoledronic acid are FDA approved for the treatment of glucocorticoid-induced osteoporosis, with the latter two also approved for prevention.

b. **Etidronate, ibandronate, and pamidronate** have also been used off-label based on some clinical trial data showing efficacy on BMD end points and low fracture risk. The UK National Osteoporosis Guidelines Group recommends continuing the bisphosphonate use as long as supraphysiologic glucocorticoid doses are being used.

c. **Teriparatide,** an anabolic agent, has also been approved for glucocorticoid-induced osteoporosis. When compared to alendronate, greater increase in spine and hip BMD were noted with teriparatide, with fewer morphometric vertebral fractures but no significant difference in nonvertebral fractures.

d. **Denosumab** has not yet been approved for glucocorticoid-induced osteoporosis; however, phase III trials are underway comparing its effect on BMD with risedronate.

4. **Endogenous glucocorticoid excess.** Cushing disease/syndrome is usually associated with severe osteoporosis resulting from glucocorticoid excess. Management is surgical or medical correction of the underlying hormonal disorder. Bone mass usually increases when glucocorticoid levels return to normal.

B. Transplantation osteoporosis

Organ transplant patients are at a high risk for marked bone loss because of the adverse effects on bone produced by both their primary disease and the effects of the glucocorticoids and other immunosupressants used after transplantation. Rapid bone loss and increased fracture incidence occur very commonly following kidney, heart, lung, liver, and bone marrow transplants. A study by Yu et al. in 2014 found significantly increased incidence of osteoporosis in solid-organ transplant patients compared to nontransplant patients, hazard ratio (HR) 5.14 (95% CI, 3.13 to 8.43) and also increased related fractures, HR 5.76 (95% CI, 3.80 to 8.74), with the highest among lung transplant patients.

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1. **Preoperatively,** all candidates for organ transplantation should have a bone evaluation, including BMD, as soon as possible, and should be started on appropriate treatment for osteoporosis or other observed bone disorders immediately. Any secondary causes of osteoporosis should also be identified and treated.

2. **Postoperatively,** the rapid bone loss is produced by the effects of high-dose **glucocorticoids**, which suppress osteoblastic bone formation and stimulates resorption, combined with the effects of **calcineurin inhibitors**, such as **cyclosporine A** and **tacrolimus** (Prograf), which appear to activate osteoclastic bone resorption directly. This results in a high-turnover bone loss state, with the most rapid bone loss occurring during the first 6 to 12 months posttransplantation. Prevention with lifestyle modifications should be encouraged both pretransplant and posttransplant. Both oral and IV bisphosphonates have been shown to be effective in preventing posttransplantation bone loss. It has been suggested that all transplantation candidates can benefit from being started on bisphosphonate therapy prior to transplantation in order to have effective concentrations in bone immediately preoperatively. The one exception would be renal transplant candidates, who might require bone biopsy to rule out adynamic bone disease (extremely low rate of bone formation) that could be aggravated by bisphosphonates.

C. Premature gonadal hormone deficiency

1. **Pathogenesis.** Congenital absence or premature loss of gonadal function invariably leads to significant bone loss. Hypogonadism is a common cause of osteopenia in adult males. Commonly encountered clinical conditions include idiopathic testicular atrophy and primary hypogonadism in men. Hypogonadism, as a result of androgen deprivation therapy for prostate cancer in men and estrogen ablation with aromatase inhibitor therapy for breast cancer in postmenopausal women, are increasingly common causes of accelerated bone loss in adults.
2. **Diagnosis.** The diagnosis of hypogonadism is made by standard measures of testicular or ovarian function (see Chapters 25 and 27).
3. **Treatment.** Initial BMD should be quantitated, and treatment with bisphosphonates or other antiresorptive agents should be started as soon as the diagnosis of hypogonadal bone loss is established, with hormone replacement generally reserved for management of hormone deficiency symptoms.

D. Hyperthyroidism

1. **Pathogenesis.** Thyroid hormone **stimulates osteoclastic resorption in excess of osteoblastic** bone formation activity,

thus producing net bone loss. Bone loss is most rapid in younger individuals, who have higher basal bone turnover rates. In these patients, transient hypercalciuria and even mild hypercalcemia can occur, especially when osteoblast function is decreased by reduced physical activity. Prolonged treatment with supraphysiologic doses of thyroid hormone can also produce significant bone loss in postmenopausal women.

2. **Diagnosis and management.** Hyperthyroidism is diagnosed by standard clinical and biochemical means. Routine weight-bearing exercise should be encouraged. Generally, only reversal of the hyperthyroid state is required, because the **bone loss is generally not severe** owing to the short duration of hyperthyroidism.

E. Diabetes mellitus

1. **Pathogenesis.** An increased incidence of osteoporosis and fracture is seen in patients with long-standing type 1 diabetes mellitus, with impaired bone formation likely resulting from the **decrease in the anabolic effects of insulin and amylin on bone.** Insulin stimulates osteoblastic differentiation that enhances osteocalcin production. Lack of insulin in type 1 diabetics increases susceptibility to bone loss. The mechanism for the reduced bone turnover in type 1 diabetes is multifactorial. The anabolic effects of insulin may be mediated through the insulin-like growth factor 1 (IGF-1) pathway, and in patients with type 1 diabetes, low levels of insulin and IGF-1 may impair osteoblast function. In contrast, obesity-induced insulin resistance in **type 2 diabetes leads to increased levels of insulin and IGF-1, with a possible anabolic effect on bone**.

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In adults with type 1 diabetes, lumbar BMD is usually normal, whereas femoral BMD is reduced. There was no relationship between BMD and the duration of diabetes or glycemic control in recently published studies.

The majority of studies demonstrated that in both men and women with type 2 diabetes, BMD is normal or increased at the lumbar spine, femoral neck, and mid and distal radius. However, in type 2 diabetes, **bone fracture incidence is increased despite a higher mean BMD**, the latter apparently in part as result of the

increased stimulatory effects of obesity-related **weight loading and adipokine effects on bone mass**. In this population, the increase in fracture incidence results from increased **risk of falling** because of peripheral neuropathy, visual impairment, and decreased physical fitness.

2. **Management.** In type 1 diabetes, good glycemic control, exercise, and optimum vitamin D and calcium intake should be maintained to optimize bone status. Bisphosphonate therapy is also effective in increasing BMD. Patients with type 2 diabetes may also benefit from frequent visual assessment, treatment of neuropathy, and regular exercise to improve muscle strength and balance.

F. Immobilization

1. **Pathogenesis.** Acute immobilization produces a rapid decline in bone formation rate as a result of **decreased physical stimulation of osteoblast** activity. Osteoclastic bone resorption initially remains unchanged. As a result, bone loss occurs. Loss is more rapid in younger individuals and others with high bone turnover rates (e.g., hyperparathyroidism, Paget disease). Total immobilization can produce hypercalciuria and hypercalcemia in such individuals.
2. **Management**. **Calcium, phosphate, and vitamin D** supplementation are **contraindicated** in acute immobilization because of the tendency toward hypercalciuria and hypercalcemia. Passive exercise and mechanical compression therapy are of minimal benefit. The patient should be mobilized as soon as possible. Good hydration is required to promote calcium diuresis and reduce urinary calcium concentration. Bisphosphonates given IV (zoledronic acid and pamidronate) in standard doses for osteoporosis may be useful in controlling hypercalcemia and attenuating bone loss.

G. Osteogenesis imperfecta (see Chapter 35)

This is a rare genetic disorder, the mildest variant of which (type 1) exhibits autosomal dominant inheritance and can first appear as severe osteoporosis at ages ranging from early childhood to early middle age.

1. **Pathogenesis.** The basis of the osteoporosis is a congenital defect in bone formation because of defective bone collagen synthesis as a result of type I collagen gene mutations. The midshaft diameter and strength of affected long bones can be

markedly reduced. Occasionally, the disorder may not become clinically apparent until the third or fourth decade.

2. **Diagnosis.** In the childhood-onset variant of type I osteogenesis imperfecta, there is a history of multiple long-bone fractures dating from early childhood. Blue sclerae, as a result of scleral thinning, are often but not always present. Hearing loss frequently appears in the third decade. Bone radiographs may demonstrate "flask deformities" of several long bones, especially the metacarpals and metatarsals. These deformities are the result of marked thinning of the midshaft. All other causes of osteoporosis must be excluded.
3. **Management.** There is **currently no specific treatment for this disorder**. However, bisphosphonate therapy can be effective in reducing vertebral fracture risk.

H. Osteomalacia and rickets (see Chapter 35)

Osteomalacia is characterized by the accumulation of **increased amounts of unmineralized bone matrix (osteoid)**. The bone formation rate is markedly reduced. In the growing child, this process results in defective mineralization of epiphyseal cartilage, leading to fraying and thickening of the epiphyses, accompanied by bowing of the weight-bearing long bones because of deficient mineralization. These clinical features are characteristic of children with rickets. Although mild osteomalacia is characterized by a tendency to bone fracture, this condition is frequently asymptomatic in adults. In more severe forms, pain in the ribs, pelvis, and lower extremities is p. 437p. 438common. Radiographs may demonstrate a mild generalized decrease in bone mass and may occasionally reveal **pseudofractures (Looser zones)**, which are painless linear radiolucencies extending perpendicularly from the cortex partway through the long bones, pelvis, and scapulae. Osteomalacia and rickets can be caused by vitamin D deficiency, defective vitamin D metabolism, chronic hypophosphatemia, and rare congenital or acquired defects of osteoblast function.

I. Vitamin D deficiency

is characterized by low serum 25(OH)D (<20 ng/mL). Sufficient 25(OH)D level is recommended to be ≥**30 ng/dL** per AACE and Endocrine Society guidelines. Vitamin D deficiency is also characterized by reduced intestinal calcium absorption, reduced

serum calcium and phosphate concentrations, reduced 24-hour urinary calcium excretion, mildly increased iPTH levels, and elevated serum bone alkaline phosphatase.

1. **Pathogenesis**
   a. **GI disorders.** Moderate-to-severe vitamin D deficiency occurs most commonly in disorders associated with fat malabsorption, including gluten-sensitive enteropathies, pancreatic insufficiency, biliary obstruction, blind-loop syndromes, and following jejunoileal bypass for obesity. Binding of dietary calcium by fatty acids to form insoluble soaps may further decrease calcium absorption. In postgastrectomy patients, altered dietary habits may contribute to vitamin D deficiency. Osteoporosis frequently occurs concomitantly, probably because of chronic calcium and protein malnutrition and increased bone resorption due to secondary hyperparathyroidism.
2. **Treatment**
   a. Management of the underlying disorder and correction of fat malabsorption are of primary importance. The amount of vitamin D required to effectively treat vitamin D deficiency depends upon the baseline level of serum 25(OH)D and an individual's capacity for vitamin D absorption. In patients with normal absorptive capacity, for every 100 units (2.5 mcg) of vitamin D_3 supplementation, serum 25(OH)D concentrations increase by about 0.7 to 1.0 ng/mL.

      Vitamin D is given orally at a dose of 50 000 units weekly or more frequently as needed to maintain the serum 25(OH)D level at 30 to 60 ng/mL. Treatment aims should also include correction of secondary hyperparathyroidism and hypocalciuria. Calcitriol (starting at 0.25 μg daily) may be needed and has a faster onset of action and is more suppressive of PTH. Calcium supplementation should be given at 1 000 to 2 000 mg/day or higher doses depending on the patient. Serum calcium and 24-hour urinary calcium should be followed frequently, because improvement in the underlying disease can be associated with a marked reduction in vitamin D requirements.
   b. **Mild nutritional vitamin D deficiency** (serum 25(OH)D ranging from 12 to 20 ng/mL) is occurring with increasing

frequency in the United States. Mild vitamin D deficiency is usually associated with low dietary vitamin D intake, limited sunlight exposure and/or use of sunscreens, and older age, when cutaneous production of vitamin D is reduced. Administration of a loading dose of vitamin D (e.g., 50 000 U weekly), followed by maintenance of physiologic dose (400 to 1 000 U/day or 50 000 units once or twice a month), is usually sufficient to normalize vitamin D status.

VII. DEFECTIVE VITAMIN D METABOLISM AND ACTION

A. Anticonvulsants and other liver oxidase enzyme-activating drugs. Long-term use of certain anticonvulsant drugs, particularly phenobarbital and phenytoin and certain other medications (e.g., rifampin), produces an increased incidence of vitamin D deficiency and osteomalacia in individuals with marginal vitamin D intake and sunlight exposure. This is primarily secondary to increased hepatic catabolism and biliary excretion of vitamin D and its biologically active metabolites. Serum 25(OH)D levels and urinary calcium excretion are reduced, and other biochemical markers of vitamin D deficiency are present. Severe cases require 2 000 to 5 000 U of vitamin D plus 1 000 to 1 500 mg of calcium per day for 6 months or longer. p. 438p. 439Routine prophylaxis is 1 000 to 2 000 U/day of vitamin D or 50 000 U once or twice per month.

B. Pseudovitamin D deficiency rickets (vitamin D–dependent rickets) is a rare autosomal disorder that mimics nutritional rickets, but requires higher doses of vitamin D (10 000 to 30 000 U/day). The basis of the disorder appears to be congenitally defective renal $1,25(OH)_2D$ production. The diagnosis is based on characteristic somatic abnormalities, normal serum 25(OH)D and reduced $1,25(OH)_2D$ levels, and failure to respond to physiologic doses of vitamin D (400 to 1 000 units/day). Another group of disorders characterized by partial vitamin D resistance and originally termed **vitamin D–dependent rickets type II** results from hereditary cellular resistance to $1,25(OH)_2D$ levels. Variable supraphysiologic doses of $1,25(OH)_2D$ are required for treatment.

C. Hypophosphatemia resulting from disorders of the PHEX/phosphatonin system. The recently described

PHEX/phosphatonin endocrine system appears to play a major role in the regulation of serum phosphate levels. Disorders of this system can cause chronic severe hypophosphatemia, resulting in osteomalacia or rickets.

Phosphatonin (primarily FGF23 and possibly other phophaturic factors) is produced by osteocytes and osteoblasts. Human FGF23 acts on the kidney to **(a)** reduce renal tubular phosphate resorption and **(b)** inhibit $1,25(OH)_2D$ production. The result is a decline in serum phosphate levels without the normal compensatory rise in serum $1,25(OH)_2D$.

D. Tumor-induced osteomalacia. Severe hypophosphatemia with osteomalacia can occur in association with a tumor. Tumor-induced osteomalacia is also called **oncogenic hypophosphatemic osteomalacia**. Although primarily described in adults, this condition can also occur in children and adolescents. These slow-growing soft-tissue or bone tumors of mesenchymal origin produce high amounts of **phosphatonin**, resulting in chronic renal phosphate wasting and **hypophosphatemia** leading to osteomalacia, bone pain, and proximal muscle weakness and aching. Serum calcium, iPTH, and 25(OH)D levels are normal, but the low to normal serum $1,25(OH)_2D$ concentration is inappropriately reduced relative to the elevated levels expected in hypophosphatemia. Renal phosphate wasting is demonstrated by a reduced renal tubular threshold maximum for phosphate (TmP/GFR). Limited data are available in the treatment of oncogenic osteomalacia. Administration of nonsodium neutral phosphate (e.g., Neutra-Phos-K, K-Phos-Neutral), 2 to 4 g/day in four or five divided doses, calcium supplements (1 000 to 1 500 mg/day), plus $1,25(OH)_2D_3$ (calcitriol, 0.5 to 3.0 μg/day), can usually reverse the biochemical abnormalities and osteomalacia if maintained chronically. Removal of the tumor is curative. However, the tumors are often difficult to locate. Alternative therapeutic approach includes treatment with octreotide when the tumor cannot be found despite intensive search. Octreotide therapy may correct phosphate wasting and hypophosphatemia, presumably mediated by somatostatin receptor expression by the tumor.

E. Familial X-linked hypophosphatemia (hypophosphatemic vitamin D–resistant rickets)

1. Clinical features. X-linked hypophosphatemia (XLH) is one of

the most common etiologies of rickets and osteomalacia. Most cases are familial, with X-linked dominant transmission, with a prevalence of approximately 1 case per 20 000 live births. The classic clinical triad is hypophosphatemia, lower limb deformities, and stunted growth rate. Clinical manifestations range from asymptomatic mild hypophosphatemia to marked hypophosphatemia with severe bone disease. Males are more severely affected. The clinical picture is that of severe rickets with general demineralization, pseudofractures, bowing of the long bones, and increased incidence of fractures. Biochemical findings include normal serum calcium, reduced phosphate, increased alkaline phosphatase, and normal iPTH. There is marked renal phosphate wasting, and urinary calcium excretion may be slightly decreased. The diagnosis can be established before 2 years of age. The severity of bone symptoms decreases after closure of the epiphyses, but severe bone disease can occur in untreated older adults.

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2. **Pathogenesis.** The basis of the disorder appears to be an inactivating mutation in the *PHEX* gene on the X chromosome. This gene codes for a cell surface-bound protein-cleaving enzyme and is expressed predominantly in the bone and teeth. The altered function of this endopeptidase results in decreased degradation of circulating phosphatonin, leading to renal phosphate wasting combined with inappropriately normal serum $1,25(OH)_2D$ levels. Serum calcium, iPTH, and 25(OH)D levels are normal. An autosomal dominant form of the disorder is caused by a mutation in the *FGF23* gene causing resistance to degradation by the PHEX endopeptidase. FGF23 appears to mediate the renal phenotypic abnormalities of XLH, primarily phosphate wasting.
3. **Treatment.** Phosphate supplementation, 1.5 to 3.0 g of elemental phosphorous per day given as nonsodium neutral phosphate (e.g., Neutra-Phos-K, K-Phos-Neutral), 2 to 4 g/day in four or five doses, $1,25(OH)_2D_3$ (calcitriol), 0.5 to 2.0 μg/day, and calcium, 1 000 to 1 500 mg/day, are given to stimulate calcium absorption, maintain serum phosphate levels, and prevent the secondary hyperparathyroidism that may be caused by the phosphate

supplementation. This regimen can produce significant reversal of radiologic and biochemical changes, and improve growth rate in children. However, responses vary.

F. Primary hyperparathyroidism (see Chapter 31)

1. **Incidence and pathogenesis. Primary hyperparathyroidism (PHPT)** is one of the most common endocrine diseases. PHPT occurs relatively commonly in the adult population (~1 in 500 to 1 in 1 000 individuals), with a 3:1 female to male ratio. At least 50% of cases occur in postmenopausal women. Only 20% of patients are symptomatic, with most cases being detected as hypercalcemia on a routine biochemical profile. Roughly, 80% of cases are as a result of a single adenoma, with 15% to 20% being due to four-gland hyperplasia. Parathyroid cancer accounts for <0.5% of patients. Some degree of loss of bone mass can be demonstrated in most patients because of a PTH-stimulated increase in bone osteoclastic activity, and is usually more marked in areas that are rich in cortical bone (forearm and hip).
2. **Diagnosis.** The diagnosis is usually readily established by demonstrating hypercalcemia, low or low-normal fasting serum phosphate, and normal or increased serum iPTH. The presence of typical biochemical findings of hyperparathyroidism in association with suppressed serum iPTH levels suggests malignancy-associated hypercalcemia because of tumor production of PTH-related peptide (PTHrP) (see Chapter 34). This latter diagnosis can be confirmed by serum PTHrP assay.
3. **Management.** Indications for surgical treatment of PHPT include:
   - **a.** symptomatic presentation (new kidney stones, nephrolithiasis or nephrocalcinosis by radiograph, ultrasound, or CT, and/or symptomatic bone disease)
   - **b.** marked hypercalcemia (mean serum calcium >1.0 mg/dL above the upper limits of normal)
   - **c.** hypercalciuria (24-hour urine calcium > 400 mg/day)
   - **d.** enlargement of existing kidney stones
   - **e.** decreasing renal function (estimated GFR [eGFR] < 60 mL/minute)
   - **f.** marked bone loss as demonstrated by bone density at the hip, lumbar spine, or distal radius that is more than 2.5 SD below

peak bone mass (T-score < −2.5) and/or previous asymptomatic vertebral fracture.

In addition, surgical intervention should be strongly considered in younger patients (<50 years of age) because of the increased risk of progression.

Thus, by current criteria, approximately 20% of patients are surgical candidates. Parathyroid surgery is increasingly being performed by minimally invasive parathyroidectomy when a single adenoma can be demonstrated by a preoperative ^{99m}Tc-sestamibi parathyroid scan. Patients with asymptomatic PHPT who do not meet surgical intervention criteria may still choose parathyroidectomy because it is the only definitive therapy.

Many patients can be managed medically by maintaining **normal** calcium and sodium intake, hydration, avoiding **thiazide diuretics (which can increase** p. 440p. 441 **serum calcium levels by reducing urinary calcium excretion)**, and increased weight-bearing exercise. Most nonsurgical candidates do quite well on this regimen, with only 2.5% showing progression of laboratory values and BMD changes over a 10-year period. Mild-to-moderate bone loss usually responds well to bisphosphonate treatment. The use of **calcimimetic agents, such as cinacalcet**, has been shown to reduce serum calcium and PTH levels and stabilize BMD for up to 3 years, and can be considered in surgical candidates who are poor operative risks.

G. Renal osteodystrophy

Renal osteodystrophy is the result of multiple disorders in bone and mineral metabolism that can occur in **chronic kidney disease**. These can include changes in serum calcium, phosphate, vitamin D, bone formation and resorption, and bone mass and quality, often in association with extraskeletal calcification. Bone pain may occur, and reduced BMD and bone quality with increased fracture risk is common.

1. **Pathogenesis.** Bone disorders range from an abnormally high-turnover state to a condition of very low turnover. Defective mineralization and increased fracture risk can occur in both

situations. The high-turnover state is driven by elevated PTH levels resulting from the hypocalcemia stimulus produced by phosphate retention and by decreased renal production of $1,25(OH)_2D$ as renal function declines. The primary bone histologic change is **osteitis fibrosa**. Low-turnover renal bone disease is characterized by an extremely low rate of bone formation termed "**adynamic bone disease**," and it is often the result of an oversuppression of PTH secretion because of excessive vitamin D metabolite and calcium supplementation. Other contributing factors include diabetes, advanced age, poor nutrition, and glucocorticoid therapy. Previously, low-turnover renal bone disease accompanied by marked osteomalacia and bone pain was often caused by aluminum accumulation at the mineralization front. However, this disorder, termed "**aluminum bone disease**," has largely disappeared in recent years after the discontinuance of the use of aluminum-containing phosphate binders and dialysis solutions. Chronic acidosis in renal insufficiency can aggravate bone loss because of increase bone resorption. Extraskeletal cardiovascular system and other tissue calcification can be aggravated by an excessive calcium load provided by calcium-containing phosphate binders. The preceding histologic patterns generally occur in combination, with one form often predominating, in a disorder termed "**mixed renal osteodystrophy**."

2. **Prevention and Treatment.** Primary goals are to **(a)** maintain blood phosphate and calcium as close to normal as possible, with the calcium X phosphate product always <55; **(b)** prevent or reverse secondary hyperparathyroidism; **(c)** avoid extraskeletal calcifications; and **(d)** prevent or reverse aluminum or iron accumulation.

   The five stages of chronic kidney disease **are stage** 1, normal or raised eGFR >90 mL/minute; **stage 2**, mild, eGFR 60 to 90 mL/minute; **stage 3**, moderate eGFR 30 to 59 mL/minute; **stage 4**, severe, eGFR 15 to 29 mL/minute; and **stage 5**, kidney failure, eGFR < 15 mL/minute.

3. Management goals by stage are as follows:
   a. **Stage 1**: Ensure good calcium and vitamin D nutrition, maintaining serum 25(OH)D in the normal range (30 to 70

ng/mL) and serum iPTH at 30 to 60 pg/mL.

b. **Stage 2**: As for stage 1, plus mild dietary phosphate restriction.
c. **Stage 3**: As for stage 2, plus moderate dietary phosphate restriction, and use of non–aluminum-containing calcium-based phosphate binders (calcium carbonate or acetate) or non–calcium-based phosphate such as sevelamer hydrochloride **(Renagel)** or lanthanum carbonate **(Fosrenal)** to keep serum phosphate at 2.7 to 4.6 mg/dL. Ensure total oral calcium supplementation of no more than 1.0 g/day, and use vitamin D metabolites, especially **paricalcitol (Zemplar)**, to maintain serum iPTH at 35 to 70 pg/mL.

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d. **Stage 4**: As for stage 3, plus increased phosphate restriction while maintaining protein intake, use of **calcimimetics, such as cinacalcet (Sensipar)**, as needed to maintain iPTH at 70 to 110 pg/mL.
e. **Stage 5**: As for stage 4, plus use of dialysate calcium concentration to control iPTH at 150 to 300 pg/mL and consideration of **parathyroidectomy** for uncontrollable secondary hyperparathyroidism.

   Oral or IV bisphosphonates may be effective in increasing BMD in stages 1 to 3 patients, but are not recommended in patients with an eGFR <30 mL/minute. To reduce the risk of adynamic bone disease, bone formation markers (osteocalcin and bone alkaline phosphatase) must be followed at 3- to 6-month intervals in renal disease patients treated with bisphosphonates, and treatment discontinued if markers fall below normal limits.

H. Paget disease

Paget disease of bone, also known historically as **osteitis deformans**, is a disorder of bone metabolism characterized by an accelerated rate of bone remodeling, often seen in asymptomatic patients, resulting in overgrowth and impaired integrity of affected bone. Commonly affected areas include the skull, spine, pelvis, and long bones of the lower extremity.

1. Clinical features

a. **Presentation.** Paget disease occurs in 1% of the population over 40 years of age, and 15% to 30% of patients have a family

history of the disorder. The disorder is frequently asymptomatic and is often detected via an **elevated serum alkaline phosphatase** on a routine blood panel. Usually, there is only local involvement of one or two bones, but extensive multifocal forms can produce marked pain, deformity, and disability. The process may "burn out," remain localized, wax and wane, or progress rapidly.

b. Symptoms are produced by the following (in approximate order of frequency): bone pain at a pagetic site, possibly caused by frequent microfractures; muscular strain and accelerated osteoarthritis caused by changes in posture and the weight-bearing axis as a result of bowing of the femur and tibia; joint deformity because of involvement of periarticular bone, especially in the hip; nerve root compression caused by vertebral enlargement; narrowing of cranial ostia with compression of cranial nerves; ostosclerosis leading to progressive air-conduction hearing loss; involvement of the base of the skull, causing platybasia and long-track damage; high-output heart failure in older individuals with extensive disease, because of increased blood flow to bone; and development of **osteogenic sarcoma** in patients with extensive, long-standing disease. This rare (<1% of patients), lethal complication occurs most commonly in the proximal humerus and manifests itself as new pain at a pagetic site.

2. **Pathogenesis.** The initiating lesion is a local increase in osteoclastic bone resorption activity, followed by a chaotic, **overexuberant increase in osteoblastic bone formation**. The basis of the increased osteoclastic activity is unknown, but it appears to be a combination of genetic susceptibility and unknown environmental factors, with a **possible viral etiology** postulated. In involved areas, bone turnover is markedly increased. Involved bones may gradually increase in size, and they are susceptible to deformity and fracture because of their disorganized structure.
3. **Diagnosis.** Characteristic radiographic findings, increase in serum bone alkaline phosphatase, and an increase ^{99m}Tcbone scan activity in radiologically involved areas are sufficient for diagnosis. In long bones, Paget disease always begins at one end and progresses toward the midshaft. Bone scanning is particularly

useful in detecting activity in unsuspected areas. Areas showing increased uptake on bone scan should be confirmed as pagetic by standard radiography. Occasionally, regions with a characteristic radiographic appearance of Paget disease do not show increased activity on bone scan. These areas represent “burned-out” disease. The earliest radiologic finding is a local radiolucency, corresponding to initial osteoclastic overactivity, and is most commonly seen as a broad lucency in one region of the skull **(osteoporosis circumscripta)**. Serum and urinary p. 442p. 443calcium levels are usually normal but may become significantly elevated when a patient with widespread involvement is put on bed rest. A bone biopsy is indicated only in the rare patient in whom radiologic findings suggest malignancy. Sudden accentuation of bone pain in a specific area in a patient with extensive, long-standing disease should raise the possibility of the development of **osteogenic sarcoma**. A characteristic “sunburst” pattern with periosteal elevation may be seen on a radiograph.

4. **Treatment** is directed toward arresting the disease and is indicated to relieve symptoms and/or prevent complications. The symptoms most likely to be relieved by treatment include bone aches or pain at pagetic sites, excessive warmth over involved bones, headache resulting from skull involvement, and back pain because of vertebral involvement with neural compression syndromes (radiculopathy and slowly progressive spinal cord compression). Preventive treatment is indicated in patients with involvement of weight-bearing long bones or joints (especially by the hip), extensive osteolytic areas, and widespread involvement of the skull (to prevent foraminal compression). Treatment for at least 6 months before elective surgery on pagetic bones (e.g., hip replacement) is indicated to increase bone strength.
   a. **General measures.** Adequate hydration and mobilization should be maintained in all patients. In patients acutely confined to bed rest, extreme care should be taken to ensure abundant fluid intake to avoid hypercalcemia. Early ambulation should be encouraged. Most patients with mild disease who manifest only

musculoskeletal and osteoarthritic symptoms, and who are not candidates for specific treatment, can receive satisfactory symptomatic relief from mild analgesic therapy, such as ibuprofen or acetaminophen.

b. **Specific treatment. Bisphosphonates** are the mainstays of therapy. It inhibits osteoclastic bone resorption, with the **osteoblastic response subsiding secondarily**. Significant reversal of neural compressive symptoms may occur after prolonged treatment. However, long-bone deformities cannot be reversed. Response is monitored by following serum alkaline phosphatase and clinical symptoms. With extensive involvement, bone scans at 12-month intervals may be useful in following disease activity. After treatment, the serum alkaline phosphatase should be followed at 6-month intervals, and treatment reinstated with disease recurrence.
    i. **Bisphosphonates** approved for use in Paget disease in the United States include oral risedronate and alendronate, and IV zoledronic acid and pamidronate. **IV zoledronic acid appears to be the treatment of choice**. Comparisons of the effects of a single 5 mg infusion of zoledronic acid versus risedronate (30 mg/day orally for 2 months), have shown zoledronic acid to be superior to risedronate in median time to initial response (64 vs. 89 days), 6-month response rate assessed by alkaline phosphatase normalization (89% vs. 58%), and maintenance of remission in initial responders at 24 months (97% vs. 60%). Suppression of bone turnover markers was also found to be sustained in patients treated with zoledronic acid. Side effects of zoledronic acid include occasional mild flulike illness and arthralgia. Adverse effects occurred more frequently in the first 3 days in those who received zoledronic acid (54% vs. 25%). Overall, both of these drugs are relatively well tolerated.
    ii. Injectable **calcitonin** is rarely used because of its relatively low effectiveness, the inconvenience of injections, and bothersome side effects. Nasal spray calcitonin (Mialcalcin) is not effective in Paget disease.

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34 Parathyroid Hormone-Related Protein

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I. GENERAL INFORMATION ABOUT PARATHYROID HORMONE-RELATED PROTEIN

A. The gene

Human parathyroid hormone-related protein (PTHrP) is encoded by a single gene on chromosome 12, *PTHLH*, that is related to the gene encoding parathyroid hormone (PTH). The exon/intron structure for both genes is similar, and they encode peptides that are highly homologous in their amino termini. PTH and PTHrP share 8 of the first 13 amino acids and a similar secondary structure over the next 21 amino acids.

In addition to PTH and PTHrP, the "PTH gene family" includes the *PTH-L* and tuberoinfundibular peptide 39 (*TIP-39*) genes. All members of this family are similar at their amino terminus where these proteins bind their receptors. Members of the PTH gene family are present in fish, amphibians, birds, and mammals.

Of all the family members, the *PTHLH* gene demonstrates the most complex genomic organization and the most interspecies variability. The added complexity of the *PTHLH* gene likely reflects the diverse biologic functions of PTHrP.

B. The protein

PTHrP was discovered following extensive studies aimed at understanding the pathophysiology of humoral hypercalcemia of malignancy (HHM). As follows from the genomic similarities between the two genes, the protein structure of PTH and PTHrP is similar in their amino terminus. This allows both peptides to bind and stimulate the same type 1 PTH/PTHrP receptor (PTHR1). Therefore, when secreted by tumors, PTHrP is able to mimic PTH, thereby leading to extensive bone resorption and hypercalcemia.

Translation of the *PTHLH* gene gives rise to a protein that is subsequently processed into multiple peptides. PTHrP peptides that

contain the amino-terminal portion are the most studied forms of PTHrP. PTHrP 1-36 is secreted from various cell types and can interact with the PTHR1. Keratinocytes and mammary epithelial cells secrete longer forms of amino-terminal containing PTHrP that can enter circulation in cancer patients and during lactation.

Nuclear PTHrP can operate either in a paracrine manner (through receptor internalization), or through a cell-autonomous pathway. In addition, mid-region PTHrP can be secreted from cells and exert biologic functions in the placenta and kidney, although the responsible receptor has not been identified.

C-terminal portions of PTHrP have also been identified and have been suggested to inhibit osteoclast function and stimulate osteoblast proliferation.

C. The receptor

The amino terminus of PTHrP binds to and activates the PTHR1, which is a member of class B of the large family of G-protein–coupled receptors.

PTH and PTHrP bind to PTH1R slightly differently and generate different temporal profiles of downstream signaling molecules. Binding of PTH favors a more stable conformation with multiple rounds of G-protein activation, resulting in generation of more cyclic adenosine monophosphate over longer periods of time, whereas PTHrP activates PTH1R in a more labile manner. Consistent with these findings, PTH fits more tightly in the receptor's binding cleft than PTHrP. Such differences could be the underlying basis for differing functions of PTH and PTHrP in physiology and disease.

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D. PTHrP in physiology

1. Cartilage and bone

PTHrP regulates the growth and development of long bones by regulating the proliferation, differentiation, and death of growth plate chondrocytes in a paracrine negative feedback loop with a molecule called Indian Hedgehog (IHH). Amino-terminal PTHrP is produced at the top of the growth plate in response to IHH and acts through the PTHR1 to promote the proliferation of undifferentiated chondrocytes and to delay the differentiation of prehypertrophic chondrocytes into hypertrophic chondrocytes. This, in turn, inhibits the production of IHH. This interaction

between PTHrP and IHH acts to control the rate of chondrocyte differentiation and thus longitudinal bone growth. PTHrP is also produced in other cartilaginous sites, such as the perichondrium of costal cartilages, subarticular chondrocytes in the vicinity of hyaline cartilage in joint spaces, and insertion sites of tendons and ligaments to bone. In these sites, PTHrP appears to be important for preventing the differentiation of chondrocytes, mineralization of these structures, and their conversion into bone.

Apart from its **role in prenatal bone development** and modeling, PTHrP has important **anabolic actions in postnatal bone**. Selective deletion of PTHrP in osteoblasts in mice leads to reduced bone mass secondary to a lower number of osteoblasts and lower rates of bone formation. These mice also have reduced osteoclast formation, but the net effect is one of lower bone mass.
Some human skeletal disorders have been identified that involve PTHrP and its receptor, PTHR1:

a. **Blomstrand chondrodysplasia** is a fatal autosomal recessive disorder characterized by shortened long bones and increased mineral density in bones secondary to a reduction in the population of proliferating and resting chondrocytes. This disorder is caused by mutations in the *PTHR1* gene that inhibits the function of the receptor. These patients also have distorted tooth development, they lack mammary buds, and they suffer from cardiovascular problems. As will be mentioned later, PTHrP has important roles in all of these organs.
b. **Jansen type metaphyseal chondrodysplasia** is an autosomal dominant disorder in which PTHR1 is constitutively active. Affected individuals have unusually short arms and legs due to premature epiphyseal closure and systemic mineral abnormalities, such as hypercalcemia and hypophosphatemia, that mimic hyperparathyroidism. These findings have been reproduced in mice engineered to express a constitutively activated form of PTHR1.
c. **Brachdactyly type E** is an autosomal dominant disorder with microdeletion of 900 kb of the *PTHLH* gene. In this disorder, there is also shortening of bones of hands and feet and sometimes short stature, as well as learning disabilities. The defect in the *PTHLH* gene is suggested to lead to a loss of coordination between PTHrP and Sox9, a master transcription

factor in chondrocyte development.

d. **A polymorphism in the *PTH1R* gene** is shown to be associated with higher adult height and reduced markers of bone resorption.

2. **Mammary gland and lactation**

PTHrP is required for normal **mammary gland formation prenatally**. PTHrP is expressed in mammary epithelial cells, and it interacts with the PTHR1 on mammary mesenchyme to promote the mesenchymal cells' ability to support epithelial duct outgrowth and development. In mice that lack PTHrP or PTHR1, mammary gland development fails. Similarly, fetuses with Blomstrand chondrodysplasia lack breast tissue.

PTHrP is also produced in large quantities by secretory epithelial cells during lactation and is **secreted into milk and into the circulation**. Although its function in milk is poorly understood, it is known that when released in the circulation, it **regulates maternal calcium and bone metabolism**. The mother's skeleton functions as a source of calcium for milk production. PTHrP produced by the lactating breast increases bone resorption to release calcium. The calcium-sensing receptor (CaSR) in breast epithelium senses this change and suppresses PTHrP p. 446p. 447production, creating a negative feedback loop. The main mediator of the effect of PTHrP in resorbing bone during lactation is believed to be osteoclastic bone resorption. Some recent studies have suggested that osteocytes may also be involved in resorbing bone (osteocytic osteolysis) and that this mechanism may play a role in lactational bone loss.

3. **Placenta**

The developing fetus requires a steady supply of calcium for mineralizing its skeleton; therefore, calcium needs to be transported across the placenta to the fetus. PTHrP plays an important role in **regulating fetal calcium levels**. It is **produced by the placenta** and promotes calcium transport from the mother to the fetus. Importantly, it is mid-region PTHrP (PTHrP 67-86 or PTHrP 38-94) presumably acting on a mid-region PTHrP receptor that mediates placental calcium transport.

However, the PTHR1 may also be involved in mediating calcium transfer to the fetus in response to PTH. In fact, both PTH and PTHrP are important in regulating fetal calcium concentrations. Interestingly, as with the breast, the CaSR regulates placental PTHrP production.

4. **Other sites**

PTHrP is **produced by smooth muscle cells in vessel walls, the gastrointestinal tract, bladder wall, and the uterus**. Its production increases in response to mechanical stretching and causes relaxation of the smooth muscle. In vessel walls, PTHrP is also increased in response to vasoconstrictive stimuli, such as angiotensin II, and can act as a vasodilator. PTHrP may also regulate smooth muscle cell proliferation in response to injury. Its expression is upregulated in vascular smooth muscle following balloon angioplasty, and it stimulates smooth muscle proliferation and neointima formation. These effects on proliferation appear to be mediated by nuclear actions of PTHrP.

PTHrP also acts as a **paracrine regulator of tooth eruption**. Normally, osteoclasts form above the tooth crypt to resorb bone and allow the tooth to erupt into the oral cavity. PTHrP produced by the stellate reticulum cells promotes osteoclast formation above the crypt. **Lack of PTHrP leads to failure of eruption and impaction of teeth**.

PTHrP is also **produced by all cell types in the pancreatic islets and β cells** and responds to PTHrP through activation of phospholipase C and intracellular calcium transients. Some recent experiments showed that PTHrP stimulates proliferation and glucose-induced insulin production in cultured human β cells and that PTHrP 1-36 improved glucose tolerance by increasing β cell mass in mouse pancreatic islets. These **findings suggest that PTHrP may be useful in maintaining β cell mass and treatment of diabetes**.

E. PTHrP in disease

1. **Hypercalcemia associated with cancer**

Malignancy-associated **hypercalcemia occurs in 20% to 30% of all cancer patients** and is the most common cause of hypercalcemia in hospitalized patients. PTHrP contributes to hypercalcemia associated with cancer in **two different syndromes**:

a. **Localized osteolytic hypercalcemia (LOH)** is caused by tumor secretion of local factors that stimulate osteoclasts to increase bone resorption. In LOH, there are extensive skeletal metastases and tumor cells that are in close proximity to osteoclasts where they secrete various chemokines and cytokines that increase bone remodeling and release calcium, including interleukin (IL)-1, IL-6, tumor necrosis factor-α, transforming growth factor-β (TGFβ), and PTHrP. Some of these local factors, such as TGFα, increase bone resorption through stimulating the release of PTHrP. Typical **causes of LOH include breast cancer and multiple myeloma**. Approximately **20%** of cancer-associated hypercalcemia cases are in this category.
b. **HHM** is the most common form of cancer-associated hypercalcemia (**80%** of cases). In HHM, tumors outside the skeleton secrete PTHrP into the circulation, and hypercalcemia ensues as a result of systemic effects of PTHrP causing bone resorption, but not due to the local effect of PTHrP around a p. 447p. 448bone metastasis. Almost all tumors can cause HHM; however, **it is most commonly associated with squamous cell carcinomas** (such as those of head and neck, esophageal, cervical, lung, and colon), **renal cell carcinoma, and breast cancer**. HHM tends to be a late complication of malignancy and **portends a very poor prognosis.** The 30-day mortality of patients with HHM is 50%, and some recent studies have reported 50-day median survival for patients with HHM.

   Hypercalcemia in HHM is the result of the evolutionary relationship between PTH and PTHrP. **With the exception of lactation, PTHrP does not normally circulate. However, when PTHrP is secreted by tumors, it can circulate** and interact with PTHR1 on osteoblasts to increase receptor activator of NFkB ligand (RANKL) secretion and inhibit osteoprotegerin (OPG) secretion. This, in turn, stimulates the differentiation and activity of osteoclasts, leading to **accelerated bone resorption**. Moreover, circulating

PTHrP also acts on the PTHR1 in the kidney to increase **calcium reabsorption**. Increased urinary calcium clearance leads to an osmotic diuresis and volume contraction, which further limits renal calcium excretion. When the amount of calcium released from the skeleton surpasses the ability of the kidneys to excrete calcium, hypercalcemia develops.

2. **Diagnosis and treatment of hypercalcemia in malignancy.** The signs and symptoms of hypercalcemia can be variable depending on the level of hypercalcemia (mild, moderate, or severe) and the rate of increase in serum calcium; and they can range from mild nonspecific symptoms, such as lethargy, to severe volume depletion, acute renal failure, and altered mental status and coma in severe cases of rapidly increasing calcium levels. Cancer-associated hypercalcemia is usually a late-stage complication of tumors that are readily detectable. However, it is crucial to consider the causes of hypercalcemia that are not directly related to cancer. **Once hypercalcemia is confirmed, routine measurement of PTH and PTHrP is warranted**. Additional laboratory tests include measurement of $25(OH)_2D$ and 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] and estimated glomerular filtration rate because renal insufficiency is common in these patients. In settings where there is suspicion of multiple myeloma, serum and urine protein electrophoresis, as well as a skeletal survey may be indicated. In the setting of other malignancies, a bone scan may be helpful if patients do not have obvious bone metastases. Typically, in patients with HHM, circulating **calcium and PTHrP levels are elevated, whereas PTH, phosphate, and $1,25(OH)_2D$ are low-normal or frankly decreased**. In patients with LOH, calcium is elevated, and the bone scan is positive. Circulating PTH and PTHrP levels are both low.

The main goal of therapy should be to manage the underlying malignancy, which may eventually resolve the hypercalcemia. However, calcium levels can also be controlled independent of therapy for the tumor by correcting dehydration and inhibiting bone resorption. Usually, treatment of hypercalcemia is started for moderate-to-severe hypercalcemia concomitant with measures taken for treating the underlying malignancy.

Rehydration in HHM patients is achieved by administration of

normal saline at a rate of 200 to 500 mL/hour with a goal of reaching a urine output >75 mL/hour. Some publications recommend rehydrating to be initiated with a bolus of 1 to 2 L of normal saline followed by maintenance fluids of 150 to 300 mL/hour for 2 to 3 days or until the volume depletion is corrected. These protocols can lower calcium by 1 to 2 mg/dL, but they can cause volume overload in patients with congestive heart failure or anuric renal failure. Loop diuretics, specifically **furosemide**, exert additional calciuretic effects. However, they must only be used after full correction of volume depletion. Otherwise, diuretics may aggravate dehydration, which, in turn, limits their calcium-lowering effects.

Bone resorption can be decreased with **salmon calcitonin** at a dose of 4 to 8 IU/kg (intramuscularly or subcutaneously) every 12 hours for 1 to 2 days, but its effects are transient due to significant tachyphylaxis within 48 hours. However, most commonly, **bisphosphonates** are used to inhibit osteoclast p. 448p. 449activity. **Denosumab**, an anti-RANKL antibody that blocks osteoclast formation, is also effective but less well studied in the setting of HHM. The two main bisphosphonates in use in the United States are **pamidronate** and **zolendronic acid**. Both of them are effective in treatment of hypercalcemia associated with cancer, but some studies suggest that when compared directly, zolendronic acid shows more potency. The median duration of action when given intravenously (IV) is around 30 days for zolendronic acid (at a dose of 4 mg), and the infusion should be over 15 to 30 minutes. Pamidronate is infused IV at 60 to 90 mg over 2 to 6 hours for 7 to 14 days. Denosumab has been reported to be effective in bisphosphonate-resistant HHM and in preventing the development of HHM in many patients with solid tumors and in multiple myeloma. Doses of 120 mg are administered subcutaneously on days 1, 8, 15, and 29 of treatment and every 4 weeks thereafter. Its actions in reducing calcium levels are reported to take effect in 10 days, and the median duration of response is 104 days. Although Denosumab does not have renal clearance, patients with renal failure may experience more

significant effects and are, therefore, at risk of developing hypocalcemia. Hence, dose adjustments in these patients are recommended.

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35 Common Bone and Mineral Disorders of Childhood

Michael A. Levine

I. INTRODUCTION

The skeleton contains about 99% of total body calcium and about 85% of total body phosphorus. These two minerals coexist within hydroxyapatite, a crystalline structure that constitutes the major inorganic matrix of bone. **This chapter describes childhood disorders of mineral metabolism** as well as other specific disorders that affect the growing skeleton.

II. CALCIUM AND PHOSPHATE HOMEOSTASIS

Approximately 50% of total serum calcium is in the ionized form (i.e., Ca^{2+}) at normal serum protein concentrations, and it represents the biologically active component of the total serum calcium concentration. Another 8% to 10% is complexed to organic and inorganic acids (e.g., citrate, sulfate, and phosphate); together, the ionized and complexed calcium fractions represent the diffusible portion of circulating calcium. Approximately 40% of serum calcium is protein bound, primarily to albumin (80%) but also to globulins (20%). The protein-bound calcium provides a reserve of available calcium that can respond immediately to an acute need for increased ionized calcium. The extracellular Ca^{2+} concentration must be maintained within narrow limits (Fig. 35-1).

Most of the body's phosphorus exists within hydroxyapatite crystal in calcified tissues. Phosphorus combines with other substances to form organic and inorganic phosphate compounds. The majority of the phosphate in the body is in the organic form as a complex with carbohydrates, lipids, and proteins. The small amount of phosphorus that is found in the extracellular fluid exists as **inorganic phosphate**, and although this represents only a small fraction of total body phosphorus, this component is easily measured and provides a useful indication of

total body phosphorus stores. Phosphorus plays important roles in cellular structure, enzymatic processes, nucleic acid synthesis, as well as in energy biogenesis (e.g., oxidative phosphorylation) and regulation of oxygen-carrying capacity of hemoglobin (e.g., within 2,3-diphosphoglycerate).

Phosphate exists in two forms in the plasma, dihydrogen phosphate (H_2PO_4) and its salt, monohydrogen phosphate (HPO_4). However, laboratory **assays measure phosphorus rather than phosphate** in the plasma. Normal serum **phosphorus concentrations are age dependent**, with higher levels present in children than adults. The concentration of serum phosphate is altered by meals and acid–base status and exhibits a diurnal variation, which reaches its nadir between 8 and 11 A.M.

Absorption of calcium and phosphate from the gastrointestinal tract is dependent upon vitamin D. Parent vitamin D, either obtained from the diet or produced in the skin after ultraviolet light irradiation, is transformed to the fully **active hormone, calcitriol**, via two sequential enzymatic hydroxylations. The first step, 25-hydroxylation, occurs principally in the liver by the cytochrome P450 (CYP) enzyme CYP2R1, and generates 25(OH)D, the principal circulating form of vitamin D and a useful biomarker for vitamin D status. In the second step, 25(OH)D is converted to calcitriol in the kidney by the 1α-hydroxylase CYP27B1 in a tightly regulated process that is stimulated by parathyroid hormone (PTH) and inhibited by the phosphatonin FGF23. Calcitrol binds to specific vitamin D receptors (VDRs) in target tissues.

A. Physiology (see Chapter 31).

B. Normal values. Normal serum calcium and phosphorus levels for infants and older children are indicated in Table 35-1. Levels tend to be marginally higher (by ~0.2 mg) p. 450p. 451in growing children compared with adults. The physiologically active component of serum calcium is the ionized calcium (Ca^{2+}). Increases in the extracellular fluid concentration of anions, such as phosphate, citrate, bicarbonate, or edetic acid, will increase the proportion of bound calcium and decrease ionized calcium. Extracellular fluid pH also affects the distribution of calcium between ionized and bound fractions. Alkalosis increases the affinity of albumin for calcium and thereby decreases the concentration of ionized calcium. By contrast, acidosis increases the ionized calcium concentration by decreasing the binding of calcium to albumin. When it is not possible, or practical, to

determine the ionized calcium concentration directly, an “adjusted” total calcium concentration can be calculated using one of several proposed algorithms that are based on plasma albumin concentrations. None of these formulas is absolutely accurate, but they often provide useful estimates of the true p. 451p. 452concentration of calcium in serum. One widely used algorithm estimates that total serum calcium declines by 0.8 mg/dL for each 1 g/dL decrease in albumin concentration, without a change in ionized calcium. The unique pattern of serum proteins in neonates can lead to inaccurate calculation of ionized calcium using formulas based on calcium–protein relationships derived from adult data.

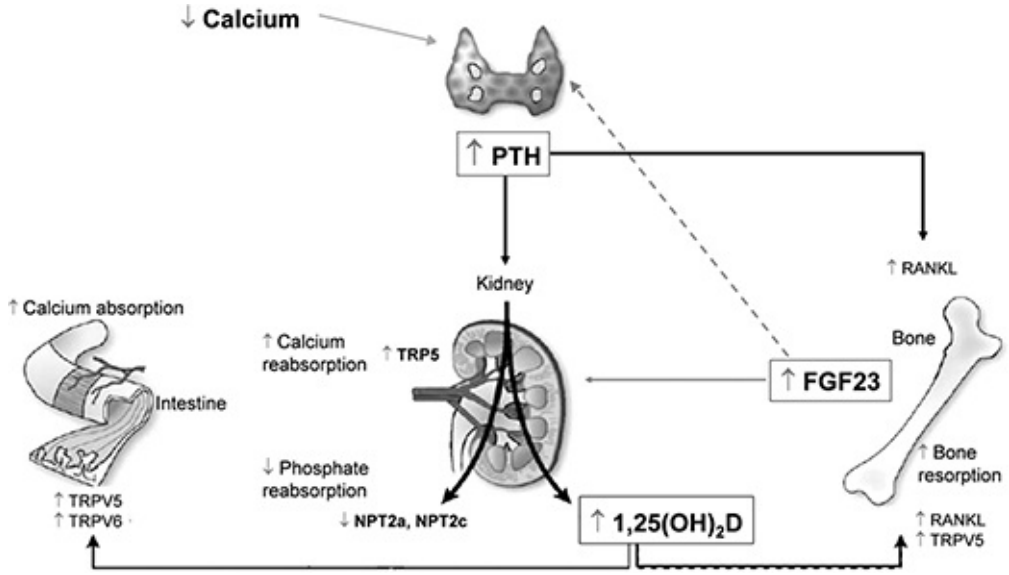

Figure 35-1. Central role of parathyroid glands in regulating extracellular ionized calcium concentration (Ca^{2+}). Parathyroid hormone (PTH) mobilizes Ca^{2+} from bone and reduces fractional renal clearance of Ca^{2+}. In turn, Ca^{2+} acts on parathyroids to inhibit PTH secretion. By stimulating renal 25-hydroxycalciferol 1*α*-hydroxylase, PTH enhances calcitriol formation and hence intestinal Ca^{2+} absorption. Calcitriol increases expression of TRPV5 and TRPV6, thus increasing calcium absorption in the intestine, calcium reabsorption in the distal tubule, and osteoclastic bone resorption. Calcitriol and PTH both increase secretion of RANKL from osteoblasts, which enhances the number and function of osteoclasts. PTH and FGF23 decrease expression of renal tubule sodium phosphate cotransporters Npt2a and Npt2c, thereby reducing phosphate reabsorption. FGF23 also decreases expression of renal 25-hydroxycalciferol 1*α*-hydroxylase. Dashed line indicates a direct inhibitory effect of FGF23 on PTH secretion.

TABLE 35-1 **Normal Values of Serum Calcium and Phosphorus in Infancy and Childhood**

Age category	Total calcium (mg/dL)	Ionized calcium (mM)	Phosphorus (mg/dL)
Newborn (0–3 mo)	8.8–11.3	1.22–1.40	4.8–7.4
Boys and girls 1–5 yr	9.4–10.8	1.22–1.32	4.5–6.5
Boys and girls 6–12 yr	9.4–10.3	1.15–1.32	3.6–5.8
Boys 15–17 yr	9.5–10.5	1.12–1.30	2.3–4.5
Boys 17–19 yr and girls 12–15 yr	9.5–10.4	1.12–1.30	2.3–4.5
Girls 15–19 yr	9.1–10.3	1.12–1.30	2.3–4.5

The concentration of serum phosphate is generally expressed in milligrams per deciliter because concentration in millimoles can vary with acid–base status. Serum levels expressed in milligrams can be converted to millimoles per liter by multiplying by 0.323. To convert to milliequivalents, multiply the concentration in millimoles by the valence (1.8 at pH of 7.40).

About 85% to 90% of serum phosphate is free and is ultrafiltrable; 10% to 15% is bound with protein.

III. DISORDERS OF CALCIUM HOMEOSTASIS

A. Hypocalcemia. Clinically important categories of hypocalcemia and some features associated with the failure of calcium control are listed in Table 35-2. Hypocalcemia is usually defined as a total serum calcium concentration of <8.5 g/dL (2.1 mmol/L) in children, <8 mg/dL (2 mmol/L) in term neonates, and <7 mg/dL (1.75 mmol/L) in preterm neonates. The symptoms and signs of hypocalcemia are largely explained by the disturbance in neuromuscular excitability attributable to a reduction in extracellular fluid Ca^{2+} concentration. Common features include neuromuscular irritability in the form of myoclonic jerks, “twitching,” exaggerated startle responses, or seizures. Apnea, cyanosis, tachypnea, tachycardia, vomiting, laryngospasm, or heart failure may also be seen. Markedly reduced ionized calcium concentrations may be associated with prolongation of the Q_o–T_c interval on the electrocardiogram and decreased cardiac contractility. Often, however, hypocalcemia is clinically silent and detected only by routine blood chemistry panels. Neuromuscular tetany and distressing paresthesias are more common in older children and adults, whereas bronchospasm and epileptic seizures are more common manifestations of hypocalcemia in babies and young

children.

1. **Neonatal hypocalcemia.** Neonatal hypocalcemia is the most common type of hypocalcemia encountered by the pediatrician. It can be divided into early p. 452p. 453hypocalcemia, which occurs within the first 3 to 5 days of life, and late neonatal hypocalcemia, which begins at the end of the first week of life. Hypocalcemia may occur in as many as **30% of infants with very low birth weight** (<1 500 g) and in as many as **89% of infants whose gestational age at birth was <32 weeks**. Hypocalcemia is also common in infants of mothers with diabetes mellitus and in infants with birth asphyxia. In the newborn, as well as in the older child, intestinal absorption of calcium occurs both passively and through a vitamin D–dependent active transport mechanism. At birth, the newborn's vitamin D status is related directly to maternal vitamin D status and to maternofetal transfer of vitamin D and its metabolites. Serum levels of both 25-hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [$1,25(OH)_2D$ or calcitriol] are lower than maternal values, and premature babies as well as babies whose mothers have marked vitamin D deficiency will have compromised vitamin D status. Circulating calcitriol concentrations rise over the first 2 days of life, and calcitriol stimulates absorption of calcium (and to a lesser extent phosphorus) in the small intestine. In newborns and young infants, passive calcium absorption accounts for most of the intestinal calcium; however, neonates, even very-low-birth-weight infants, can absorb and metabolize vitamin D, and **supplementation with vitamin D can increase calcium absorption within 4 weeks of birth**. Under usual circumstances, **human milk is not an adequate source of vitamin D**, and the predominant sources of vitamin D in the breast-fed infant are endogenous synthesis after exposure to sunlight or supplementation.

TABLE 35-2 Clinically Important Categories of Hypocalcemia

Category	Serum level			
	Phosphorus	25-OHD	$1,25(OH)_2D$	PTH

Neonate				
Early hypocalcemia	N	N	N or L	N or L
Late hypocalcemia				
Hypoparathyroidism	H	N	N or L	L
Transient hypocalcemia	H	N	N	N or H
Older Child				
Critical illness	N	N	N	L
Hypoparathyroidism	H	N	L	L
Pseudohypoparathyroidism	H	N	L	H
Vitamin D deficiency	L, N, or H	L	L, N, or H	H
Vitamin D dependency type 1a	L	N	L	H
Vitamin D dependency type 1b	L	L	L or N	H
Vitamin D dependency type 2	L	N	H	H
Acute phosphorus overload	H	N	?	H

H, high; L, low; N, normal; PTH, parathyroid hormone.

Because the maternal calcium concentration and vitamin D status during pregnancy influence parathyroid function in the developing fetus, a thorough evaluation of the newborn with hypocalcemia (or hypercalcemia) must include analysis of mineral metabolism in the infant's mother. Moreover, the association of some forms of congenital hypoparathyroidism with dominantly inherited defects in the genes encoding the calcium-sensing receptor (CaSR) or the G-protein (Gα11) that couples the CaSR to downstream signaling pathways in parathyroid cells provides strong justification to determine the serum calcium levels in the child's biologic father and siblings as well.

Hypomagnesemia predisposes to neonatal hypocalcemia and can exacerbate its symptoms. The basis for these effects is not well understood but may relate to the association of hypomagnesemia with impaired PTH release or action.

a. Early neonatal hypocalcemia

i. Clinical features. In the neonate, jittery movements, convulsions, and, occasionally, apnea and myocardial dysfunction may all represent manifestations of hypocalcemia. Any newborn with these signs should have the serum calcium level determined, preferably by direct measurement of ionized calcium. A Ca^{2+} concentration <2.5

mg/dL (0.63 mmol/L) can be clinically significant and is often accompanied by cardiac abnormalities. The electrocardiography hallmark of hypocalcemia is the **prolongation of the rate-corrected Q-T interval** (Q_o–T_c) because of lengthening of the ST segment, which is directly proportional to the degree of hypocalcemia.

ii. **Etiology and pathophysiology.** This disorder commonly affects low birth weight and sick neonates between 1 and 4 days of age. It is often considered an exaggeration of the physiologic fall in the plasma calcium concentration that occurs in all newborn infants during the first 2 to 3 days of life. Early neonatal hypocalcemia apparently results from (a) insufficient release of PTH by immature parathyroid glands or (b) inadequate responsiveness of the renal tubule cells to PTH. An (c) exaggerated rise in calcitonin secretion in premature infants may play a contributory role. Maternal diabetes mellitus is a significant risk factor and is commonly associated with hypomagnesemia, birth asphyxia, and prematurity. Prematurity, low birth weight, hypoglycemia, difficult delivery, and respiratory distress syndrome are other risk factors for early-onset hypocalcemia.

In the premature, small, or sick neonate, maintenance of a normal Ca^{2+} concentration is further jeopardized by the lack of substantial food p. 453p. 454(and hence calcium) intake. It is also possible that stress hormones such as calcitonin and cortisol act to stabilize bone, diminishing PTH-induced calcium release. In addition to these risk factors, transfusion of large volumes of citrate- or phosphate-containing whole blood can lower ionized calcium through the formation of nonionizable calcium phosphates or citrates. The overly rapid correction of acidosis with bicarbonate or by hyperventilation can also lead to a rapid fall in Ca^{2+} by increasing the fraction of circulating calcium bound to protein. A more severe form of transient neonatal hypoparathyroidism and tetany occurs in infants who were exposed in utero to maternal

hypercalcemia, which can lead to suppression of parathyroid activity in the developing fetus and reduce responsiveness of the parathyroid glands to hypocalcemia after birth.

b. **Late neonatal hypocalcemia.** This term describes hypocalcemia that occurs at 5 to 10 days of age in full term and apparently healthy neonates, and which can occur as late as 6 weeks after birth. Late-onset hypocalcemia is invariably associated with **elevations in serum phosphorus levels**. Hyperphosphatemia, and consequent hypocalcemia, generally reflects a **high intake of phosphate**, which typically occurs through ingestion of commercial infant formulas but which may also occur by rectal administration of phosphate-based enema solutions. Late-onset hypoparathyroidism is usually associated with serum levels of PTH that are low or insufficiently elevated relative to the degree of hypocalcemia. This may reflect an inability of the parathyroid gland to secrete adequate amounts of PTH or partial resistance of the immature kidney to PTH. Rarely, late-onset hypocalcemia may occur as a manifestation of maternal hypercalcemia. **Hyperphosphatemia increases deposition of calcium into the skeleton** and into other tissues. In addition, hyperphosphatemia increases circulating levels of the **phosphatonin FGF23**, which participates in a negative feedback loop by reducing renal reabsorption of phosphate and decreasing activity of CYP27B1, the 1-hydroxylase that converts 25(OH)D to the fully active $1,25(OH)_2D$. These actions may be aimed at decreasing the serum levels of phosphate, but often have the undesirable consequence of reducing the plasma calcium level.

c. **Other causes of neonatal hypocalcemia.** Congenital hypoparathyroidism may present in the neonatal period but is less common than transient hypoparathyroidism associated with maternal hypercalcemia. Serum levels of calcium should always be checked in both parents when infantile hypocalcemia is not transient to identify potential dominantly inherited forms of congential hypoparathyroidism (see below).

   i. **Phosphorus overload. Cows' milk contains six times as much phosphorus as human milk** (950 vs.

162 mg/L). Ingestion of a calorically adequate volume of cows' milk overwhelms the capacity of the neonatal kidney to excrete phosphate, with consequent hyperphosphatemia. However, even in modern "humanized" cows' milk–based formulas, the calcium to phosphorus ratio is lower than in breast milk. Because human milk is low in phosphate, breast-fed infants rarely, if ever, develop late-onset hypocalcemia. Compared with breast-fed babies, infants receiving these formulas have slightly but significantly lower serum Ca^{2+} levels during the first 2 weeks of life.

ii. **Uremia.** Renal failure can present in the first week or two of life with seizures or tetany. These signs might be due to hypocalcemia secondary to renal phosphate retention. The blood urea nitrogen and creatinine should be measured in all cases of neonatal hypocalcemia with hyperphosphatemia.

iii. **Transient pseudohypoparathyroidism (PHP) of the newborn.** Although most newborns with late-onset hypocalcemia have low levels of PTH, approximately 25% of affected babies have **elevated levels of PTH**. Hypocalcemia is associated with hyperphosphatemia, which is due to increased renal reabsorption of phosphate from the glomerular filtrate (i.e., an elevated transport maximum of phosphate) despite elevated PTH p. 454p. 455levels. Serum levels of magnesium and vitamin D metabolites are typically normal. These biochemical features strongly resemble those of PHP, but, in contrast to genetic forms of PHP that are associated with defects in the *GNAS* gene, infants with this transient form of PTH resistance show normal nephrogenous cyclic adenosine monophosphate (cAMP) responses to administered PTH. By contrast, the phosphaturic response to the PTH infusion is typically impaired. Affected newborns respond to treatment with calcium and/or active (i.e., 1α-hydroxylated) metabolites of vitamin D. The condition appears to be transient, and normal serum levels of calcium, phosphorus,

and PTH are achieved by 6 months of age. These features are suggestive of delayed maturation of the post-cAMP signaling pathway in the proximal renal tubule.

iv. **Defects in vitamin D supply or action.** Vitamin D deficiency can cause hypocalcemia at any age (see below), but is an uncommon cause of neonatal hypocalemia. Congenital vitamin D deficiency can manifest as late-onset neonatal hypocalcemia when intestinal absorption of calcium begins to rely on vitamin D–dependent transport. Because neonatal stores of vitamin D are derived entirely from maternal sources in utero, it is not surprising that maternal vitamin D insufficiency is usually associated with this condition. Defects in activation or responsiveness to vitamin D usually manifest as hypocalcemia and/or rickets in late infancy.

v. **Critical illness.** Hypocalcemia has long been known to occur in infants and children who are critically ill or who have sustained a significant burn injury. Often such hypocalcemia is noted after cardiac surgery or major injury. There are conflicting views as to whether hypocalcemia in these cases is a result of relative hypoparathyroidism or of other factors, such as hypercalcitoninemia, increased glucocorticoids, or inflammatory cytokines.

vi. **Hypoparathyroidism.** Hypoparathyroidism is characterized by hypocalcemia and hyperphosphatemia as a result of inadequate or deficient secretion of PTH. The causes of hypoparathyroidism, together with some of the clinical features associated with specific disorders, are listed in Table 35-3. Hypoparathyroidism can be an isolated endocrine defect or part of a more complex syndrome. Functionally, hypoparathyroidism can result from defects in parathyroid gland formation, destruction of the parathyroid glands, or reduced parathyroid gland secretion of PTH.

a) **Developmental disorders. DiGeorge sequence (DGS)** is a common developmental disorder that occurs in approximately 1:2 500 live births. DGS is associated with dysembryogenesis of the third and fourth pharyngeal pouches, with consequent hypoplasia of the thymus and parathyroid glands. Patients also usually

manifest cardiac and aortic arch defects (e.g., interrupted aortic arch defects, septal defects, and tetralogy of Fallot), cleft palate, dysmorphic facies, and developmental delays. Additional developmental defects are common, including renal anomalies and disturbances in facial muscle development can lead to "asymmetric crying facies" in affected infants. **Hypoparathyroidism is present in up to 60% of patients with DGS.** DGS is the leading cause of persistent hypocalcemia of the newborn, but hypoparathyroidism may resolve during childhood, and hypocalcemia often recurs during times of medical or surgical stress. Surprisingly, other endocrine defects such as primary **hypothyroidism and growth hormone deficiency have also been described in children with DGS**, albeit far less frequently than hypoparathyroidism. Thymic defects are associated with impaired T-cell–mediated immunity and frequent infections.

Molecular mapping has attributed most (70% to 80%) cases of DGS to hemizygous microdeletions within a critical 250-kb region of 22q11.21–q11.23, and these microdeletions represent the most common contiguous gene deletion disorder in humans. Deletions within this critical genomic region can cause other related syndromes with overlapping features, including the conotruncal anomaly face syndrome and the **velocardiofacial syndrome** **p. 455p. 456****(VCFS)**. VCFS is typically diagnosed later in childhood, and hypocalcemia has been found to be present in up to 20% of cases. Because of the phenotypic variability of the various overlapping syndromes, these conditions are all included within the acronym "CATCH-22," representing a syndrome of **C**ardiac abnormality, **A**bnormal facies, **T**hymic hypoplasia, **C**left palate, and **H**ypocalcemia with deletion. In addition to

these genetic defects, DGS can arise in infants who were exposed in utero to maternal or gestational diabetes, to alcohol, and to other toxins (e.g., retinoids).

TABLE 35-3 Hypoparathyroidism and Related Disorders in Childhood

Type	Parathyroid	Age of onset[a]	Associated features
Transient neonatal	Physiologic suppression	2–10 d	Maternal hypercalcemia
DiGeorge sequence	Parathyroid dysgenesis	0–1 mo	Del22q11; *TBX1* mutation Cardiac and thymic (immune) deficits
Type 1 polyglandular autoimmune syndrome	Autoimmune destruction or activating antibodies	3+ yr	Mutation of *AIRE* gene Mucocutaneous candidiasis, adrenal failure
Autosomal dominant hypocalcemia	Reduced: "set point" for Ca^{2+}-mediated inhibition of PTH secretion	Infancy and childhood	Mutation of *CaSR* or *GNA11* genes; positive family history; hypercalciuria
Autosomal recessive hypoparathyroidism	Impaired parathyroid development or PTH secretion	Infancy and childhood	*GCM2* or *PTH* gene with isolated hypoparathyroidism; *GATA3* with hypoparathyroidism, deafness and renal dysplasia
Autosomal dominant hypoparathyroidism	Decreased PTH secretion or parathyroid development	Infancy to childhood	*PTH* gene mutation; *GCM2* mutation
Thalassemia/iron overload	Iron deposition	Adolescence and beyond	Cardiac, liver, and endocrine dysfunction
Postsurgical	Removal or damage	Any	Following thyroidectomy
Pseudohypoparathyroidism	Resistance to PTH	Infancy to 10 yr	
Hypomagnesemia	Reduced PTH production and/or resistance to PTH	Any	Specific intestinal defect or generalized malabsorption

PTH, parathyroid hormone.
[a]Most typical ages given. Individual cases may vary widely.

Hypoparathyroidism is also a common feature of the **CHARGE** sequence (OMIM 214800), which consists of coloboma, heart defects, choanal atresia, retarded growth and development, genital abnormalities, and ear anomalies. CHARGE is usually caused by heterozygous mutation in the *CHD7* gene on chromosome 8q12.

b) The **hypoparathyroidism, sensorineural deafness, and renal dysplasia syndrome** (**HDR**; MIM 146255) is another complex disorder that p. 456p. 457 includes hypoparathyroidism. Unlike DGS/CATCH-22, individuals with HDR do not exhibit cardiac, palatal, or immunologic abnormalities. Patients may have only one or two of the three defining features of HDR, but **deafness** appears to be a consistent finding in patients with hypoparathyroidism. The HDR disorder is a result of haploinsufficiency of the GATA-binding protein-3 (*GATA3*) gene.

c) Hypoparathyroidism-retardation-dysmorphism and Kenny-Caffey syndromes. The hypoparathyroidism-retardation-dysmorphism syndrome (HRD; MIM 241410), also known as the **Sanjad-Sakati syndrome**, is a rare form of autosomal recessive hypoparathyroidism that is associated with other developmental anomalies. In addition to parathyroid dysgenesis, affected patients have severe growth and mental retardation, microcephaly, micro-ophthalmia, small hands and feet, and abnormal teeth. This disorder is seen almost exclusively in individuals of **Arab descent**. Kenny-Caffey syndrome type 1 (MIM 244460) is an allelic disorder that is characterized by hypoparathyroidism, dwarfism, medullary stenosis of the long bones, and eye abnormalities.

d) Isolated hypoparathyroidism. The leading cause of isolated hypoparathyroidism is inactivation of the *GCM2*

(*GCMB*) gene at 6p23–24 (MIM 146200), which can be either autosomal recessive or dominant. Parathyroid aplasia or dysplasia is associated with severe hypocalcemia and low or undetectable levels of plasma PTH.

Isolated hypoparathyroidism can also be inherited as an X-linked recessive trait (MIM 307700). Affected males present with infantile hypocalcemic seizures, whereas hemizygous females are unaffected. Autopsy of an affected individual revealed complete agenesis of the parathyroid glands as the cause of hypoparathyroidism.

e) Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (see Chapters 31 and 84)

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) or autoimmune polyglandular syndrome type-1 (APS1; MIM 240300) classically manifests as a triad of features that can be remembered by the acronym "HAM" for **H**ypoparathyroidism, **A**drenal insufficiency, and **M**ucocutaneous candidiasis. In addition, patients commonly manifest other features that indicate APECED/APS1 is a generalized disturbance in autoimmune regulation, including hepatitis, keratitis, periodic rashes with fever, intestinal malabsorption, severe obstipation, alopecia, vitiligo, hypogonadism, hypothyroidism/hyperthyroidism, type 1 diabetes, pernicious anemia, dental enamel hypoplasia, or nail pitting. APECED/APS1 is caused by mutations in *AIRE*, which encodes a transcription factor that functions as an important regulator in thymic epithelial cells. In most cases, APECED/APS1 is autosomal recessive, but in some patients, an autosomal dominant mode of inheritance has also been described. Studies indicate that most patients with APECED/APS1 develop hypoparathyroidism because of circulating antibodies that damage or destroy the parathyroid glands. An alternative pathophysiology implicates the presence of circulating antibodies that bind and activate the CaSR, thereby reducing PTH secretion from parathyroid cells

(and increasing calcium excretion from the kidney). Patients with this pathophysiology may have a reversible form of hypoparathyroidism.

The natural history of APECED/APS1 is quite predictable, with the appearance of mucocutaneous candidiasis and hypoparathyroidism in the first decade of life, followed by primary adrenal insufficiency before 15 years of age. **Addison disease can mask the presence of hypoparathyroidism**, or may manifest only after improvement of the hypoparathyroidism, with a reduced requirement for calcium and vitamin D. By diminishing gastrointestinal absorption of calcium and increasing renal calcium excretion, **glucocorticoid therapy for the adrenal insufficiency may exacerbate p. 457p. 458the hypocalcemia** and could cause complications if introduced before the hypoparathyroidism is recognized.

f) **Autosomal dominant hypocalcemia** (ADH) most commonly occurs as a result of an activating mutation of the *CaSR* gene (601199) on chromosome 3q21 encoding the CaSR (autosomal dominant hypocalcemia-1; HYPOC1; OMIM 146200). In about 15% to 20% of cases, ADH is caused by a gain-of-function mutation in the *GNA11* (139313) gene. This second form of ADH is termed autosomal dominant hypocalcemia-2 (HYPOC2; OMIM 615361). In both cases, the mutant proteins lead to increased sensitivity of parathyroid cells to extracellular calcium as a result of a lowered set point for inhibition of PTH secretion. The effect is to reduce PTH secretion and thereby produce a state of functional hypoparathyroidism. Nephrocalcinosis and nephrolithiasis are common complications of vitamin D therapy. Although the degree of hypocalcemia and hypercalciuria are often mild and well tolerated with low-normal PTH levels, in many patients, ADH is associated with severe and symptomatic hypocalcemia. Moreover, some patients with activating mutations of the *CaSR* gene will also develop significant

hypomagnesemia and hypokalemia, a complication that is termed **type 5 Bartter syndrome**.

g) ***PTH* gene mutations** (see Chapter 31).

h) **Anti-CaSR antibodies.** Many patients with late- or adult-onset primary hypoparathyroidism have circulating antibodies that activate the CaSR and impair release of PTH rather than produce irreversible destruction of the parathyroid glands. It is likely that these antibodies also activate the CaSR in the distal nephron, which may account for the increased urinary excretion of calcium in these patients. Hence, affected patients resemble those with ADH (see above) and activating mutations of the *CaSR*.

i) **Mitochondrial disease.** Several syndromes caused by deletions in mitochondrial DNA have been associated with hypoparathyroidism. These include **Kearns-Sayre syndrome** (encephalomyopathy, ophthalmoplegia, retinitis pigmentosa, and heart block), **Pearson marrow-pancreas** syndrome (sideroblastic anemia, neutropenia, thrombocytopenia, and pancreatic dysfunction), and **maternally inherited diabetes and deafness syndrome**. Hypoparathyroidism has also been described in **MELAS** (**M**itochondrial myopathy, **E**ncephalopathy, **L**actic **A**cidosis, and **S**trokelike episodes) **syndrome**, a result of point mutations in mitochondrial tRNA. Because renal magnesium wasting is frequently seen in these conditions, a readily reversible form of hypoparathyroidism caused by hypomagnesemia should also be considered.

j) **Parathyroid gland destruction** (see Chapter 31).

2. **Pseudohypoparathyroidism** (see Chapter 31).
   a. **PHP type 1a** (see Chapter 31).
   b. **PHP type 1b** (see Chapter 31).
   c. **PHP type 1c** (see Chapter 31).
   d. **Osteoma cutis and progressive osseous heteroplasia (POH). Osteoma cutis** and **POH** represent alternative manifestations of **Albright hereditary osteodystrophy (AHO)** in which only heterotopic ossification occurs. In

osteoma cutis, ectopic ossification is limited to the superficial skin, whereas in POH, heterotopic ossification involves the skin, subcutaneous tissue, muscles, tendons, and ligaments (Fig. 35-2). POH can be disabling because extensive dermal ossification occurs during childhood, followed by widespread ossification of skeletal muscle and deep connective tissue. Nodules and lacelike webs of heterotopic bone extend from the skin into the subcutaneous fat and deep connective tissues and may cross joints, leading to stiffness, joint locking, and permanent immobility.

Heterozygous inactivating *GNAS* mutations have been identified in most patients with osteoma cutis and POH, and in each case, the defective allele was paternally inherited. Although patients with POH lack other features of p. 458p. 459AHO or PHP, maternal transmission of the defective *GNAS* allele leads to the complete PHP type 1a phenotype in affected children.

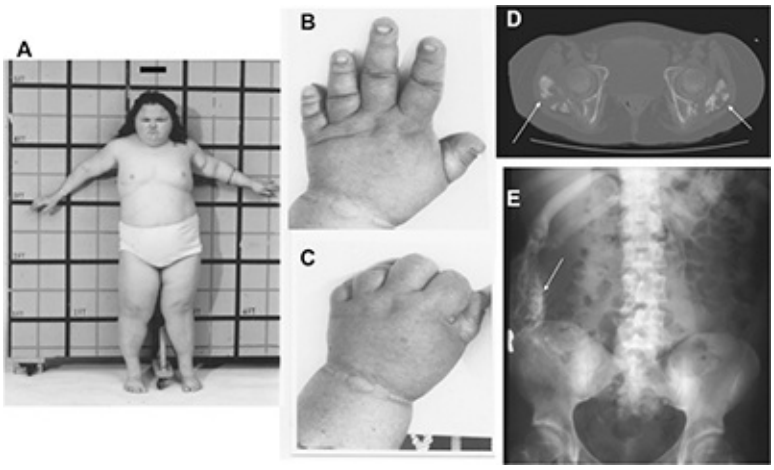

Figure 35-2. Young woman with typical features of AHO and PHP type 1a. Panel **A** shows short stature, round face, obesity, and sexual immaturity; panels **B** and **C** show brachydactyly, with Archibald dimples rather than knuckles visible when a fist is made; panel **D** shows CT scan of lower extremity with heterotopic ossification present in deep muscle *(arrows),* whereas panel **E** shows superficial heterotopic ossification in the abdominal wall subcutaneous tissues *(arrow)*. AHO, Albright hereditary osteodystrophy; CT, computed tomography; PHP, pseudohypoparathyroidism.

e. PHP type 2 (see Chapter 31).

3. **Management of hypocalcemia.** Although mild hypocalcemia might not require therapy, any neonate with a serum calcium level <7.5 mg/dL (Ca^{2+} < 2.8 mg/dL) or an older child with a serum calcium level < 8 mg/dL should be evaluated and treated in order to prevent tetany and other symptoms.

   a. **Acute.** In acute symptomatic hypocalcemia, intravenous therapy is required. **(a)** Rapid injection of calcium can cause serious cardiac dysrhythmias and **(b)** all calcium salts are locally toxic and can lead to tissue damage upon accidental extravasation. **Calcium gluconate is less irritating to veins and to adjacent tissues, if extravasated, than calcium chloride**. To relieve severe symptoms of hypocalcemia rapidly, an intravenous **bolus of 9 to 15 mg elemental calcium/kg (1 g calcium gluconate = 93 mg elemental calcium) can be infused over 10 to 30 minutes**; more rapid injection of calcium may cause vasodilation, decreased blood pressure, bradycardia, cardiac arrhythmias, syncope, and cardiac arrest. Further administration of calcium can be given as either intermittent boluses or by continuous intravenous infusion (1 to 3 mg/kg/hour of elemental calcium in 0.9% w/v sodium chloride or 5% w/v dextrose). If **only a peripheral line is available, calcium gluconate is the preferred** salt, and should be infused with caution as a dilute solution (e.g., 1 mg of elemental calcium/mL of intravenous solution). **When a central line is available, either calcium salt may be administered**. Owing to the very short plasma half-life of intravenous calcium, a **continuous infusion of elemental calcium** is superior to intermittent bolus infusions. A transition to oral forms of calcium can be made when the serum calcium concentration is within a safe range and the levels of vitamin D metabolites are adequate to ensure absorption of calcium from the gastrointestinal tract.

   b. **Chronic.** In the absence of symptoms of hypocalcemia (e.g., tetany, paresthesias, or seizures) or marked hypocalcemia, therapy with oral calcium and/or appropriate forms of vitamin D will generally be sufficient. Spontaneous recovery of normal

mineral homeostasis typically occurs after a few weeks in p. 459p. 460p. 460p. 461infants with neonatal hypocalcemia, but serum calcium levels can be increased within 1 to 2 days by supplementing artificial formulas with sufficient calcium to achieve a high (3:1 to 4:1) molar ratio of calcium to phosphorus. Our practice has been to supplement a low-phosphorus formula, such as **Similac PM 60/40** (11.2 mg calcium and 5.5 mg phosphorus/oz). For example, 5 oz of Similac PM 60/40 contains 1.4 mmol (56 mg) of calcium and 0.90 mmol (28 mg) of phosphorus, which corresponds to a Ca:P molar ratio of only 1.6:1. In order to achieve the desired 4:1 Ca:P ratio, one would have to add 2.2 mmol of calcium to 5 oz of the Similac PM 60/40 formula, which could be achieved by addition of 220 mg of calcium carbonate (88 mg of elemental calcium). Infants and older children who require more protracted treatment can be given 50 to 100 mg/kg of elemental calcium per day in three to four divided doses that are given with meals.

TABLE 35-4 Classification of Hypercalcemia in Childhood

	Serum				Urine	
Type	**Phos**	**Calcidiol**	**Calcitriol**	**PTH**	**Ca**	**Notes**
Williams syndrome	N	N	N or H	L	H	Elastin (*ELN*) gene deletion in 17q11.23. Cognitive impairment. Elfin facies, aortic stenosis
Idiopathic hypercalcemia of infancy	N to L	H	H	L	H	Mutation in *CYP24A1* associated with low serum 24,25$(OH)_2$D level; some patients have *SLC34A1* mutation
Childhood hyperparathyroidism	L	N	H	H	H	Usually adenoma, sometimes genetic as syndrome (*MENIN*) or isolated (*GCM2*).
Severe neonatal hyperparathyroidism	L	N	H	H	L/N	Loss-of-function mutation (generally homozygous) in *CaSR* gene
Familial hypocalciuric hypercalcemia	N	N	N	N	L	Loss-of-function mutation (generally heterozygous) in *CaSR*, *GNA11*, or *AP2S1* genes
Immobilization	N	N	L	L	H	
Hypophosphatasia	N	N	L	L	H	Mutations in tissue nonspecific alkaline phosphatase gene, *ALP*
Ketotic hypercalcemia	N	N	L	L	H	Ketogenic diet; low alkaline phosphatase
Malignancy (metastatic)	N	N	L	L	H	
Malignancy (nonmetastatic)	L	N	L	L	H	Unregulated and excessive secretion of bone-resorbing substances; notably PTHrP, less frequently 1,25$(OH)_2$D

CaSR, calcium-sensing receptor gene; PTH, parathyroid hormone; PTHrP, parathyroid hormone–related peptide.

4. **Oral calcium supplements.** Once adequate levels of active vitamin D are present, some patients may not require calcium supplements. In young children, liquid **calcium glubionate** (1 g contains 64 mg of elemental calcium; 1 mL of solution contains 24 mg of elemental calcium) is often the preferred form of oral

calcium because it is available as a somewhat pleasant-tasting syrup. The usual daily dose is 50 to 100 mg of elemental calcium/kg. High doses of calcium glubionate can cause diarrhea because of the preparation's high-sugar content. Alternatively, a suspension of calcium carbonate (100 mg of elemental calcium/mL) can be used. The supplemental calcium should be administered in divided doses and taken with meals. Tablets of calcium gluconate, carbonate, citrate, or lactate can be given as an alternative to the glubionate syrup or suspension of calcium carbonate. In clinical practice, all calcium salts perform similarly. The gluconate consists of about 9% elemental calcium, the carbonate 40%, citrate 21%, and the lactate 13%.

5. **Vitamin D supplements.** Treatment of chronic hypocalcemia, except in the mildest cases, will require administration of vitamin D or its metabolites in addition to calcium.

   1-Hydroxylated vitamin D (e.g., calcitriol) does not require PTH for full activation. Patients with hypoparathyroidism who are treated with parent vitamin D will require very large daily doses (e.g., 50 000 to 200 000 IU) to achieve the high circulating levels of 25(OH)D that are necessary to effect a vitamin D response, because 25(OH)D binds to VDRs with far lesser affinity than calcitriol. Both calcitriol and alfacalcidol (1α-hydroxyvitamin) do not require PTH-dependent 1-hydroxylation and, therefore, are active in patients with hypoparathyroidism when used in small, physiologic doses. Calcitriol is more potent than alfacalcidol because it does not require either hepatic or renal hydroxylation to have full activity in vivo. Therefore, **calcitriol has become the treatment of choice for patients with chronic hypocalcemia or hypoparathyroidism**. Calcitriol has a very short half-life, about 24 hours, and overall its duration of action is no more than 1 to 2 days.

   The **dosage of calcitriol** in childhood (e.g., 50 to 90 ng/kg/day) is generally higher on a weight-adjusted basis than that in adults. Anything from 0.25 to 3.0 μg/day may be needed. The medication is administered once or twice daily, and the dosage adjusted until the serum calcium target is attained. Because the renal threshold for calcium excretion is lowered by the absence of PTH, our practice is to maintain serum calcium at the lower end of the normal range in order to minimize hypercalciuria and the risk

of urolithiasis. A low-salt diet, and occasionally a thiazide diuretic, such as **chlorothiazide or hydrochlorothiazide, can be added to the regimen to reduce urinary calcium losses**.

B. Hypercalcemia (Table 35-4)

The clinical features of hypercalcemia depend on the underlying disorder, the age of the child, and the degree of hypercalcemia. Infants with mild increases in serum calcium (11 to 13 mg/dL or 2.75 to 3.25 mmol/L) often fail to manifest specific symptoms of hypercalcemia. Nonspecific signs and symptoms, such as anorexia, vomiting, abdominal pain, and constipation (rarely diarrhea), may occur with moderate-to-severe hypercalcemia. Neurologic symptoms can range from drowsiness p. 461p. 462or irritability to confusion; in extreme cases, stupor and coma can ensue. Chronic hypercalcemia may cause only failure to thrive. Unrecognized hypercalcemia in newborns or infants can cause significant morbidity or death. Polyuria as a result of renal resistance to vasopressin can lead rapidly to severe dehydration in infants. Elevated serum concentrations of calcium can cause hypertension and affect cardiac conduction, with shortening of the ST segment and heart block. Severe hypercalcemia can affect the nervous system and cause lethargy and seizures. Renal complications, such as nephrocalcinosis, nephrolithiasis, or hematuria, may be the earliest clinical manifestation of hypercalcemia and hypercalciuria.

The **laboratory evaluation of hypercalcemia** must also include determination of the serum levels of PTH, alkaline phosphatase, and phosphorus. **Hypophosphatemia can cause hypercalcemia**, particularly in the case of the premature or very-low-birth-weight infant who receives inadequate dietary phosphorus. Hypophosphatemia suppresses secretion of FGF23, thereby stimulating renal synthesis of calcitriol with consequent activation of intestinal absorption of calcium (and phosphate) and osteoclastic bone resorption, increasing transport of calcium (and phosphorus) into the circulation. Other causes of iatrogenic hypercalcemia include the use of extracorporeal membrane oxygenation, which can cause transient hypercalcemia in up to 30% of infants, and vitamin D intoxication, either from administration of excessive vitamin D supplements or use of concentrated infant formulas that contain very high concentrations of vitamin D.

1. Familial hypocalciuria hypercalcemia (FHH). FHH, also

termed familial benign hypercalcemia, is genetically related to **neonatal severe primary hyperparathyroidism (NSPHT)**.

a. Etiology. Although adults and older children with FHH have moderate and asymptomatic hypercalcemia, infants with FHH may manifest NSPHT, a severe, life-threatening condition characterized by **marked hypercalcemia** during the first few days of life. NSPHT is associated with elevated PTH levels, normal-to-low serum phosphate, normal-to-high serum magnesium, elevated alkaline phosphatase, and inappropriately normal or low urinary calcium excretion. In addition, affected newborns may have osteopenia. In most cases, FHH and NSPHT are caused by mutations in the *CaSR* gene at 3q13.3–21 that inactivate the CaSR expressed on the surface of the parathyroid cell. In many families, NSPHT and FHH are the respective homozygous and heterozygous manifestations of the same genetic defect. NSPHT can also occur in some heterozygous infants born to affected fathers but unaffected normocalcemic mothers, or in infants with heterozygous *CaSR* mutations enoding CaSR proteins that can inhibit the activity of CaSRs produced by the normal *CaSR* allele (i.e., dominant suppressor mutations). FHH and, rarely, NSPHT can also occur in neonates with an apparent de novo heterozygous mutation in the *CaSR* gene. Decreased receptor activity in the kidney is thought to account for relative hypocalciuria, the hallmark of the disorder. Children who survive NSPHT but who remain hypercalcemic can have poor feeding with failure to thrive, hypotonia, and developmental delay, and they may be at risk of subsequent neurodevelopmental deficits.

FHH is genetically heterogeneous, and recent studies have now identified the molecular basis for three variants: type 1, type 2, and type 3 due to heterozygous loss of function mutations in the *CaSR*, *GNA11*, and *AP2S1* genes, respectively. In all cases, calcium-mediated signaling through the CaSR is attenuated, leading to increased secretion of PTH by parathyroid cells and decreased excretion of calcium by the distal renal tubule cells.

The diagnosis of NSPHT or FHH is based on the presence of inappropriately normal or elevated PTH levels along with relative hypocalciuria in an infant with hypercalcemia. Care

must be taken to distinguish these disorders from the transient neonatal hyperparathyroidism associated with maternal hypocalcemia, as seen in mothers with PHP or renal tubular acidosis. Genetic testing of the *CaSR*, *GNA11*, and *AP2S1* genes is diagnostic for FHH and NSPHT, and is available in many commercial reference laboratories.

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b. Clinical findings. By comparison with equivalently hypercalcemic individuals with primary hyperparathyroidism (PHPT), subjects with FHH have higher creatinine clearances and serum magnesium levels and lower values for PTH and nephrogenous cAMP excretion. A characteristic of FHH is the lower-than-expected (for the degree of hypercalcemia) urinary calcium excretion. The fractional excretion of calcium (FeCa) rather than the calcium to creatine ratio is the preferred method to analyze renal clearance of calcium, and it can be calculated using a spot urine sample or a 24-hour collection. The FeCa is <1% in patients with FHH or NSPHT, and it is increased in most patients with other causes of hypercalcemia. NSPHT is a life-threatening form of hyperparathyroidism with severe hypercalcemia, skeletal demineralization, low fractional excretion of urinary calcium, and markedly elevated serum levels of PTH. NSPHT manifests within the first few days of life and is also associated with hypotonia, respiratory failure, intestinal dysmotility, and failure to thrive; without appropriate treatment, NSPHT has a mortality rate that is greater than 50%. **Hypercalcemia usually responds to intravenous bisphosphonates and saline diuresis**, and in some cases, PTH levels may be decreased by type 2 calcimimetics. Many symptomatic infants will require subtotal parathyroidectomy, however. By contrast, because of the benign nature of FHH, treatment is not usually needed.

2. **Williams syndrome.** Williams syndrome (OMIM 194050) is characterized by facial anomalies, cardiovascular and renal defects, hyperacusis, and visuospatial cognitive impairment, and it is often accompanied by hypercalciuria and transient infantile hypercalcemia. The cognitive impairment does not appear to be a consequence of high serum calcium levels in infancy. The facies

are characteristic, and the cardiovascular anomalies, for example, supravalvular aortic stenosis and peripheral pulmonary stenosis, also form an easily recognizable combination. The hypercalcemia may be severe and is exacerbated by dietary vitamin D supplementation.

a. **Etiology.** Williams syndrome is classically associated with heterozygous microdeletions in the chromosomal region 7q11.2, which contains some 16 genes, including the elastin gene. The loss of the elastin gene may account for some of the vascular and cardiac defects, but the molecular cause of the hypercalcemia remains mysterious. Serum concentrations of calcitriol have been found to be elevated in many, but not all, subjects with Williams syndrome and hypercalcemia. A disturbance in vitamin D metabolism has been proposed as the basis of the hypercalcemia and has been tentatively attributed to loss of the Williams syndrome transcription factor gene within the common Williams syndrome microdeletion. A similar sensitivity to vitamin D occurs in some children who lack the typical clinical and molecular features of Williams syndrome; this has been termed “idiopathic infantile hypercalcemia” (IIH; see below).

3. **Idiopathic infantile hypercalcemia.** It (OMIM 143880) is an uncommon disorder of vitamin D metabolism that is characterized by **hypersensitivity to vitamin D**. It is associated with **severe hypercalcemia** and hypercalciuria, suppressed serum levels of PTH, and elevated levels of vitamin D metabolites, particularly the active form of vitamin D, $1,25(OH)_2D$. Biallelic loss-of-function mutations of *CYP24A1*, the gene encoding a P450 24-hydroxylase enzyme that represents the principal pathway for inactivation of vitamin D metabolites, cause the most common and severe form of IIH. Although IIH is usually diagnosed in infants who present with severe hypercalcemia, failure to thrive, and nephrocalcinosis, inactivating mutations of *CYP24A1* have also been reported in adults with nephrocalcinosis and/or recurrent nephrolithiasis associated with hypercalciuria. Patients with *CYP24A1* mutations have a lifelong defect in vitamin D metabolism that increases risk for nephrocalcinosis, nephrolithiasis, and renal insufficiency. In some infants, symptomatic hypercalcemia is associated with renal

phosphate wasting, a variant of IHH. These infants have elevated serum levels of calcitriol but normal serum levels of 25(OH)D and 24,25$(OH)_2$D and in most cases, they carry loss of function mutations in the *SLC34A1* gene encoding the sodium-phosphate cotransporter 2A.

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IIH must be distinguished from hypercalcemia that occurs in infants with **subcutaneous fat necrosis**, an uncommon disorder characterized by firm, mobile, erythematous nodules and plaques that appear in the first several weeks of life over the trunk, arms, buttocks, thighs, and cheeks. Although subcutaneous fat necrosis usually appears during the first 6 weeks of life, the onset may be delayed up to months after birth. In the majority of cases, the lesions are self-limited and resolve spontaneously within 2 to 4 weeks without atrophy or scarring. Hypercalcemia is a rare complication of subcutaneous fat necrosis, but there is a high mortality rate up to 15%. The pathogenesis of hypercalcemia is unknown, but likely involves unregulated production of calcitriol from the macrophages in the site of the granulomatous inflammatory process.

4. **Hyperparathyroidism**
   a. **Pathophysiology.** PHPT is characterized by hypercalcemia and elevated serum levels of PTH. Hypercalciuria is common, and can be a useful parameter that distinguishes patients with PHPT from patients with FHH. In some cases, these classical biochemical features may not be consistently present, and an elevated serum calcium level may be intermittent, and the PTH may be inappropriately normal or nonsuppressed. PHPT is far less common in the pediatric population than in adults, although childhood neck irradiation is a significant risk factor for the later development of parathyroid adenoma as an adult. Affected children are hypercalcemic because of increased bone resorption and increased calcium absorption, the latter being a consequence of enhanced PTH-mediated calcitriol synthesis. Serum phosphorus is low because PTH decreases the renal tubular reabsorption of phosphate. Hence, serum levels of both PTH and calcitriol are elevated. Low bone density and

hypercalciuria, with nephrocalcinosis or nephrolithiasis, are more common in children and adolescents than in adults with PHPT. Similar to adults, most pediatric patients with PHPT have a solitary parathyroid adenoma. Mutations in a variety of genes have been associated with PHPT, and can cause either isolated PHPT or more complex syndromes (e.g., MEN 1 or MEN 2) in which additional endocrine and nonendocrine tissues are involved. Thus, the etiology of PHPT includes (a) multigland hyperplasia resulting from germline mutations in the *MENIN*, *RET*, *GCMB,* and *CDKN1B* (encoding p27Kip1) genes; (b) single parathyroid adenomas that represent monoclonal neoplasms, many of which are associated with somatic mutation in *MENIN* or *PRAD1*; and (c) distinct parathyroid adenomas caused by germline or somatic mutations in *HPRT2* (CDC 73) and which have a predisposition to parathyroid carcinoma.

In **secondary hyperparathyroidism**, overactivity of the parathyroids is an appropriate adaptive response to hypocalcemia. Secondary hyperparathyroidism occurs in the setting of vitamin D deficiency rickets and in uremia and is discussed in Chapter 31.

Tertiary hyperparathyroidism is the term used to describe the development of hypercalcemia in patients with long-standing secondary hyperparathyroidism. Chronic stimulation of the parathyroid glands by hypocalcemia, as in chronic renal insufficiency or vitamin D deficiency, apparently induces the development of parathyroid tumors that have decreased sensitivity of calcium and which secrete excessive amounts of PTH. Serum levels of calcium and PTH are both elevated, and clinical and biochemical features resemble those of PHPT. Tertiary hyperparathyroidism is very rare in childhood.

5. **Immobilization**
   a. **Pathophysiology.** Prolonged immobilization or even the weightlessness of space travel can lead to rapid loss of skeletal mineral and an increased risk of fracture. Children and young adults are particularly susceptible to extensive bone loss when immobilized, resulting in hypercalciuria and often hypercalcemia. However, most of the time, hypercalcemia

follows high spinal cord injuries that result in traumatic quadriplegia. The hypercalcemia appears to be almost entirely attributable to increased bone resorption. Parathyroid function and the production of calcitriol are suppressed.

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6. **Vitamin D–dependent hypercalcemia** (see Chapter 31).
7. **Malignancy** (see Chapter 31).
8. **Neonatal transient hyperparathyroidism** may occur in infants born to mothers with poorly treated hypoparathyroidism or PHP. The birth weights of these infants are frequently <2 500 g, but otherwise they usually appear clinically normal at birth. The pathogenetic mechanism probably involves fetal hyperparathyroidism secondary to decreased calcium transport from the hypocalcemic mother to the fetus, leading to fetal hypocalcemia. The secondary increased secretion of fetal PTH mobilizes calcium from the fetal skeleton, causing generalized skeletal demineralization and subperiosteal resorption. The hyperfunction of the parathyroid glands may persist after birth, resulting in moderate transient hypercalcemia, although most neonates have been normocalcemic and have had somewhat elevated rather than depressed plasma phosphate concentrations. Following birth, the skeleton avidly takes up calcium, and the bone lesions heal spontaneously within 4 to 6 months. Similarly, mild and transient hypercalcemia with elevated levels of PTH can be seen in some infants with antenatal **Bartter syndrome** caused by mutation of *SLC12A1*. Hypercalcemia usually resolves during early childhood, but hypercalciuria persists.
9. **Other causes of PTH-independent hypercalcemia.** A variety of unusual conditions can also cause hypercalcemia in a non–PTH-dependent manner. In these disorders, serum levels of PTH are either low (less than 25 pg/mL) or suppressed. **Blue diaper syndrome** is caused by a defect in tryptophan metabolism that leads to urinary excretion of excessive amounts of indole derivatives, including a derivative called “indican” that gives the urine-soaked diaper a blue tint. The mechanism of hypercalcemia in this disorder is unknown. **Congenital lactase and disaccharidase deficiency** can cause hypercalcemia and hypercalciuria during the first few months of life. The etiology of

the hypercalcemia is unclear but is thought to be related to metabolic acidosis and/or an increase in intestinal calcium absorption secondary to increased gut lactose. Similarly, excessive intake of dietary calcium or calcium supplements, often by drinking too much milk and taking certain antacids, especially calcium carbonate or sodium bicarbonate (baking soda), can cause **milk-alkali syndrome**.

Hypercalcemia can also occur in children with the **IMAGe** syndrome, which consists of **I**ntrauterine growth retardation, **M**etaphyseal dysplasia, **A**drenal hypoplasia congenital, and **Ge**nital defects.

Hypercalcemia and hypercalciuria are frequent findings in the **infantile form of hypophosphatasia** and reflect the imbalance between intestinal calcium absorption and skeletal deposition. The plasma concentrations of vitamin D metabolites are appropriate for the high plasma calcium with normal $25(OH)D_3$, low calcitriol, and relatively high plasma $24,25(OH)_2D$ concentration. Serum PTH levels are low or suppressed in hypercalcemic patients. Infantile hypophosphatasia presents before 6 months of age when failure to thrive and hypotonia become apparent. The characteristic radiologic findings are severe demineralization of the skeleton but less pronounced than in the perinatal form. The fontanels appear widely open because of hypomineralized areas of calvarium, but in fact, functional craniosynostosis can occur with raised intracranial pressure. The patients develop hypercalcemia, hypercalciuria, and some nephrocalcinosis with renal failure. Rachitic skeletal deformities, including flail chest, predispose to pneumonia, and >50% of patients die during the first year of life. Those children who survive beyond infancy seem to show some improvement.

Chronic hypervitaminosis A appears after ingestion of excessive doses for several weeks or months. The child develops anorexia, pruritus, irritability, bone pain, and tender swellings of bone. Roentgenograms might show osteopenia, signs of increased osteoclastic bone resorption, hyperostosis of the shafts of the long bones, and osteophyte formation, particularly in the thoracic spine. Spontaneous recovery with alleviation of hypercalcemia follows discontinuation of vitamin A intake. Neonates and children who have impaired renal function appear to be at particular risk of

vitamin A–induced hypercalcemia.

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Children with **Jansen metaphyseal chondrodysplasia** have hypercalcemia and bone lesions that are typical of PHPT but have suppressed PTH levels. This unusual disorder is a result of mutations in the *PTH1R* gene that lead to ligand-independent activation of the receptor. This causes increased bone resorption, metaphyseal defects, elevated serum levels of $1,25(OH)_2D$, and growth delay. Hypercalcemia may also occur in patients who have severe hyperthyroidism, acute adrenal insufficiency, or renal tubular acidosis as well as children who are on the ketogenic diet.

10. **Management of hypercalcemia.** The first principle to the medical treatment of severe or symptomatic hypercalcemia is to **increase the urinary excretion of calcium; secondary principles include limiting intestinal absorption of calcium and reducing release of calcium from the skeleton**. Because renal clearance of sodium and calcium is tightly linked, increasing delivery of **salt and water to effect a saline diuresis is the first step to treating hypercalcemia**. Infants are frequently dehydrated, and two thirds to full-strength saline containing 30 mEq of potassium chloride/L should be infused to correct dehydration and maximize glomerular filtration rate. Loop diuretics are generally not required and are usually not more effective than optimal infusion of saline alone. When a patient is unable to tolerate large volumes of intravenous saline, a loop diuretic such as furosemide (1 mg/kg intravenously at 6- to 8-hour intervals) may be useful.

    In most cases, hypercalcemia is a result of excessive release of calcium (and phosphorus) from the skeleton, and treatment will require an agent that can directly reduce osteoclastic bone resorption. **Calcitonin** (1 to 4 U/kg every 6 to 12 hours) given by subcutaneous injection can reduce the serum concentration of calcium modestly (i.e., 1 to 2 mg/dL) but usually does not completely correct hypercalcemia. Direct inhibition of bone resorption can be achieved with intravenous bisphosphonates, such as pamidronate (1 to 2 mg/kg) or zoledronate (0.025 to 0.05 mg/kg) (see Chapter 31).

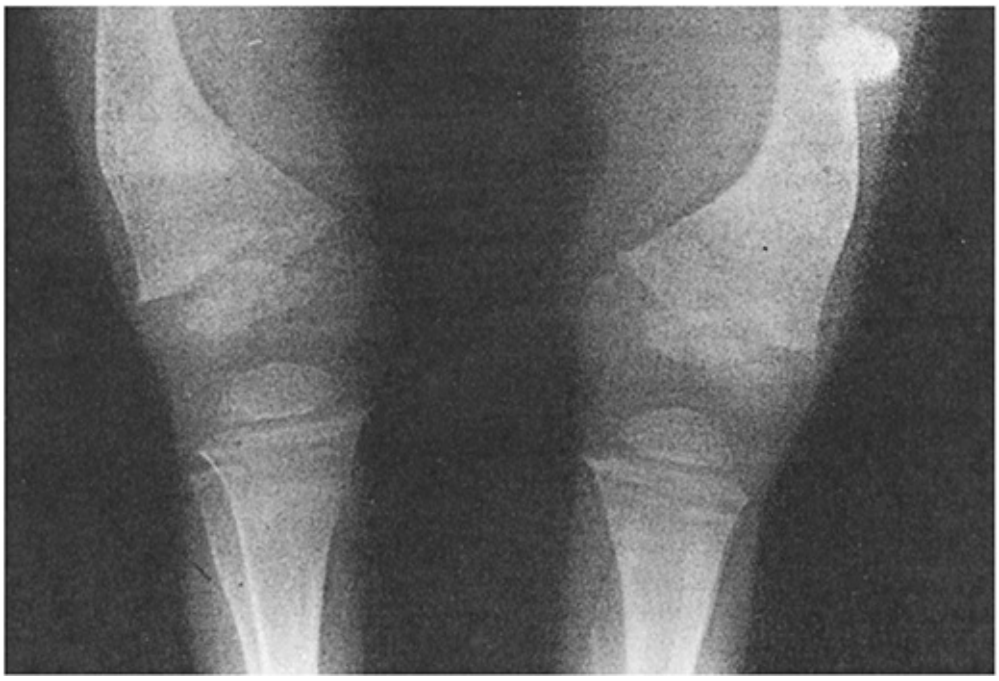

Figure 35-3. Long-standing rickets in a 5-year-old child. Note flared lower femoral and upper tibial epiphyses as well as marked angulation of lower femoral as a result of osteomalacia.

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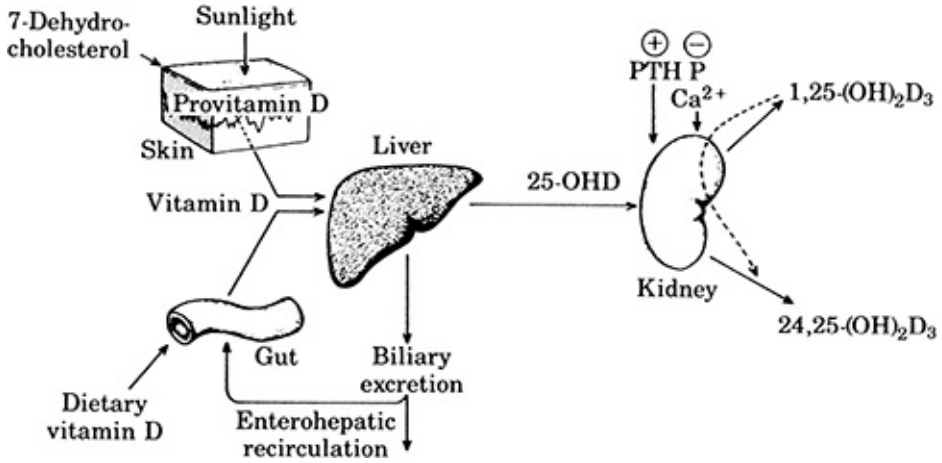

Figure 35-4. Sources and metabolic fate of vitamin D in humans. Factors promoting or antagonizing renal 1*α*-hydroxylation of calcidiol are indicated by + and −, respectively. 24-Hydroxylation is stimulated by calcitriol as shown by *dotted line*. (From Gertner JM. Disorders of bone and mineral metabolism. In: Clayton BE, Round JM, eds. *Chemical Pathology and the Sick Child.* Oxford: Blackwell Scientific; 1984.)

Some unique forms of hypercalcemia deserve specific comments. Patients with Williams syndrome, IIH, vitamin D intoxication,

granulomatous disorders, and subcutaneous fat necrosis often respond to a low-calcium (<400 mg calcium/day) and low–vitamin D diet. Severe hypercalcemia can be treated effectively by administration of bisphosphonates; some patients will respond to corticosteroids (hydrocortisone, 10 mg/kg/day), but it is the author's opinion that the risks of glucocorticoid therapy generally outweigh their benefits. The hypercalcemia of Williams syndrome usually remits between 9 and 18 months of age, but hypercalciuria may persist, with an increased risk of renal calcification. Because the hypercalcemia is self-limiting, the need for continued therapy should be reassessed regularly.

Treatment of hypercalcemia due to immobilization and most malignancies is based on reducing excessive osteoclast-dependent bone resorption. Hydration with saline (up to 4 L/day in a fully grown adolescent, proportionately less for younger children) can increase renal calcium excretion. Agents that inhibit bone resorption, such as calcitonin or bisphosphonates, may be needed when hypercalcemia or hypercalciuria is intractable or when bone loss is associated with an increased risk of fracture.

IV. METABOLIC BONE DISEASE

Metabolic bone diseases constitute a variety of acquired or genetic disorders that affect production, mineralization, or structure of bone tissue. Common metabolic bone diseases include rickets and osteomalacia, osteoporosis, osteogenesis imperfecta, osteopetrosis, fibrous dysplasia, and Paget disease of bone.

A. Rickets

1. **General principles.** The term rickets describes a childhood condition of defective skeletal mineralization and abnormal development of the growth plate (Fig. 35-3) (see Chapter 4). It is important to appreciate that rickets is a clinical and radiologic diagnosis, with biochemical and genetic testing used to identify or confirm the underlying cause. Rickets concerns the disruption of the growth plate architecture, whereas the term osteomalacia refers to impaired mineralization of the bone matrix. **Rickets and osteomalacia occur together** in children, whereas in adults, the equivalent defects in mineral metabolism result only in osteomalacia. Growth plate cartilage is mineralized, and later

vascular invasion p. 467p. 468p. 468p. 469converts this tissue into primary bone spongiosa. In the bone tissue below the growth plate (metaphysis), the mineralization defect leads to the accumulation of osteoid. These abnormalities reduce bone strength and lead to compensatory widening of the growth plate and the associated metaphysis.

TABLE 35-5 Biochemical Features of Rickets

Type of rickets		Serum						Urine
		P	Ca	HCO_3	25-(OH)D	$1,25(OH)_2D$	PTH	Cal
Nutritional	Vitamin D deficiency	L to H	L	N	L	L to H	H	L
	Ca deficiency	L	L	N	N	H	H	L
	Prematurity[a]	L	N	N	N	H	N	H
Hypophosphatemic	X-linked (*PHEX*)	L	N	N	N	N	N to H	N to H[b]
	Autosomal dominant (*FGF23*)/autosomal recessive (*DMP1 or ENPP1*)	L	N	N	N	N	N	N
	Hereditary hypophosphatemic rickets with hypercalciuria (*SLC34A3*)	L	N	N	N	H	L	H
	Fanconi syndrome	L	N	L	N	N to L	N to H	N to H
Vitamin D–dependent rickets	Type 1a (1α-hydroxylase deficiency; *CYP27B*)	L to N	L	N	N	L	H	L
	Type 1b (25-hydroxylase deficiency; *CYP2R1*)	L to N	L	N	L	L to N	H	L
	Type 2 (calcitriol resistance, *VDR*)	L to N	L	N	N	H	H	L
Uremic	Osteodystrophy	H	L to H	L	N	L	H	L to H

Alkaline phosphatase and other markers of bone turnover are increased in all forms.
H, high; L, low; N, normal; PTH, parathyroid hormone.
[a]Most commonly caused by relative phosphorus deprivation.
[b]Elevated PTH and urine Ca seen as consequences of treatment.

Deformity because of uneven bone growth and softening of the long bones is common in severe rickets cases. The nature of the deformity is age dependent. The typical lower limb deformity is genu varum ("bow legs") when the age of onset is less than 3 or 4 years and genu valgum ("knock knees") when rickets starts in school-aged children.

Although vitamin D deficiency is the most common cause of rickets and osteomalacia, these conditions can also result from nutritional deficiency of calcium or genetic defects. Regardless of the etiology, a common feature of rickets and osteomalacia is a low-normal or low serum phosphorus level, which directly impacts maturation of chondrocytes. Without an adequate calcium–phosphorus product, mineralization of newly synthesized osteoid, the collagen-rich bone matrix, is diminished, resulting in the development of rickets in children and osteomalacia in adults.

2. **Nomenclature.** A summary of key biochemical findings of different forms of rickets is presented in Table 35-5.

a. Causes of rickets

i. Vitamin D deficiency rickets. The sources and metabolism of vitamin D are outlined in Figure 35-4. Vitamin D and its metabolites participate in various nonskeletal processes such as regulation of innate and adaptive immunity as part of the "osteoimmune" system. Therefore, vitamin D deficiency can not only impair mineral metabolism but can also have important effects on immune function.

The efficiency of the intestinal absorption and renal reabsorption of calcium and phosphorus is increased by $1,25(OH)_2D$, and vitamin D deficiency leads to hypocalcemia and secondary hyperparathyroidism. Elevated levels of PTH reduce renal tubular reabsorption of phosphate from the glomerular filtrate, thereby leading to hypophosphatemia.

The early manifestations of vitamin D deficiency are slight hypocalcemia with some or only moderate elevation of alkaline phosphatase activity (Table 35-5). The fall in plasma calcium leads to increased PTH secretion, which, in turn, normalizes the plasma calcium level. However, if the rickets proceed to a **moderate stage**, the compensatory secondary hyperparathyroidism leads to increased urinary excretion of cAMP, aminoaciduria, phosphaturia with subsequent fall in plasma phosphate, and rise of alkaline phosphatase. In **severe** vitamin D deficiency, increased PTH secretion and calcium mobilization from bone can no longer compensate for the deficient calcium absorption from the intestine, and the plasma calcium concentration may drop sufficiently to induce symptoms of tetany (Table 35-5).

The plasma concentration of 25(OH)D is the most reliable index of vitamin D status, and is typically very low (i.e., less than 10 ng/mL) in patients with clinical nutritional rickets. Nevertheless, the risk of nutritional rickets will be influenced not only by vitamin D status but also by the calcium intake. Most pediatric societies have proposed that serum levels of 25(OH)D that are greater than 20 ng/mL (50

nM) are sufficient to ensure bone health in children. By contrast, some professional organizations have proposed that serum 25(OH)D levels between 30 and 50 ng/mL may be optimal for overall health. It is worth noting that **measurements of serum 1,25(OH)$_2$D are of no use in assessing vitamin D status, because the plasma concentration of calcitriol can be low, normal, or elevated** in nutritional vitamin D deficiency.

Elevated levels of circulating PTH induce phosphaturia and result in a low-normal or low serum phosphorus level. Without an adequate calcium–phosphorus product, mineralization of the skeleton is diminished, leading to osteomalacia, and mineralization of teeth is impaired, leading p. 469p. 470to delayed tooth eruption, increased caries and periodontal disease, and premature loss of teeth. Children with vitamin D deficiency rickets often manifest bone pain and myopathy, the combination of which can lead to delayed walking in affected infants. Hypocalcemia can lead to tetany and even convulsions.

b. Risk factors

1) Vitamin D deficiency is now recognized to be common throughout the world, particularly in countries where milk is not fortified with vitamin D. Vitamin D can be obtained from the diet or synthesized in the skin after exposure to ultraviolet B (UVB) irradiation. Use of sunscreens that block UVB radiation, dark skin pigment, and a conservative style of dress that covers most of the skin can also decrease cutaneous synthesis of vitamin D. Additional risks of vitamin D deficiency are present in infants who are born prematurely or to mothers who themselves are vitamin D insufficient. Infants who are exclusively breast fed for more than 6 months and do not receive recommended supplementation with vitamin D are at particular risk, because under usual circumstances, **human milk is an inadequate source of vitamin D**.

Moreover, infants who are fed an artificial baby formula are unlikely to receive the recommended daily intake of vitamin D (400 IU) until they are consuming 1 L of formula per day.

2) Vitamin D deficiency rickets is common in children (and adults) who have **gastrointestinal disorders** that affect absorption of fats. These conditions include biliary atresia, cystic fibrosis, inflammatory bowel disease, and celiac disease. The vitamin D deficiency probably results from complex causes involving reduced exposure to sunlight, reduced dietary intake of vitamin D, and malabsorption in patients with steatorrhea. In most types of chronic liver disease, mean plasma levels of 25(OH)D are usually low normal, and in patients with rickets and osteomalacia, they are usually subnormal. Vitamin D–binding protein is needed for 25(OH)D to enter proximal renal tubule cells, where it is converted to calcitriol. Therefore, low levels of vitamin D–binding protein can affect vitamin D metabolism. Similarly, loss of vitamin D–binding protein in children with nephrotic syndrome or protein-losing enteropathy can have similar adverse effects. True vitamin D deficiency should be associated with elevated plasma levels of PTH.

3) Vitamin D deficiency rickets is seen in children on long-term anticonvulsant therapy with specific agents that induce CYP450 drug-metabolizing enzymes (e.g., CYP3A4) that are present in the liver and other sites. These drugs increase the demand for vitamin D by accelerating its elimination. **Phenobarbital, carbamazine, and diphenylhydantoin** have been incriminated in the **pathogenesis of anticonvulsant osteopathy and rickets**. The doses and duration of therapy that can lead to the development of rickets have not been defined clearly. However, it is evident that only modest supplementation with vitamin D can prevent anticonvulsant rickets and that this condition affects

epileptic children who are already receiving inadequate vitamin D from the diet and inadequate exposure to sunlight. A variety of other drugs that can similarly induce CYP3A4, such as **rifampin**, have also been implicated in this pathophysiology.

a) Medical management

Rickets can be prevented by exposure to UVB radiation (290 to 315 nM) and/or by oral supplementation of vitamin D. However, because sunlight is not an adequate source of UVB radiation during winter in the temperate zones to ensure sufficient cutaneous generation of vitamin D, it is necessary to provide vitamin D supplements (600 IU/day for children older than 1 year of age) during these months. **Breast-fed babies and babies who consume less than 1 L of infant formula will also require daily supplements p. 470p. 471of vitamin D**, 400 IU/day, commencing within the first few days of life. **Nursing mothers who consume 5 000 to 6 400 IU of vitamin D_3 per day can fortify their breast milk** to provide the equivalent of 400 IU/day of vitamin D to their nursing babies. Vitamin D_3 (cholecalciferol) is preferred over vitamin D_2 (ergocalciferol) because $25(OH)D_3$ has greater affinity for vitamin D–binding protein than $25(OH)D_2$, and thereby has a longer serum half-life and greater biologic activity.

1) **Vitamin D treatment.** Vitamin D deficiency rickets can be safely and effectively healed by daily doses of 50 to 100 μg or **2 000 to 4 000 IU of vitamin D_3 for 12 weeks**; it is the **practice of this author to initiate treatment with a single dose of 50 000 IU vitamin D_3 in the clinic**. Supplemental calcium (25 to 50 mg/kg/day of elemental calcium, not to exceed 1 to 2 g/day) is also recommended. Early radiologic signs of healing will

usually be evident within 4 weeks, but complete biochemical, radiologic, and clinical **resolution of rickets will take 8 to 12 weeks**, at which point the daily vitamin D dose may then be reduced to the recommended daily allowance (RDA), 600 IU daily. In some cases, it may be more practical to administer a large dose of vitamin D (100 000 to 600 000 IU; 2 500 to 15 000 μg) over a short period of time, an approach known as **stoss therapy** (from the German "to push"). This involves a single oral or intramuscular dose of vitamin D based on the age and vitamin D level of the patient because of poor compliance. If healing is incomplete or does not occur at all after repletion of vitamin D stores, it is likely that the basis of rickets is more complex and/or is due to another cause (see below). **Anticonvulsant-induced rickets** can be prevented by the daily administration of larger daily doses of vitamin D (e.g., 1 000 to 2 000 IU) than the RDA. In cases of hepatobiliary or intestinal disease where fat malabsorption is significant, the optimum oral replacement dose of vitamin D may be as high as 500 000 IU of vitamin D_3/day. These patients may benefit from transdermal delivery of vitamin D_3 using vitamin D_3 patches.

The earliest biochemical sign that treatment is effective will be an increase in the serum phosphate concentration as serum levels of PTH decline. Vitamin D treatment is also associated with rapid increases in the plasma level of calcitriol due to secondary hyperparathyroidism, which can sometimes cause transient hypercalcemia.

b) Orthopedic treatment. Surgery may be needed in severe cases.

c. Calcium deficiency rickets. In recent years, it has become clear that in some children, **nutritional rickets** may be due wholly or in part to calcium deficiency. Risk factors include restricted diets (e.g., vegan) that contain little or no dairy

products or reduced amounts of bioavailable calcium. Plasma concentrations of 25(OH)D are typically normal, but patients develop secondary hyperparathyroidism (and elevated levels of calcitriol) because of the lack of dietary calcium. Urinary excretion of calcium is very low. The reasons why some children on low calcium intake develop rickets whereas others, on the same low intake, do not, remain unclear.

i. **Treatment.** In a 24-week controlled trial carried out in Nigeria, calcium supplementation (1 000 mg of elemental calcium per day) with or without vitamin D was more effective in the management of childhood rickets than vitamin D alone.

d. Rickets (osteopathy) of prematurity

i. **Etiology.** Premature and low birth weight babies can develop rickets. In most cases, this is due to phosphorus deficiency, and levels of 25(OH)D and PTH are normal although levels of alkaline phosphatase are characteristically elevated (>800 units). In some cases, hypophosphatemia will develop in otherwise well premature babies who are fed standard infant formula or breast milk, as not only the phosphorus but also the calcium content of human milk is inadequate for the needs of the rapidly growing low birth weight baby Recently, an p. 471p. 472association between use of amino acid-based elemental formulas (e.g., Neocate) and idiopathic hypophosphatemia has been identified. Hypophosphatemic rickets occurs due to deficient dietary supply or severe malabsorption of phosphate, despite apparently adequate formula composition.

ii. **Therapy.** Appropriate therapy lies in supplementing the affected infant’s diet with **additional phosphorus**. It has been suggested that early supplementation of the feed of very-low-birth-weight infants can **prevent** rickets. Vitamin D supplements are not sufficient to prevent the rickets of prematurity and, indeed, the serum concentration of calcitriol is elevated, as might be expected under conditions

of dietary phosphorus deprivation. Many infants will also require additional calcium, particularly if phosphate supplementation leads to secondary hyperparathyroidism. With appropriate mineral supplementation, no more than the RDA for vitamin D (400 IU/day) need be given to these infants.

e. Vitamin D–dependent rickets 1a

i. Etiology and genetics. Vitamin D–dependent rickets type 1a is similar to vitamin D deficiency rickets, but rickets develops despite a history of adequate vitamin D intake. The defect in these children is an **inability to convert 25(OH)D to 1,25(OH)$_2$D** (calcitriol). Therefore, serum levels of 25(OH)D are normal, but levels of 1,25(OH)$_2$D are low or absent despite markedly elevated levels of PTH. As with nutritional vitamin D deficiency, serum calcium may be normal or reduced, serum phosphate levels are reduced, and alkaline phosphatase is elevated. A wide variety of mutations in the *CYP27B1* gene at 12q13.3 has been described in subjects with VDDR1a. Although VDDR1A is an uncommon cause of autosomal recessive rickets, the disorder occurs with unusual frequency in the French Canadian population.

ii. Treatment. The drugs of choice in treatment are **calcitriol** or alfacalcidol (1α-hydroxyvitamin D), both of which are 1-hydroxylated and thereby circumvent the enzymatic defect in vitamin D activation. The recommended doses for treatment of active rickets are 2 to 8 μg/day of alfacalcidol or 1 to 4 μg/day of calcitriol, plus elemental calcium. Lifelong replacement therapy will require more physiologic doses, 1 to 3 μg/day of alfacalcidol or 0.5 to 2 μg/day of calcitriol.

f. Vitamin D–dependent rickets 1b

i. Etiology and genetics. Vitamin D–dependent rickets 1b (VDDR1B; OMIM 600081) is a very **uncommon** form of rickets that is due to an inability to convert parent vitamin D to 25(OH)D. Mutations in the human *CYP2R1* gene at 11p15.2 are the basis for VDDR1B, and the clinical and biochemical severity is related to the number of defective

CYP2R1 alleles a patient carriers. Patients do not respond to the conventional doses of vitamin D that are efficacious in patients with simple vitamin D deficiency.

Genetic variation in CYP2R1 also has an important role in determining vitamin D requirements, and 25(OH)D concentrations, in normal subjects.

ii. **Treatment.** The most logical choice of vitamin D analog is **calcifediol**, also known as **calcidiol**, which is 25-hydroxycholecalciferol [or 25(OH)D]. One can adjust doses of calcifediol to achieve normal serum levels of 25(OH)D, which will assure an adequate source of substrate for PTH-regulated conversion in the kidneys into calcitriol [$1,25(OH)_2D_3$], thereby restoring mineral metabolism to normal homeostasis.

g. Vitamin D–dependent rickets 2

i. **Etiology.** Vitamin D–dependent rickets 2 (VDDR2; OMIM) is a rare usually autosomal recessive form of rickets that is characterized by target-organ **resistance to calcitriol** VDDR2A (OMIM 277440) caused by a defect in the *VDR* gene. Most patients have total **alopecia** in addition to rickets. VDDR2B (OMIM 600785) has a phenotype that is similar to VDDR2A but a normal VDR, and end-organ resistance to calcitriol is caused by a nuclear ribonucleoprotein that interferes with the VDR–DNA interaction. The hallmarks of VDDR2 include **onset of rickets within the first 1 to 2 years of life**, hypocalcemia and hypophosphatemia with marked p. 472p. 473secondary hyperparathyroidism, and **very high plasma concentrations of calcitriol**. Patients with VDDR2 appear normal at birth and develop features of calciferol deficiency over the first 2 to 8 months of life. Alopecia, generally developing at 2 to 12 months of age, may be total or incomplete. Other ectodermal defects have been reported in small numbers of cases.

ii. **Treatment.** Most patients with VDDR2 are responsive to very high doses of calcitriol, or alfacalcidol, with or without

calcium supplementation. Such treatment can often heal the rickets and normalize calcium homeostasis, but **alopecia never improves**. Cases with mild-to-moderate resistance may respond to very high doses of vitamin D, which should then be of the order of 0.5 to 5 mg/day, that is, 200 000 to 2 million IU/day. A supplementation dose of about 2 g of elemental calcium per day is an important adjunct to avoid fluctuations of the plasma concentration of calcium caused by variable dietary calcium content.

In the most severely affected patients, there is complete refractoriness to calcitriol action, and the only effective therapy is high doses of oral calcium or daily intravenous infusions of calcium.

h. Hypophosphatemic rickets

i. Etiology. Hypophosphatemia is a general characteristic of rickets. In cases of rickets due to deficiency or impaired action of vitamin D or calcium deficiency, hypophosphatemia occurs because **secondary hyperparathyroidism decreases renal tubular reabsorption of phosphate**. Hypophosphatemic rickets also occurs in the absence of secondary hyperparathyroidism in patients with genetic forms of hypophosphatemic rickets, tumor-induced osteomalacia, nutritional phosphorus deficiency, and primary renal tubular disorders (Table 35-5). It is believed that in such cases, the extracellular phosphate concentration is lower than that needed for optimal skeletal mineralization and for proper maturation of the growth plate.

By far the most common cause of hypophosphatemic rickets, particularly in children, is **X-linked hypophosphatemic rickets** (XLH; formerly termed hypophosphatemic vitamin D–resistant rickets, MIM 307800), which occurs with a prevalence of about 1 in 20 000. Serum levels of phosphate are reduced, and serum calcitriol levels are reduced or inappropriately normal, whereas serum calcium and PTH levels are normal. In children with active rickets, there is also a variable degree of reduced intestinal absorption of both phosphate and calcium. XLH is a dominant condition. In its fullest

expression, XLH is associated with rickets (osteomalacia in adults), lower extremity deformities, short stature, bone pain, enthesopathy, and dental abscesses.

XLH is caused by mutations in the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) that lead to a loss of enzymatic function. Commercial laboratories now provide clinical testing for mutations in the *PHEX* gene, and defects can be identified in 80% of patients with suspected XLH. However, the presence of the trait may be readily ascertained in most patients by 6 months of age by documentation of a reduced age-corrected concentration of plasma phosphate.

Patients with XLH, and the *Hyp* mouse homolog, have elevated plasma levels of FGF23, a phosphate-regulating hormone that is the principal circulating "phosphatonin." FGF23 acts directly on the kidney to alter phosphate transport and renal parameters of vitamin D metabolism. FGF23 reduces expression of the renal tubular sodium phosphate cotransporters Npt2a and Npt2c, thus impairing phosphate reabsorption in the proximal renal tubule that leads to hypophosphatemia. In addition, FGF23 suppresses activity of the renal CYP27B1 (1α-hydroxylase) while inducing activity of the renal CYP24A1 (24-hydroxylase), which may in part explain the inappropriately normal (or low) circulating concentrations of $1,25(OH)_2D$ despite hypophosphatemia.

In addition to XLH, at least **four additional forms** of inherited hypophosphatemic rickets have now been identified. **Autosomal dominant** **p. 473p. 474hypophosphatemic rickets** (ADHR; MIM 193100) is caused by mutations in the *FGF23* gene that encode the phosphatonin FGF23 that prevents degradation of the protein. Autosomal recessive hypophosphatemic rickets (ARHR) can occur in patients with mutations in either *DMP1* or *ENPP1*. It is worth noting that biallelic

mutations in *FAM20C* have been identified in patients with elevated serum levels of FGF23 and hypophosphatemia, hyperphosphaturia, dental anomalies, intracerebral calcifications, and osteosclerosis of the long bones in the absence of rickets. Hypophosphatemic rickets also occur in patients with **hereditary hypophosphatemic rickets with hypercalciuria** (HHRH; see later), which is caused by homozygous mutations in the *SLC34A3* gene. In addition to these hereditary conditions, hypophosphatemia and rickets and/or osteomalacia can occur due to excessive production of FGF23 by rare paraneoplastic and other disorders, including tumor-induced osteomalacia, fibrous dysplasia, neurofibromatosis, linear nevus sebaceous syndrome, and osteoglophonic dysplasia.

ii. **Pathogenesis.** Hypophosphatemia appears in the first year of life. The biochemical findings (Table 35-5) are dominated by hypophosphatemia with normocalcemia. The ratio of renal tubular threshold maximum for phosphate to glomerular filtration rate (TmP/GFR) is always subnormal in hypophosphatemic rickets. The normal calcitriol concentration in the face of hypophosphatemia (which generally stimulates calcitriol formation) reflects the elevated circulating concentrations of FGF23 in these disorders.

iii. **Clinical findings.** The primary clinical manifestations of hypophosphatemic rickets are skeletal pain and deformity, bone fractures, slipped epiphyses, and abnormalities of growth. Classic skeletal features of rickets, such as frontal bossing, may appear as early as 6 months of age in untreated infants. Boys with XLH have early severe deformities, namely, shortness of stature and skeletal disproportions, which become apparent during childhood with the legs short relative to the trunk. The deformities include bilateral coxa vara, anterior and lateral femoral bowing, genu valgum or varum, and medial deviation and torsion of the lower third of the tibia. Unlike the findings in infants with vitamin D deficiency rickets, **craniotabes and rachitic rosary are not seen**. In addition to the mineralization defect induced by hypophosphatemia, an

intrinsic osteoblast defect contributes to the bone disease and does not appear to respond to conventional treatment (see below).

Proximal myopathy is absent, in contrast to the findings in hypophosphatemia that occurs in patients with tumor-induced osteomalacia or antacid-induced hypophosphatemia. Thus, the waddling gait seen in boys, and severely affected girls is probably due to coxa vara. Poor dental development and spontaneous tooth abscesses may occur. There is considerable variation in the severity of the disease.

In **middle age**, other clinical problems begin to appear, with mineralization of the spinal ligaments and thickening of the neural arches. There is loss of mobility of the spine, shoulders, elbows, and hips. The lumbar spine is flat and rigid, and reduction in the diameter of spinal canal can lead to cord compression at more than one level. Painful secondary osteoarthritis in the hips and knees is common, as is a unique disorder of the entheses (tendons, ligaments, and joint capsules), with exuberant calcification of tendon and ligament insertions and of joint capsules, particularly in the hand and sacroiliac joints.

Radiologic manifestations are evident by 1 to 2 years of age and include widening, splaying, and cupping of the metaphyses and coarse trabeculation of the whole skeleton. These findings are most pronounced in the lower extremities.

Although the primary renal lesion consists of isolated proximal tubular phosphate wasting, renal glycosuria can also be seen in some older patients. In contrast to XLH and ARHR, there seems to be greater variability in the age of onset and expression of the biochemical and clinical features of ADHR. Those with childhood onset look phenotypically like XLH, but some patients present with an apparent adult-onset form of the p. 474p. 475disorder, with osteomalacia, bone pain, weakness,

and fractures, but no skeletal deformity. Thus, ADHR is a phenotypically variable disorder with incomplete penetrance, delayed onset, and, in several kindreds, postpubertal spontaneous resolution of the biochemical defect.

iv. **Therapy. A combination of activated vitamin D and oral phosphorus** is the most effective therapy. The main role of activated vitamin D (e.g., calcitriol) is to counter the tendency of phosphate therapy to induce hypocalcemia and secondary hyperparathyroidism. **Calcitriol** is the preferred vitamin D metabolite in the **management of hypophosphatemic rickets** because it bypasses the FGF23-mediated inhibition of CYP27B1. Moreover, its short half-life greatly lessens the risk and severity of iatrogenic hypercalcemia or hypercalciuria. Current practice is to use calcitriol (25 to 50 ng/kg/day) together with a neutral phosphate preparation (25 to 50 mg/kg of phosphorus/day). Calcitriol can be given once or twice per day, whereas phosphate supplements should be given in four to five divided doses over the day. The dosage of calcitriol is adjusted to maintain the PTH in the mid-normal range without inducing hypercalciuria or hypercalcemia. The goal of therapy is to heal rickets and not to normalize the serum phosphate level; hence, a normal age-adjusted serum alkaline phosphatase level and height velocity are appropriate indicators of therapeutic efficacy. Medullary nephrocalcinosis is common and usually caused by excessive urinary phosphate excretion, but can be associated with nephrolithiasis when hypercalciuria occurs as well. Tertiary hyperparathyroidism can occur in patients who do not receive sufficient calcitriol to prevent secondary hyperparathyroidism. Patients who have tumor-induced osteomalacia will receive greatest benefit from surgical removal of the tumor that is producing FGF23, but these lesions are often quite small and difficult to locate. The use of biologic antagonists to FGF23 action, including anti-FGF23 monoclonal antibodies, represents a promising alternative to conventional therapy of hypophosphatemic rickets with calcitriol and phosphate. Moreover, recent

studies suggest that this approach may also reduce the risks of renal calcification.

i. **Hereditary hypophosphatemic rickets with hypercalciuria**

   i. **Etiology.** HHRH is an autosomal recessive disorder (OMIM 241530) that can be distinguished from other forms of inherited hypophosphatemic rickets (described previously) by the presence of elevated levels of urinary calcium and plasma calcitriol and suppressed concentrations of plasma FGF23 and PTH. HHRH is caused by mutations in *SLC34A3* that reduce expression or activity of the NaPi-IIc renal sodium phosphate cotransporter. Other renal phosphate-wasting syndromes, such as **Fanconi syndrome and Lowe syndrome**, that affect these transporters directly, can **present with similar biochemical features**. Clinical features resemble those of other forms of hypophosphatemic rickets.

   ii. **Pathogenesis.** As with other forms of renal phosphate wasting, the ratio of TmP and GFR is reduced, and the serum phosphate level is below the age-adjusted reference range. By contrast to other forms of hypophosphatemic rickets discussed above, plasma levels of FGF23 are appropriately suppressed in the presence of low serum phosphate levels in HHRH. As a result, activity of renal 1α-hydroxylase (CYP27B1), the rate-limiting enzyme in the two-step activation process of vitamin D, is disinhibited, with a consequent excessive synthesis of $1,25(OH)_2D$. The elevated serum levels of $1,25(OH)_2D$ stimulate absorption of dietary calcium and activate bone resorption, leading to hypercalciuria and osteopenia. Serum levels of PTH are appropriately suppressed or very low.

   iii. **Treatment.** Patients with HHRH have very high serum levels of calcitriol. Such high levels of calcitriol may lead to a higher-than-usual efficiency of calcium absorption from the gastrointestinal tract and reduced synthesis and secretion of PTH. Together, such physiologic changes in calcium homeostasis favor hypercalciuria and thereby promote kidney stone formation. Treatment with phosphate

salts alone, without calcitriol, leads to p. 475p. 476improvement of clinical and radiologic skeletal abnormalities, decreases serum concentrations of calcitriol, and reduces urinary calcium excretion. Therefore, routine use of activated forms of vitamin D is not necessary and may worsen hypercalciuria and exacerbate renal calcification.

TABLE 35-6 A Classification of Osteoporosis in Childhood

Category	Diagnosis	Comment
Genetic disorders of connective tissue matrix	Osteogenesis imperfecta, Ehlers-Danlos syndrome, osteoporosis-pseudoganglioma syndrome	
Locally mediated bone resorption	Malignancies, including Leukemia, thalassemia, and other causes of myeloid expansion or proliferation	Skeletal pain may be severe May be exacerbated by chelating agents used to manage iron overload
Cytokine-mediated catabolic states affecting connective tissue matrix	Inflammatory bowel disease Inflammatory arthritis	May be worsened by corticosteroid use May be worsened by corticosteroid use
Endocrine and metabolic	Hypercortisolism, iatrogenic or due to pituitary, or adrenal disease Thyrotoxicosis Hypogonadism Anorexia nervosa	Includes failure to convert androgens to estrogens (i.e., aromatase deficiency) and rare estrogen-receptor defects
Disuse and underuse	Congenital and acquired paraplegia Muscular dystrophy	
Unclassified	Idiopathic juvenile osteoporosis	Usually remits at puberty; heritable disorders of collagen identified in some cases

B. Osteoporosis

1. **Definition.** Functionally, osteoporosis is a condition of reduced

bone mass and architectural deterioration that leads to bone fragility and a consequent increase in the risk of fracture. Mineralization of bone tissue is normal (see Chapter 33). The definition of osteoporosis that is used by the World Health Organization (WHO) is based on T scores, which reflect the number of standard deviations (SDs) that the bone mineral density (BMD) for a specific site is above or below the peak BMD achieved by healthy adults of the same race and gender. Accordingly, osteoporosis is defined as a BMD corresponding to a T score of at least −2.5, and defines osteopenia as a BMD that is between −1 and −2.5 SDs below peak BMD. Obviously, definitions that are based on T scores are not appropriate for children, because young subjects typically have low T scores because they have not yet achieved peak BMD. An alternative methodology has been designed for young patients and uses Z scores, which reflect SD scores from the mean in comparison to BMD (or bone mineral content, BMC) of healthy subjects of the same age, gender, and, in some cases, also race. The International Society for Clinical Densitometry has developed official positions on the use and interpretation of bone densitometry in children. First, the **diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometric criteria (i.e., Z scores) alone**; there must be clinical evidence of bone fragility. Second, the finding of one or more vertebral compression (crush) fractures in the absence of p. 476p. 477p. 477p. 478p. 478p. 479p. 479p. 480p. 480p. 481local disease or high-energy trauma is indicative of osteoporosis. In such children and adolescents, measuring BMD adds to the overall assessment of bone health but is not necessary for the diagnosis of osteoporosis. Third, in the absence of vertebral compression fractures, the diagnosis of osteoporosis is indicated by the presence of both a clinically significant **fracture history and low BMD (i.e., a Z-score ≤ −2.0**). A clinically significant fracture history is one or more of the following: (a) two or more long bone fractures

by 10 years of age; (b) three or more long bone fractures at any age up to 19 years. And lastly, as in adults, a normal BMD (i.e., Z-score > −2.0) does not preclude the possibility of skeletal fragility and increased fracture risk. A summary of some causes of osteoporosis in childhood is given in Table 35-6.

TABLE 35-7 Expanded Sillence Classification of Osteogenesis Imperfecta (OI)

Sillence type	Biochemical group	OMIM number	Gene symbol	Protein	Bone deformity	Sclerae	Dentinogenesis imperfecta	Other distinguishing features
	Group A: Defects in collagen synthesis, structure, or processing							
I	Autosomal dominant	166200	*COL1A1*	Collagen type I, 1	Rare to very severe	Normal, gray to dark blue	Absent to common	
II	Autosomal dominant	166210	*COL1A1*	Collagen type I, α1	Rare to very severe	Normal, gray to dark blue	Absent to common	
III	Autosomal dominant	259420	*COL1A1*	Collagen type I, α1	Rare to very severe	Normal, gray to dark blue	Absent to common	
IV	Autosomal dominant	166220	*COL1A1*	Collagen type I, α1	Rare to very severe	Normal, gray to dark blue	Absent to common	Type IV OI/EDS is caused by mutations at the first 85 amino acids of α1(I); normal bone mass form is caused by mutations blocking C-propeptide processing
I	Autosomal dominant	166200	*COL1A2*	Collagen type I, α2	Rare to very severe	Normal, gray to dark blue	Absent to common	
II	Autosomal dominant	166210	*COL1A2*	Collagen type I, α2	Rare to very severe	Normal, gray to dark blue	Absent to common	
III	Autosomal dominant	259420	*COL1A2*	Collagen type I, α2	Rare to very severe	Normal, gray to dark blue	Absent to common	
IV	Autosomal dominant	166220	*COL1A2*	Collagen type I, α2	Rare to very severe	Normal, gray to dark blue	Absent to common	Type IV OI/EDS is caused by mutations at the first 85 amino acids of α2(I); normal bone mass form is caused by mutations blocking C-propeptide processing
XIII	Autosomal recessive	614856	*BMP1*	Bone morphogenic protein 1/procollagen C-proteinase	Mild to severe	Normal	Absent	Umbelical hernia, normal bone mass
XVII	Autosomal recessive	616507	*SPARC*	Osteonectin	Rare to very severe	Normal, gray to dark blue	Absent to common	No skeletal fragility at birth; trabecular bone is hypermineralized
	Group B: Defects in collagen modification							
VII	Autosomal recessive	610682	*CRTAP*	Cartilage-associated protein	Severe rhizomelia	Normal or gray	Absent	
VIII	Autosomal recessive	610915	*LEPRE1/P3H1*	Leucine proline-enriched proteoglycan 1/prolyl 3-hydroxylase 1	Severe rhizomelia	Normal	Absent	

IX	Autosomal recessive	259440	*PPIB*	Peptidylprolyl isomerase B/ cyclophilin B	Severe	Gray	Absent	
XIV	Autosomal recessive	615066	*TMEM38B*	Transmembrane protein 38 B	Severe	Normal to blue	Absent	
	Group C: Defects in collagen folding and cross-linking							
X	Autosomal recessive	613848	*SERPINH1*	Serpin peptidase inhibitor, clade H, member 1/heat shock protein 47	Severe	Blue	Present	Skin blisters and bullae at birth; inguinal hernia
XI	Autosomal recessive	610968	*FKBP10*	FK506-binding protein 65	Mild to severe	Norma or gray	Absent	Variable congenital contractures; encompasses Bruck and Kuskokwim syndromes
	Autosomal recessive	609220	*PLOD2*	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	Moderate to severe			Progressive joint contractures
	Group D: Defects in bone mineralization							
V	Autosomal dominant	610967	*IFITM5*	Interferon-induced transmembrane protein 5	Variable	Normal to blue	Absent	Ossification of the interosseous membrane between radius and ulna; radial head dislocation; subephyphyseal metaphyseal radiodense band
VI	Autosomal recessive	613982	*SERPINF1*	Pigment epithelium-derived factor	Moderate to severe	Normal	Absent	No skeletal fragility at birth; bone histology shows mineralization defect and fish scale appearance of lamellar bone; increased serum levels of ALP, reduced serum levels of PEDF
	Group E: Defects in osteoblast development with collagen insufficiency							
XII	Autosomal recessive	613849	*SP7*	Transcription factor 7/osterix	Severe	Normal	Absent	Midface hypoplasia and delayed tooth eruption
XV	Autosomal recessive	615220	*WNT1*	Wingless-type MMTV integration site family, member 1	Severe	White	Absent	Possible neurologic defects

ALP, alkaline phosphatase; EDS, Ehlers-Danlos syndrome; PEDF, pigment epithelium-derived factor.

2. **Radiologic assessment of bone health.** There is no generally accepted method for determination of bone mass in children and adolescents. In children, bone modeling occurs at many sites that are not measured by these machines. Dual-energy X-ray absorptiometry (DXA) is the preferred technique in children and adolescents. Population-based reference curves for DXA assessments of BMC and areal BMD for total body less head (TBLH), lumbar spine, hip, femoral neck, and distal, one third radius for children in the United States are available from the Bone Mineral Density in Childhood Study. Unlike adult patients in whom the bone volume does not change over time, a child's bones grow and model over time. Therefore, appropriate reference

databases that allow for adjustments, if any, for bone size or patient height must be used (see https://bmdcs.nichd.nih.gov/zscore.htm). For clinical use, **DXA measurements of the lumbar spine (L1-4) and TBLH are considered the most useful sites in the pediatric population**; hip measurements should not be assessed until a patient is over 16 years and/or the femoral head growth plates have closed.

Quantitative computed tomography (qCT) is an exact method to determine volumetric BMD (vBMD) in children, with adequate separation of cortical and trabecular compartments. However, enthusiasm for qCT is reduced by the **relatively high radiation dose** delivered. An alternative technology, which today is **limited to research use, is peripheral qCT** of the tibia or forearm. Peripheral qCT has the ability to measure bone density in the cortical and cancellous compartments separately, provides true vBMD, and is not affected by bone size.

An important general limitation to the use of bone densitometry in children is that the clinical implications of low BMD are less certain than in adults.

However, it is likely that BMD alone does not explain fracture risk in children (or adults). Thus, it has not been possible to establish BMD criteria for "fracture threshold" in children. By contrast, the proven association between low BMD and fractures in older adults led the WHO to propose quantitative criteria for "osteopenia" and "osteoporosis" that are based solely on BMD T scores, which reflect the number of SD above or below peak bone mass. It is inappropriate to express BMD in children using T scores, because children and adolescents have not yet achieved peak bone mass, and they will normally have negative T scores. The use of T scores, rather than age-adjusted Z scores, to express BMD in children and adolescents, is a leading cause of misinterpretation of bone densitometry and often results in the inappropriate diagnosis of osteoporosis. Bone densitometry by itself should not be used to make a diagnosis of osteoporosis in pediatrics.

3. Etiology of osteoporosis

Table 35-6 provides a general classification of osteoporosis in children and adolescents. Up to 90% of peak bone mass is acquired by age 20 in males and by age 18 in females, and bone mass can

continue to increase until around age 30, well after cessation of statural growth (see Chapter 33). A gender difference in bone mass is due to a longer period of bone maturation in males than in females. Indeed, over the 3 to 4 years of pubertal development, a BMD at both the lumbar spine and the femoral neck increases four- to sixfold in females and males, respectively.

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a. Secondary osteoporosis

In children, reduced bone mass is often a consequence of **disuse atrophy** of the skeleton (e.g., after immobilization for severe trauma), **neuromuscular disease** (e.g., Duchenne muscular dystrophy), or a consequence of **glucocorticoid therapy**. Osteoporosis can also occur in children with **malignancy** (e.g., leukemia or neuroblastoma) and in cancer survivors, and after bone marrow and solid-organ transplantation. Low bone density is also present in many children with celiac disease or cystic fibrosis as well as in many chronic inflammatory diseases (e.g., inflammatory bowel disease and idiopathic juvenile arthritis). In addition to glucocorticoids, a variety of medications can result in low bone density, including heparin, antiretrovirals, medroxyprogesterone and **gonadotropin-releasing hormone superagonists**, anticonvulsants, and doses of **thyroid hormone** that suppress thyroid-stimulating hormone. In addition, low **bone mass is a characteristic of Klinefelter, Ehlers-Danlos, Marfan, and Turner syndromes**. Reduced bone density is also common in children with **delayed puberty, hypogonadism, anorexia nervosa**, and the female athlete triad (amenorrhea, disordered eating, and osteoporosis). Reduced bone mass also occurs in **approximately 40% of children with idiopathic hypercalciuria**. Osteoporosis is also a feature of many rare inherited disorders, such as **homocystinuria, galactosemia**, as well as osteoporosis pseudoglioma syndrome (OPPG) (see below).

b. Idiopathic early-onset osteoporosis. Recent molecular studies have disclosed a number of genes that cause autosomal dominant (*WNT1* and *LRP5*) and X-linked (*PLS3*) forms of early-onset osteoporosis. *LRP5* and *WNT1* mutations impair

WNT/-catenin signaling in osteoblasts, which is critical for bone formation. The Wnt pathway is a very important regulator of bone mass. Less is known about the role of PLS3. Reduced expression of PLS3 is likely to play a role in osteocyte dendrite function and skeletal mechanosensing. Affected patients present with multiple and progressive fractures, both peripheral and spinal compression fractures, and low BMD.

c. **OPPG** is caused by biallelic loss-of-function mutations in LRP5. OPPG is characterized by severely reduced bone mass and neovascularization of the retina, which, in turn, leads to retinal detachment and blindness. These activating mutations in *LRP5* cause **familial high bone mass syndrome**, an autosomal dominant form of osteopetrosis that is associated with nonpathologic high bone mass. The Wnt signaling pathway is also regulated by sclerostin, which is expressed exclusively by osteocytes in bone. Loss of sclerostin expression in humans results in the high bone mass disorders (Van Buchem disease and sclerosteosis), providing compelling evidence that osteocytes can control bone mass. Thus, osteocytes exert negative feedback control of osteoblast number and bone formation via production of sclerostin.

d. **Idiopathic juvenile osteoporosis (IJO)** occurs in previously apparently healthy children. Patients present with osteoporotic collapse of one or more (usually lumbar) spinal vertebrae or with fractures of long bones, mostly at metaphyseal sites, upon minor trauma. A waddling gait is common. Bone histology sometimes shows an excess of osteocytes associated with woven bone and normal mineralization. There are no extraskeletal biochemical abnormalities.

   Although disability and deformity can be severe during the active phase of the disease, IJO **tends to remit spontaneously** soon after the onset of puberty, although skeletal deformity may persist. The recovery presumably occurs under the influence of gonadal steroid secretion. In some patients, the disease continues into adulthood and can result in lifelong disability. The cause of the disease is unknown, and no satisfactory methods of therapy have been described.

e. **Osteogenesis imperfecta (OI)** describes several inherited conditions characterized by low bone mass and an increased

incidence of bone fractures in connection with minimal trauma. Of the various forms of OI, type I is the most common, and overall OI occurs with an incidence at birth of approximately 1 p. 482p. 483in 50 000, with a population prevalence of about 1 in 20 000. All ethnic and racial groups seem to have a similarly affected frequency.

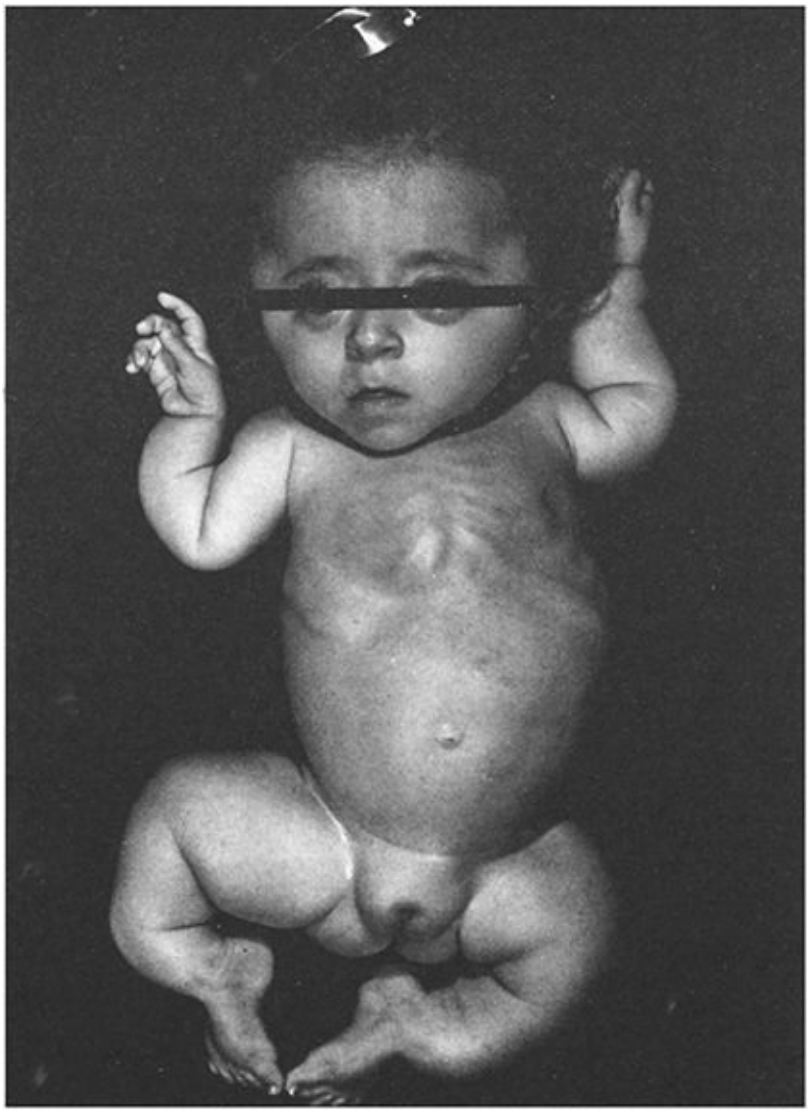

Figure 35-5. Severe deformities of long bones and ribs in a 5-year-old child with osteogenesis imperfecta. (From Gertner JM, Root L. Osteogenesis imperfecta. *Orthop Clin N Am* 1990;20:151–162.)

i. Etiology. The various types of OI are caused by defects in

proteins that affect the nature or synthetic rate of the peptide chains that constitute type I collagen, the major collagen of the skeleton. The principle clinical manifestations of OI, and the severity of the disorder, are a reflection of the increased skeletal fragility that results from **inadequate type I collagen function**. About 85% to 90% of cases of OI are caused by structural or quantitative mutations in the genes that produce type I collagen, which is an essential structural component of the bone, tendons, skin, sclerae, and dentin. Type I OI is typically caused by heterozygous null mutations in *COL1A1* that cause haploinsufficiency and inadequate proα1(I) production, resulting in frequent fractures during childhood that abate after adolescence. In contrast, types II to IV OI are typically caused by heterozygous mutations in *COL1A1* or *COL1A2* that alter collagen structure. Types V p. 483p. 484to XVIII OI have been named according to the order in which causative genes have been identified.

ii. **Taxonomy.** The growing number of molecular causes of OI is challenging the traditional categorization of OI, which was based on clinical presentation, with type I OI being the least severe, type II OI causing perinatal lethality, type III OI causing severe progressive deformities, and type IV OI causing variable moderate deformities.

iii. **Inheritance.** Types I, IV, and V are inherited as autosomal dominant conditions, whereas the other forms of OI are usually inherited in an autosomal recessive manner. Germline mosaic in one of two healthy parents has been proposed as an explanation for the occurrence of more than one affected child with a dominant form of OI.

iv. **Clinical features.** Table 35-7 summarizes the typical and many distinguishing features of the various forms of OI. In general, babies affected at birth have a poor prognosis. Individuals with milder forms of OI, for example, some patients with **type I**, may have normal stature, no deformities, and no fractures, and the condition may be

diagnosed only when a radiograph is taken for other reasons. Those with **Sillence type II** are born with multiple fractures that have arisen in utero, some healing with shortening and broadening of the long bones. Stillbirth or early death usually results from respiratory failure or brain damage. In **type III**, the fractures are less widespread. These children often survive for several years with progressive severe deformities of the long bones (Fig. 35-5). Once again, **respiratory failure is often the terminal event**.

Basilar invagination is an uncommon but potentially fatal complication of OI. Other neurologic manifestations of OI include idiopathic seizures, macrocephaly and benign communicating hydrocephalus, and cerebral atrophy. Hearing problems may be present in approximately 50% of individuals with types I and IV caused by mutations in the genes encoding type I collagen. Because bone remodeling rates are increased in most forms of OI, hypercalciuria is common and may occur in approximately 40% of individuals.

Types I and IV of Sillence are milder conditions in which the mode of inheritance is dominant. The skeletal tendency to excess fracturing is accompanied by lax jointedness, easy bruisability, and conductive deafness. Joint laxity can lead to dislocation of hips and radial heads. Constipation, sprains, flat feet, and hernias may occur. The **teeth can be affected by dentinogenesis imperfecta (the so-called subtypes Ia and IVa)**, whereas patients with **subtypes Ib and IVb have normal teeth**. The distinguishing characteristic **of type I is a persistent blueness of the sclerae** (blue sclerae are normal in infancy) and, in most cases, normal stature. The first fracture typically occurs in preschool children, and fractures may be present at birth. Cardiovascular problems, particularly aortic valve disease and mitral valve prolapse, can be present. Type I OI is often a consideration during the evaluation of a child with nonaccidental fractures who is suspected to be the victim of abuse. Type IV patients present a very similar clinical picture, but the sclerae are a

normal white.

Type V OI is moderately deforming, and patients exhibit moderate-to-severe bone fragility of long bones and vertebral bodies. Patients experience fractures in the first year of life but do not have blue sclerae or dentinogenesis imperfecta. Type V OI is characterized by **three distinctive radiographic features**: hyperplastic callus formation at fracture sites; calcification of the interosseous membrane between the radius and ulna; and radio-opaque metaphyseal bands adjacent to the growth plates. Other radiologic findings include flattened, wedge-shaped, or biconcave vertebrae and Wormian bones of the skull. Levels of biochemical bone markers are generally within the reference range, but serum alkaline phosphatase and urinary collagen type I N-telopeptide excretion increase during periods of active hyperplastic callus formation.

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Type VI OI is a rare, moderate-to-severe form of the disease that is caused by biallelic null mutations of *SERPINF1*, which encodes pigment epithelium-derived factor (PEDF). Affected subjects have an unusual clinical presentation: there are typically **no fractures in the first year of life**, but subsequently patients develop a severe **progressive deforming bone dysplasia**, with frequent long bone fractures, vertebral compressions, and markedly decreased BMD. Serum levels of PEDF are reduced. Bone turnover is reduced, which likely explains the poor response to bisphosphonates.

Type VII and type VIII OI share similar phenotypes. Type VIII OI is a lethal/severe form of OI that is caused by mutation in the *LEPRE1* gene. Accordingly, type VIII OI closely resembles type VII OI clinically. The phenotype of this form of OI overlaps Sillence lethal type II/severe type III OI. Affected patients have severe osteoporosis, shortened long bones, and a soft skull with wide open fontanels. Several features distinguish type VIII from other lethal forms of OI, including white sclerae, a round face, and a short barrel-shaped chest.

Types IX through XVII are very uncommon forms of OI. The distinctive or unusual features of these forms of OI are described in Table 35-7.

v. **Treatment of osteoporosis.** It is recommended that such children maintain an adequate calcium intake and receive sufficient supplemental vitamin D to sustain serum levels of 25(OH)D that are adequate for bone mineralization (i.e., >20 ng/mL). To prevent immobilization bone loss, weight-bearing activity should be maximized. For children with extreme bone fragility, swimming and hydrotherapy may be beneficial. In nonambulant children with cerebral palsy, a standing frame to facilitate an upright position has been shown to improve BMD.

Bisphosphonates have been shown to increase bone density and reduce fractures in children and adolescents with a variety of forms of osteoporosis, but **these agents must still be considered investigational and experimental in children**. Histomorphometric studies in OI have shown that pamidronate increases bone mass by increasing cortical thickness and trabecular number. Pamidronate and **zoledronate**, powerful nitrogen-containing bisphosphonates, can suppress bone turnover in children to well below that of normal age-matched controls. This can interfere with bone modeling and result in undertubularization of long bones. In the growing skeleton, a reduction in bone remodeling results in the accumulation of mineralized cartilage within the bone. The mineralized cartilage has a high density, which contributes to the increase in bone density seen with treatment with pamidronate or zoledronate treatment. Oral bisphosphonates may result in chemical esophagitis.

Bisphosphonates are contraindicated during pregnancy, and all females of reproductive age should have a negative pregnancy test before each treatment cycle or before commencing oral bisphosphonates.

Administration of bisphosphonates, particularly **cyclical intravenous pamidronate** (4.5 to 9 mg/kg/year, given every 3 to 4 months) to children with

severe OI can alleviate bone pain, reduce the incidence of fractures, enhance growth, and improve overall quality of life. It appears that the **best response to pamidronate** therapy occurs in children who are **first treated in infancy**. The mean incidence of radiologically confirmed fractures decreased by 1.7/year ($P < 0.001$), but treatment did not alter the rate of fracture healing, the growth rate, or the appearance of growth plates. Mobility and ambulation improved in 16 children and remained unchanged in the other 14.

Both intravenous and oral bisphosphonates have been used in children and adolescents with other forms of osteoporosis, with improved BMD and reduced fractures in most studies. Treated children have reported rapid pain relief following the first treatment, followed by large increments in lumbar spine bone density over 1 year.

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C. Uremic osteodystrophy

1. Pathogenesis

a. Growth failure, skeletal deformity, and severe orthopedic problems, especially in the weight-bearing lower limbs, can all result from uremic osteodystrophy (UOD). Growth failure and biochemical and histologic abnormalities can occur in children with mild renal impairment (GFR 25 to 50 mL/min/1.73 m^2), but the most severe forms are confined to children with more pronounced renal failure.

b. The bony disorder arises principally from a **combination of inadequate vitamin D activation and hyperparathyroidism**. The latter is itself a result of compensation for the calcium-lowering effects of low levels of calcitriol and high plasma phosphate concentrations. Histologically and radiologically, the bones show a combination, to varying degrees, of osteomalacia with rickets and hyperparathyroid bone disease. The hyperparathyroidism contributes to bone resorption. Severe destruction and lysis of epiphysial areas, particularly the hips, can occur, giving rise to the so-called rotting stump appearance or to necrosis of the

femoral heads.

c. The biochemical features accompanying UOD are given in Table 35-5. Acidosis may contribute to the severity of the skeletal problem.

2. Treatment. Adequate nutrition, including an adequate calcium intake, should be maintained and acidosis corrected. The tendency to hyperphosphatemia can be reduced by dietary restriction and the administration of phosphorus-binding substances. Several different calcium salts (e.g., calcium carbonate and calcium acetate) as well as nonabsorbable calcium- and aluminum-free agents (e.g., lanthanum carbonate and sevelamer hydrochloride) are now preferred over aluminum hydroxide gel for this purpose. These agents work by binding to phosphate in the gastrointestinal tract, thereby making it unavailable to the body for absorption. Therefore, for optimal efficacy, these drugs must be taken with meals to bind any phosphate that may be present in the ingested food.

Active vitamin D metabolites, usually calcitriol, are given to maintain the serum calcium, to improve skeletal mineralization, and to suppress secretion and synthesis of PTH. PTH secretion can also be directly inhibited using calcimimetics that modulate activity of CaSRs that are expressed on the surface of parathyroid cells. Patients with end-stage renal disease tend to have fewer and/or less sensitive CaSRs. Therefore, cinacalcet, a type II calcimimetic agent that binds to the transmembrane region of the CaSR, induces a structural configuration that increases the sensitivity of CaSRs to ambient Ca^{2+} concentrations and thereby reduces PTH secretion.

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SECTION 6

Thyroid Disorders

36

Evaluation of Thyroid Function

Caroline T. Nguyen and Peter A. Singer

I. GENERAL PRINCIPLES OF THYROID HORMONE SECRETION AND METABOLISM

A. Hypothalamic-pituitary-thyroid axis. The thyroid hormones thyroxine (T_4) and tri-iodothyronine (T_3) are secreted under the stimulatory influence of pituitary thyrotropin (thyroid-stimulating hormone or TSH). TSH secretion is primarily regulated by a dual mechanism.

1. **Thyrotropin-releasing hormone (TRH),** a hypothalamic tripeptide, traverses a venous plexus connecting the stalk median eminence and the anterior pituitary and stimulates the synthesis and release of TSH.
2. **The thyroid hormones** T_4 and T_3 directly inhibit pituitary TSH secretion. T_4 has more of an inhibitory effect than T_3, and exerts its effect on the thyrotroph via intracellular conversion to T_3. Thyroid hormone also exerts a lesser negative feedback effect on the hypothalamus.

   Figure 36-1 depicts the hypothalamic-pituitary-thyroid axis. (Note that a number of other factors alter TSH secretion, either directly or indirectly, although the role of any of these agents as a physiologic regulator of TSH secretion is most likely minor.)

B. Thyroid-binding proteins and free hormone. Thyroid hormone exists in circulation in both free (or unbound) and bound forms. The amount of free hormone, which is the metabolically active component of thyroid hormone, is extremely small, accounting for approximately 0.03% of total circulating T_4 and approximately 0.3% of total circulating T_3, respectively. The majority of hormone is avidly bound to thyroid-binding proteins, the most important of which is thyroxine-binding globulin (TBG), which accounts for 75% of thyroid hormone binding. The other binding proteins, thyroid-binding prealbumin (TBPA), also termed transthyretin, and albumin, account for approximately 15% and 10% of binding of T_4, respectively. T_3 is only minimally bound to TBPA, and approximately 25% is bound to albumin.

1. Alterations in the concentrations of the thyroid-binding proteins, mainly TBG, result in changes in the concentrations of T_4 and T_3. An increase in TBG results in increased thyroid hormone levels, and TBG deficiency results in lower total T_4 and T_3 concentrations. However, the amounts of free hormone *do not change*, so that thyrometabolic status remains unchanged, despite alterations in TBG concentrations. The states of altered TBG concentrations are shown in Table 36-1.

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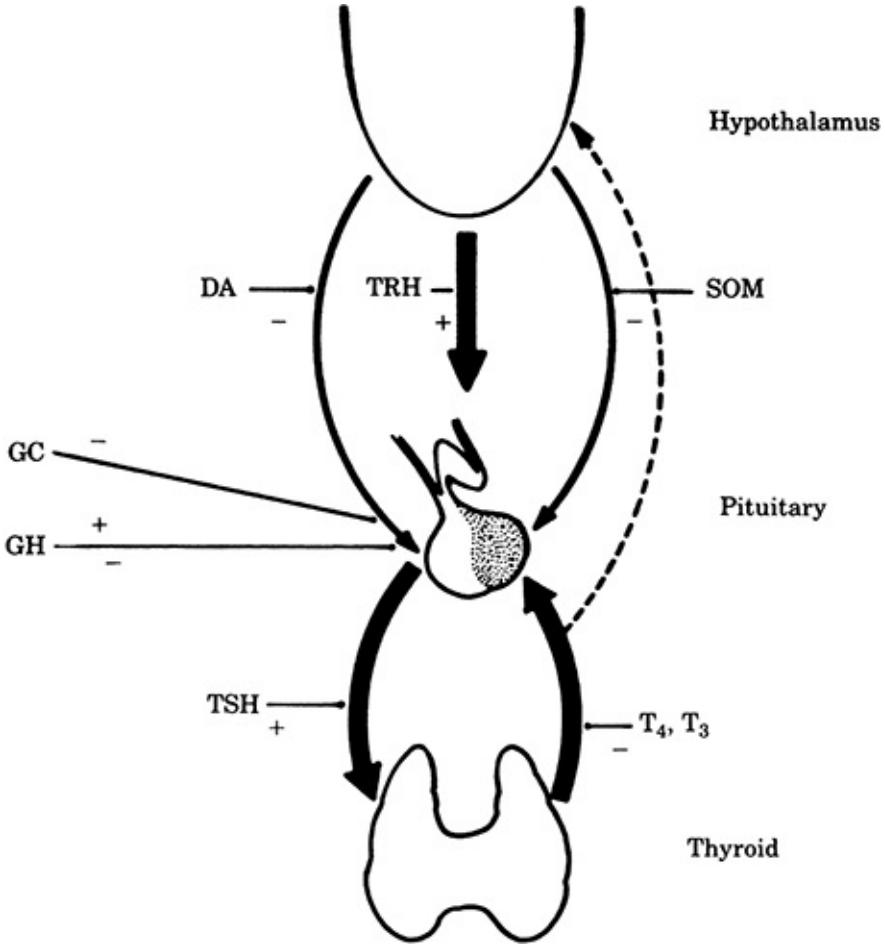

Figure 36-1. Hypothalamic-pituitary-thyroid axis. Dopamine (DA) and somatostatin (SOM) may be minor physiologic regulators of thyroid-stimulating hormone (TSH) secretion. The possible inhibitory effects of growth hormone (GH) may be via stimulating hypothalamic SOM synthesis. Glucocorticoids (GC) may have effects on both the thyrotrope and the hypothalamus. TRH, thyrotropin-releasing hormone; T_3, tri-iodothyronine; T_4, thyroxine.

2. Changes in the concentrations of either TBPA or albumin lead to less significant alterations in serum T_4 levels because of the significantly smaller binding affinity of T_4 for these proteins. There is, however, a syndrome of familial euthyroid T_4 excess, in which abnormal binding of T_4 (but not of T_3) to serum albumin occurs. In this disorder, free T_4 (FT_4) remains normal. Also, there is a rare disorder of increased serum levels of TBPA, in which total T_4 is elevated and FT_4 is normal.

C. Peripheral metabolism of thyroid hormone

1. The thyroid gland is the sole source of circulating T_4. Approximately 80% of circulating T_3, however, is derived from

peripheral tissue deiodination of T_4 to T_3. Therefore, only 20% of the daily production of T_3 is derived from thyroid gland secretion. Approximately 80 to 90 μg of T_4 is secreted by the thyroid gland daily, and the average daily production of T_3 is approximately 20 to 30 μg.

2. In certain conditions in which T_4 to T_3 conversion is inhibited, an alternative deiodinative pathway is employed, and a stereoisomer of T_3, **reverse T_3 (RT_3)**, is produced. **RT_3 has no known tissue biologic effect or feedback effect** on the pituitary gland. Obtaining an RT_3 level is rarely useful because it can be elevated in patients with sick euthyroid illness due to various acute and chronic illnesses. p. 489p. 490One situation it may be useful in is to distinguish between sick euthyroid illness and central hypothyroidism. RT_3 is low in the later because there is insufficient substrate, T_4, to produce RT_3. It is not useful in diagnosing mild hypothyroidism because it may be normal or mildly elevated.

TABLE 36-1 Altered TBG States Affecting Thyroid Hormone Concentrations

TBG Excess
Increased TBG production
Hereditary (X-linked dominant)
Hepatitis (acute or subacute)
Decreased TBG clearance
Estrogens (pregnancy, OCPs, estrogen-secreting tumors)
Drugs (tamoxifen, 5-fluorouracil, clofibrate, methadone, heroin)
Acute intermittent porphyria
TBG Deficiency
Decreased TBG production
Hereditary (X-linked recessive)
Androgens
Drugs (L-asparaginase, danazol, niacin)
Increased TBG clearance
Nephrotic syndrome
Protein-losing gastroenteropathy
Severe liver disease (cirrhosis)

Hormonal abnormalities
Glucocorticoid excess (Cushing or exogenous)
Acromegaly
TBG, thyroxine-binding globulin.

3. The daily production rate of RT_3 is approximately 30 μg, the majority of which is derived from T_4. Factors that impair T_4 to T_3 conversion are listed in Table 36-2.

II. THYROID FUNCTION TESTS

A. In vitro tests

1. **Serum T_4** (average reference range 5 to 12 μg/dL). Serum T_4 is measured by immunochemiluminometric assay (ICMA) methods and usually reflects the functional state of the thyroid. However, changes in the concentration of p. 490p. 491thyroid-binding proteins, usually secondary to estrogen therapy or pregnancy, alter the concentration of T_4 without affecting thyrometabolic status (see Section I.B.1). Other factors that may alter the concentration of total T_4 without changing metabolism include nonthyroidal illness, peripheral resistance to thyroid hormone, endogenous antibodies to T_4, and certain drugs (see Section IV). Thus, in some circumstances, the serum T_4 may not accurately reflect the metabolic status of the individual. Nonthyroidal systemic illnesses may also be associated with abnormal total T_4 levels, with low concentrations of T_4 in approximately 25% of seriously ill individuals, and mildly elevated T_4 levels in approximately 2% of ill patients.

TABLE 36-2 Factors that Inhibit T_4 to T_3 Metabolism

Systemic illness (acute or chronic)
Caloric deprivation: fasting, anorexia nervosa, protein-calorie malnutrition
Surgery
Newborn status
Aging
Glucocorticoids

Propranolol Amiodarone Ipodate, iopanoic acid Propylthiouracil
T_3, tri-iodothyronine; T_4, thyroxine.

2. **FT_4** (average reference range 0.8 to 2.0 ng/mL). The serum FT_4 most accurately reflects metabolic status and should not be affected by alterations in serum proteins or nonthyroidal illness. The "gold standard" is measurement of FT_4 by **equilibrium dialysis**, which separates FT_4 from T_4 bound to plasma proteins; however, the dialysis method is time-consuming and relatively expensive, so its clinical usefulness is limited. Most commercial FT_4 assays are not dialysis methods; they are ICMAs. These are sufficiently accurate in most settings, automatable, and inexpensive. However, they may be affected by changes in binding proteins. Serum samples with low binding capacity (low serum TBG; e.g., nonthyroidal illness) tend to yield lower than true results, whereas samples with high binding capacity (e.g., pregnancy) tend to yield higher than true results. To overcome this limitation, a reasonably accurate estimate of FT_4 may be calculated. This is done by multiplying the serum total T_4 by an indirect assessment of TBG capacity. Indirect TBG methods vary; they include the T_3 uptake test, the thyroid uptake test, and the thyroid uptake ratio. Whatever method is used, an estimate of FT_4 (also termed free T_4 index, FT_4I) generally correlates closely with FT_4. Many laboratories nowadays have abandoned doing T_3 uptake tests, so clinicians need to rely on FT_4 measurements rather than on estimates of FT_4.
3. **Serum T_3** (average reference range 80 to 180 ng/dL). T_3 is measured by ICMA methods. Because T_3 is bound to TBG, it is subject to the same changes as T_4 because of alterations of binding proteins. Therefore, a free T_3 index (FT_3I) can be obtained using the same method as that used in calculating a FT_4I. Because the principal source of circulating T_3 is T_4, the conditions that affect the metabolism of T_4 also affect T_3 levels (see Table 36-2).

Alternatively, FT_3 may be measured, either by radioimmunoassay or by dialysis. Equilibrium dialysis is often considered the reference method. However, it is often only readily available in reference laboratories. Unfortunately, FT_3 hormone immunoassays appear to be more variable and less reliable than total hormone measurements. Clinically, illness is the most common nonthyroidal condition associated with low serum T_3.

4. **Serum TSH** (average reference range 0.3 to 3.0 mU/L). Methodologic advances in the measurement of TSH have resulted in this test being ideally suited for detecting very mild thyroid dysfunction. Most commercial assays have a functional sensitivity of 0.01 mIU/L and enable clinicians to detect even the mildest forms of hyperthyroidism. TSH is typically measured by ICMA methods. Although TSH assays are highly sensitive and reproducible, the TSH test has limitations, especially in hospitalized patients (see Section III).

B. In vivo tests

1. **Radioactive iodine uptake (RAIU) test.** The RAIU test is performed by administering ^{123}I orally and measuring the percent uptake of the radionuclide dose from 4 to 24 hours later. The test is most useful for differentiating between high- and low-uptake types of hyperthyroidism and should be performed in hyperthyroid patients in whom a diagnosis of Graves disease is not evident. The average normal range for the 24-hour RAIU test in the United States is 8% to 25%. Table 36-3 classifies hyperthyroidism according to the RAIU test. Large doses of exogenous iodine (e.g., contrast media or iodine-containing drugs) can suppress RAIU temporarily.
2. **TRH test.** This test historically was used to assess pituitary TSH reserve, as well as the degree of TSH suppression. As a result of the widespread availability of p. 491p. 492sensitive TSH assays, this test is rarely used in the United States today, although it is still used occasionally in other countries, especially in Latin America.

TABLE 36-3 RAIU in Hyperthyroid States

High RAIU	Low RAIU
Graves disease	Subacute thyroiditis
Toxic multinodular goiter	Painless thyroiditis
Toxic adenoma	Graves disease with acute iodine load
Hashitoxicosis	Iodine-induced hyperthyroidism
Choriocarcinoma	Thyroid hormone therapy
Hydatidiform mole	Metastatic functioning thyroid carcinoma
TSH-producing pituitary tumor	Struma ovarii

RAIU, radioactive iodine uptake; TSH, thyroid-stimulating hormone.

3. **T_3 suppression test.** This is also a test of historical interest and was designed to test autonomous thyroid function. Thyroid uptake and scan was measured at the end of a 7-day course of T3 75 to 100 μg daily. A normal response included a decrease in greater than 50% in thyroid radioiodine uptake. The widespread availability of accurate biochemical tests and thyroid imaging techniques has rendered this test obsolete.

C. Other serologic tests. A number of tests associated with thyroid autoimmunity, such as measurement of antithyroglobulin and antimicrosomal antibodies, antibodies to T_4 and T_3, and thyroid-stimulating and thyroid-blocking antibodies, are discussed in Chapter 38. The usefulness of serologic tests for thyroid cancer, such as measurement of thyroglobulin and calcitonin, is discussed in Chapter 39.

III. EVALUATION OF SUSPECTED THYROID DYSFUNCTION

A. Hypothyroidism

1. **Primary hypothyroidism.** The laboratory diagnosis of primary hypothyroidism is established by the presence of a low serum T_4 (or FT_4) and an elevated serum TSH. The serum TSH is the most sensitive test in the diagnosis of primary hypothyroidism. In mild hypothyroidism, the T_4 level may be within normal limits in the presence of TSH elevation. This is termed **subclinical hypothyroidism**. A suggested algorithm for evaluation of suspected hypothyroidism employing the serum TSH is shown in Figure 36-2.
2. **Secondary hypothyroidism.** A low serum T_4 and a normal or

low serum TSH suggest the diagnosis of secondary (pituitary) or tertiary (hypothalamic) hypothyroidism. Such patients must be further evaluated for suspected pituitary or hypothalamic disease. Patients with low serum T_4 and normal or low serum TSH levels secondary to nonthyroidal illness must also be differentiated from patients with secondary and tertiary hypothyroidism (see Chapter 38).

3. **Serum T_3.** The serum T_3 is not useful in the evaluation of suspected hypothyroidism, because it **may be normal in up to one third of hypothyroid individuals**. Therefore, this test is not recommended for patients with suspected hypothyroidism.

B. Hyperthyroidism

1. Figure 36-3 outlines a strategy for evaluating patients with suspected hyperthyroidism. Note that the serum TSH is important in this strategy, in part because rare types of hyperthyroidism, including TSH-producing pituitary tumors and central thyroid hormone resistance, are associated with inappropriately normal or only mildly elevated TSH concentrations.
2. The serum T_4 (or FT_4) is elevated with all types of hyperthyroidism except for "T_3 toxicosis," in which serum T_3 levels are elevated and serum T_4 may be normal.

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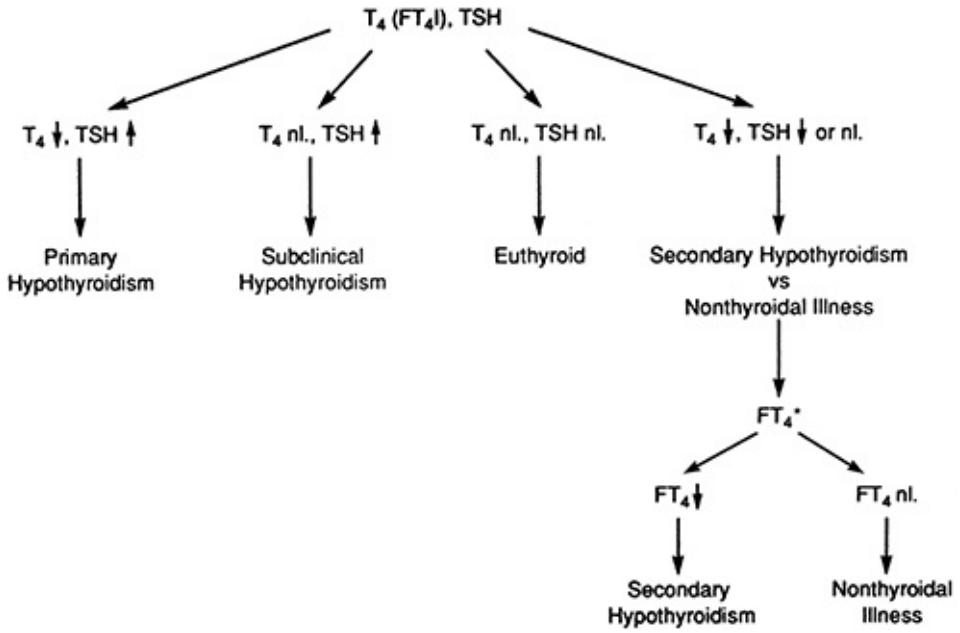

Figure 36-2. Laboratory evaluation of suspected hypothyroidism. FT_4, free T_4; FT_4I, free T_4 index; nl, normal; TSH, thyroid-stimulating hormone; T_4, thyroxine. (*Where there is uncertainty about the clinical diagnosis, FT_4 should be measured by equilibrium dialysis to avoid changes induced by binding proteins.)

3. Serum T_3 levels are elevated in virtually all patients with hyperthyroidism, and patients with Graves disease have disproportionate T_3 elevations in comparison with other types of hyperthyroidism. It is not necessary to obtain T_3 levels to make a diagnosis of hyperthyroidism. However, a T_3 measurement is helpful in the following situations:

a. In patients with symptoms suggestive of hyperthyroidism in whom serum TSH levels are suppressed and FT_4 levels are normal or borderline elevated. Such patients may include those being treated for thyrotoxic Graves disease, or those with autonomously functioning thyroid adenomas.

b. In patients with hyperthyroxinemia who have normal TSH concentrations. Such individuals may have the inherited defect of peripheral resistance to thyroid hormone, or an inherited defect in binding-carrier proteins. Table 36-4 outlines hyperthyroxinemic states without hyperthyroidism.

C. Pitfalls of TSH measurements. It should be stressed that the serum TSH is most reliable if measured in otherwise healthy, ambulatory individuals. There are a number of conditions in which the

serum TSH does not accurately reflect thyrometabolic status.

1. **Nonthyroidal illness (sick euthyroid syndrome).** The serum TSH may be low or even suppressed in hospitalized patients with severe illness. During recovery, the TSH may become elevated, although usually not above 20 mU/L. Despite alterations in TSH concentrations during illness, FT_4 levels remain normal, and patients are euthyroid. A pitfall in the measurement of FT_4 levels, though, is that commercial and hospital laboratories do not routinely employ dialysis methods, so FT_4 measurements may also be affected by illness, or by significant changes in binding proteins.
2. **Changing thyroid status.** Thyroid status must be stable to allow reliable interpretation of the serum TSH. Although a suppressed TSH level is indicative of hyperthyroidism in the untreated thyrotoxic individual, patients who are being treated with antithyroid drugs or who have undergone thyroid ablation with radioactive iodine for hyperthyroidism may exhibit suppressed TSH levels for p. 493p. 494several months after serum T_4 and T_3 have reached normal levels. This reflects prolonged suppression of the hypothalamic-pituitary-thyroid axis.

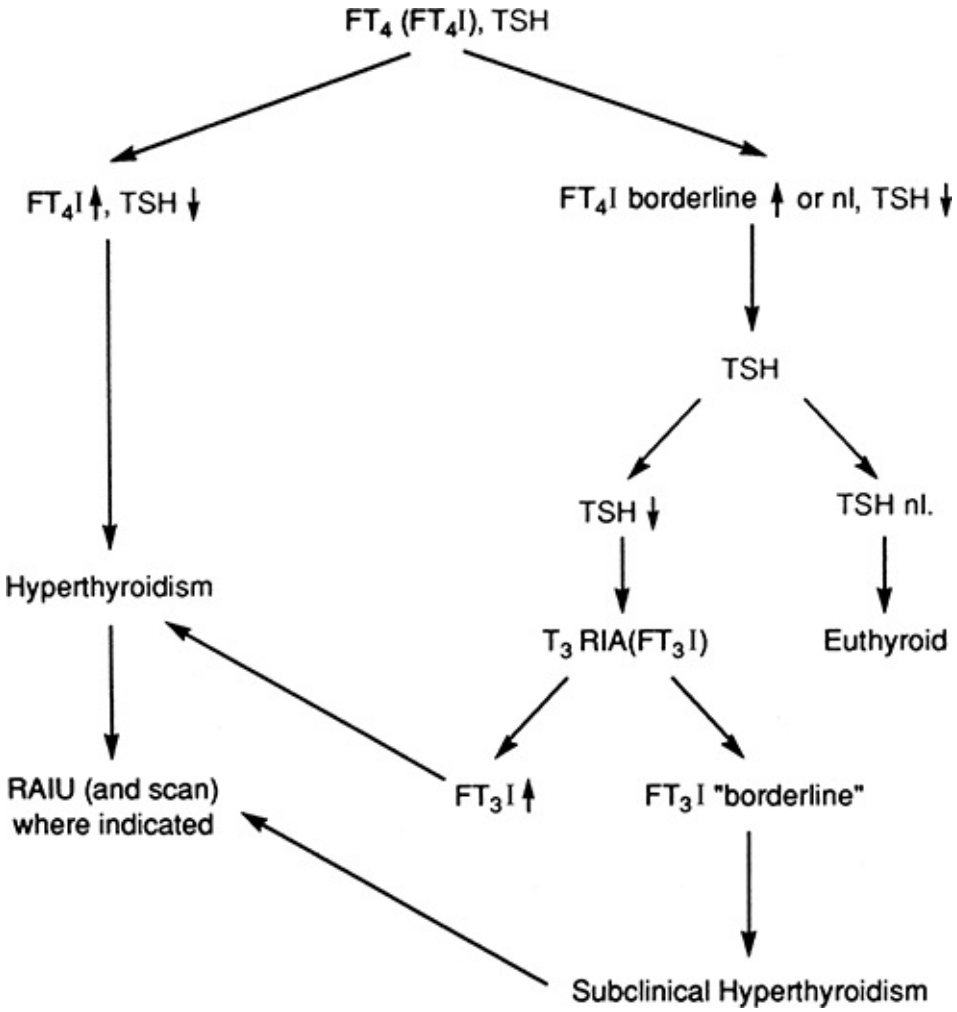

Figure 36-3. Laboratory evaluation of suspected hyperthyroidism. This approach can be used for evaluation of obvious hyperthyroidism. Otherwise, serum TSH should be used as a first-line test (see text). FT_3, free T_3; FT_3I, free T_3 index; FT_4I, free T_4 index; nl, normal; RAIU, radioactive iodine uptake; T_3, tri-iodothyronine; TSH, thyroid-stimulating hormone; T_4, thyroxine.

TABLE 36-4 Thyroid Function Tests in Hyperthyroxinemia without Hyperthyroidism

State	Test				
	T_4	T_3	FT_4I	Free T_4	TSH
TBG excess	↑	↑	N	N	N
Abnormal albumin binding	↑	↑ or N	↑	N	N
Increased TBPA	↑	N	↑	N	N
Peripheral thyroid hormone resistance	↑	↑	↑	↑	N or ↑
Nonthyroidal illness (mild)	↑	↓	↑	N, ↑, or ↓	N
Amiodarone therapy	↑	N	↑	↑	N

FT_4I, free T_4 index; N, normal; TBG, thyroxine-binding globulin; TBPA, thyroxine-binding prealbumin; TSH, thyroid-stimulating hormone; T_3, tri-iodothyronine; T_4, thyroxine; ↑, elevated; ↓, lowered.

Hypothyroid patients recently begun on thyroid hormone therapy may also have discordant serum TSH and T_4 levels because of the **lag in fall of TSH after initiation of thyroid hormone therapy**. Thus, normal serum T_4 and elevated TSH levels after a month or so of therapy may not necessarily reflect underreplacement with levothyroxine (L-T4). This underscores the recommendation that dose changes should be made no more frequently than every 6 to 8 weeks, unless the clinical situation dictates otherwise.

Variable compliance L-T4 therapy may also give misleading results. Patients who take medication intermittently, or who take it consistently for only a few weeks prior to an office visit, may have relatively normal serum T_4 and elevated serum TSH levels.

3. **Central hypothyroidism.** As mentioned previously, hypothyroidism due to either hypothalamic or pituitary disease is characterized by low serum T_4 and normal TSH levels. Therefore, relying on the serum TSH to screen for possible hypothyroidism in such patients will result in a failure to make the correct diagnosis. Fortunately, most individuals with central hypothyroidism exhibit additional hormone deficiencies or have symptoms of a mass effect (such as visual abnormalities), thus decreasing the likelihood that the correct diagnosis may be overlooked.
4. **Hyperthyroidism associated with inappropriate TSH secretion**
   a. **TSH-secreting pituitary tumor.** Serum TSH levels are elevated or inappropriately normal in patients with hyperthyroidism due to TSH-producing tumors. Such lesions are rare, comprising only approximately 0.5% of all pituitary tumors, and are typically macroadenomas.
   b. **Central resistance to thyroid hormone.** This rare genetic disorder is characterized by **elevated serum T_4 and T_3 levels and inappropriately normal or mildly elevated TSH concentrations**. As with patients with TSH-producing pituitary tumors, awareness of this disorder will prevent inappropriate therapy for hyperthyroidism.

D. Other uses for serum TSH.

In addition to screening for thyroid dysfunction, measurement of serum TSH is useful for **(a)** assessing adequacy of thyroid hormone replacement in patients with hypothyroidism and **(b)** assessing adequacy of thyroid hormone–suppressive therapy in patients with differentiated thyroid cancer.

IV. EFFECTS OF DRUGS ON THYROID FUNCTION (Table 36-5)

Many pharmacologic agents can significantly affect thyroid function by **(a)** altering central regulation of TSH secretion, **(b)** altering thyroid hormone synthesis or release, **(c)** affecting the concentration of thyroid-binding proteins and binding affinity of thyroid hormones for proteins, **(d)** altering peripheral thyroid hormone metabolism or thyroid hormone uptake into cells, and **(e)** impairing gastrointestinal absorption of administered hormones.

A. Drugs that affect central regulation of TSH secretion

1. **Dopamine,** an agent that is commonly used in the intensive care unit, causes central inhibition of TSH secretion; therefore, a low TSH in a patient receiving dopamine is often not reliable. The degree of TSH inhibition with dopamine is insufficient to result in central hypothyroidism, however.
2. **Glucocorticoids,** when given in pharmacologic amounts, inhibit TSH secretion. Hospitalized patients receiving steroids frequently have **low TSH** levels. As with dopamine, patients receiving glucocorticoids do not become hypothyroid because of inhibition of TSH (see Section IV.D.1).
3. **Octreotide,** a synthetic analog of somatostatin used in the management of acromegaly, **decreases TSH** levels but does not cause hypothyroidism because the effects on TSH secretion are minor.
4. **Bexarotene,** a retinoid x-receptor ligand, is currently approved for the treatment of cutaneous T-cell lymphoma. It affects thyroid function by inhibiting TSH production and results in secondary hypothyroidism.

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TABLE 36-5 **Effects of Pharmacologic Agents on Thyroid Function**

Site of action and drug	Test: Serum T_4	Free T_4	T_3	TSH	Comments
Hypothalamic-Pituitary Axis					
Dopamine	↓	↓	↓	↓	
Levodopa	N	N	N	↓	Clinical hypothyroidism not seen in normal individuals
Glucocorticoids	↓	↓	↓	↓	
Amphetamines	↑	↑	↑	N or ↑	Clinical effects minor
Metoclopramide	N	N	N	↑	TSH increase is transient
Bexarotene	↓	↓	↓	↓	Clinically hypothyroid
Thyroid Synthesis/Release					
Sulfonamides, sulfonylureas, PAS, phenylbutazone, aminoglutethimide, 6-mercaptopurine	↓	↓	↓	↑	Effects minor and usually with underlying thyroid abnormality
Lithium carbonate	↓	↓	↓	↑	Synergistic with iodides producing hypothyroidism
Iodides	↓	↓	↓	↑	
Sunitinib	↓	↓	↓	↑	
Altered Protein Binding					
Estrogens, perphenazine, clofibrate, heroin, methadone	↑	N	↑	N	Increased TBG concentrations; normal FT_4, FT_3
Androgens, danazol, glucocorticoids, L-asparaginase,	↓	N	↓	N	Decreased TBG concentrations; normal FT_4
Phenytoin	↓	↓	N	N	Inhibits T_4, T_3 binding to TBG; additional effects on metabolism (see text)
Salsalate, salicylates, fenclofenac	↓	N		N	Inhibits T_4, T_3 binding to TBG
Altered Thyroid Hormone Metabolism					
Propranolol, propylthiouracil, glucocorticoids	N	N	↓	N	Inhibits peripheral T_4 to T_3 conversion
Ipodate, iopanoic acid, amiodarone	↑	↑	↑	↓	Inhibits intrapituitary as well as peripheral T_4 to T_3 conversion; also iodide effects with amiodarone
Phenytoin	↓	↓	N	N	Accelerates cell uptake and disposal of T_4 clinical changes observed in T_4-treated patients with hypothyroidism
Phenobarbital	↓	↓		↑	Accelerates disposal; changes noted only in T_4-treated patients
Heparin	N	↑	N	N	Decreased cell uptake of T_4
Ipodate	↑	↑	↓	↑	Decreased cell uptake of T_4

Inhibits Gastrointestinal Absorption of Thyroid Hormone					
Cholestyramine, colestipol, ferrous sulfate, calcium carbonate, aluminum hydroxide, sucralfate, proton pump inhibitors, orlistat	↓	↓	↓	↑	Take L-T_4 at least 4 hr apart

FT_3, free tri-iodothyronine; FT_4, free thyroxine; N, normal; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone; T_3, tri-iodothyronine; T_4, thyroxine; ↑, elevated; ↓, lowered.

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B. Drugs that affect thyroid hormone synthesis or release

1. Decreased thyroid function

a. Iodides may cause hypothyroidism by inhibiting thyroid hormone release. Hypothyroidism secondary to iodides most often occurs in individuals with underlying thyroid disease, especially chronic autoimmune (Hashimoto) thyroiditis or previously treated Graves disease. Common over-the-counter cold preparations contain sufficient amounts of iodides to result in thyroid hormone **inhibition**.

Amiodarone, an antiarrhythmic drug, contains 37% iodine by weight and has been shown to produce primary hypothyroidism in approximately 10% of patients treated with this agent in the United States, particularly those individuals with underlying chronic autoimmune thyroiditis. This is due to a failure to **escape from the Wolff-Chaikoff effect**, resulting in preserved radioiodine uptake.

b. Lithium carbonate, an agent used in the management of manic depression, inhibits thyroid hormone release, resulting in decreased T_4 and increased TSH concentrations in 15% to 40% of patients, most with underlying autoimmune thyroid disease. If used in conjunction with iodides, the effects tend to be significant.

c. Ketoconazole, an antifungal agent known to inhibit adrenal steroidogenesis, also has been reported to cause hypothyroidism, probably by impairing thyroid hormone synthesis. The clinical effects of ketoconazole are minor.

d. Cytokines (see Chapter 37), especially interferon-α and interleukin-2, may cause hypothyroidism, usually in individuals with underlying chronic autoimmune thyroiditis.

e. **Thionamides** (methimazole and propylthiouracil), used in the treatment of thyrotoxicosis, decrease thyroid hormone synthesis.
f. **Tyrosine kinase inhibitors (sunitinib, sorafenib, and imatinib),** used for the treatment of advanced renal cell cancer, refractory gastrointestinal stromal tumors, and hepatocellular cancer, can cause hypothyroidism in up to 40% of patients. The mechanism is not completely known, but it may relate to a form of thyroiditis, because a significant number of patients have suppressed TSH levels prior to developing primary hypothyroidism (with elevated TSH levels). It has also been associated with increased type 3 deiodination activity and subsequently decreased T_4 and T_3.
g. **Checkpoint inhibitor immunotherapy (cytotoxic T-lymphocyte–associated antigen 4 and programmed cell death-1 receptor antibodies)**, used in p. 497p. 498advanced melanoma and other malignancies, is associated with hypohysitis and subsequent central hypothyroidism and primary hypothyroidism. Frequency of endocrinopathies is not known, but it is recommended that TSH is checked prior to each dose.

2. **Increased thyroid function**
   a. In addition to **inhibiting** thyroid function, iodides can **increase** thyroid function. Patients with nodular goiter who have autonomously functioning thyroid tissue may develop hyperthyroidism following exogenous iodide ingestion or intravenous administration, usually within 2 to 3 weeks.
   b. **Amiodarone** may also cause hyperthyroidism, either because of iodide excess in patients with underlying goiter or because of induction of a painless thyroiditis-type syndrome in patients without a history of thyroid disease (see Chapter 37).
   c. **Cytokines** may result in hyperthyroidism by producing a thyroiditis-typical response (see Chapter 37).
   d. **Lithium** has been associated with an increased risk of thyrotoxicosis. The mechanism is unclear; however, one study reported increased incidence of silent thyroiditis.

3. **Hyperthyroidism and hypothyroidism**
   a. **Alemtuzumab.** A humanized anti-CD52 mAb recently approved for the treatment of multiple sclerosis is associated with a risk of autoimmunity, including thyroid disease in approximately 30% of patients. Graves accounts for half of the cases. Periodic thyroid function tests should be obtained before treatment.

C. Drugs that affect thyroid-binding proteins

1. **Alterations in thyroid-binding protein concentrations**
   a. **Increased TBG** concentration is usually caused by pregnancy or estrogen-containing compounds, but may also be increased by other drugs (see Table 36-1).
   b. **Decreased TBG** concentrations are produced by androgens, such as danazol (an agent used in the treatment of endometriosis) and L-asparaginase (an anticancer drug).
   c. The net effect of altering TBG concentrations is to produce corresponding increases in total T_4 and T_3 when TBG is increased, or, when TBG levels are lowered, a decrease in T_4 and T_3 levels. Free hormone concentrations remain unaltered, and patients are euthyroid.
2. **Alterations in thyroid-binding protein affinity.** Several drugs inhibit binding of thyroid hormone to TBG. Clinically, the most frequently observed changes occur with **phenytoin**, where the effect is to lower total T_4 levels without changing TSH. High-dose **furosemide**, fenclofenac, and salsalate may also cause similar changes. **Heparin** may also cause acute and transient increases in serum FT_4 because of displacement of T_4 from binding proteins.

D. Drugs that alter metabolism of thyroid hormone

1. **Peripheral T_4 deiodination.** A number of pharmacologic agents inhibit T_4 to T_3 deiodination, with a resultant **decrease in T_3. Propranolol, propylthiouracil, and glucocorticoids** exert their effects primarily via hepatic and renal deiodinative pathways. Iodate, iopanoic acid, and amiodarone, in addition to decreasing peripheral T_4 to T_3 conversion, inhibit intrapituitary T_4 to T_3 conversion. This may result in a mild increase in TSH secretion, with a secondary mild increase in serum T_4 and FT_4 levels.

Increased T_4 levels have also been observed in patients taking large doses of propranolol.

2. **Agents that affect cellular uptake of thyroid hormone.** Phenytoin appears to increase the cellular uptake of T_4 into tissues; in addition, it accelerates T_4 metabolism, by increased liver activity of cytochrome P450. This is important to recognize because patients taking thyroid hormone for hypothyroidism who also take phenytoin will require greater doses of thyroid replacement. Similarly, **phenobarbital**, as well as the antituberculosis drug rifampin, appears to accelerate T_4 metabolism, and hypothyroid patients receiving replacement therapy may also require increased doses of T_4.

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E. Agents that affect absorption of administered thyroid hormone

The hypolipidemic agents cholestyramine and colestipol, as well as soybean flour, inhibit absorption of exogenous thyroid hormone by binding T_4 and T_3 in the gut. The anti-inflammatory agent **sucralfate** may also have similar effects, as does ferrous sulfate, especially when taken with thyroid hormone. Calcium carbonate, when ingested along with levothyroxine, has also been shown to cause mild inhibition of thyroxine absorption. **Orlistat**, a lipase inhibitor and weight loss medication, may also have a similar effect. Therefore, patients taking thyroid hormone should be instructed to take their medication several hours apart from drugs that interfere with thyroid hormone absorption.

F. Drugs that affect the thyroid function tests

Biotin, a B vitamin, often marketed as vitamin B_7, vitamin H, and coenzyme R, for improvement in hair, nails, and skin, has been found to cause abnormal thyroid function tests (TSH, FT_4 and total T_4, T_3, and thyrotropin or TSH receptor antibodies [TRAB]). Almost all immunoassays rely on a biotin–streptavidin attraction. Large amounts of biotin in the sample can interfere with this process leading to falsely high, such as with competitive immunoassays (T_4, T_3), or low result, as with immunometric assays.

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37 Thyroiditis

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The various types of thyroiditis encompass a heterogeneous group of inflammatory disorders of diverse etiologies and clinical features. With all forms of thyroiditis, destruction of the normal follicular architecture occurs, yet each disorder has distinctive histologic characteristics. Varying classifications of thyroid inflammatory disorders have been proposed. For the purpose of this chapter, thyroiditis is subdivided into painful and painless types (Table 37-1).

I. PAINFUL THYROIDITIS

A. Acute thyroiditis (suppurative thyroiditis, acute bacterial thyroiditis, and pyogenic thyroiditis)

1. **Etiology.** This rare disorder generally occurs only in immunocompromised hosts, although before the advent of antimicrobial therapy, it was typically associated with mastoiditis or severe pharyngeal infections. It is usually caused by a bacterial pathogen, most commonly *Staphylococcus aureus*, *Streptococcus hemolytica*, *Streptococcus pneumoniae*, or anaerobic streptococcal organisms. Infection due to other bacterial pathogens, such as *Meningococcus*, *Salmonella*, and *Escherichia coli*, has been reported, as well as fungal infections such as coccidioidomycosis. Infection occurs either secondarily to hematogeneous or lymphatic spread, or as a result of direct introduction of an infective agent by direct trauma. Persistent thyroglossal duct abnormalities have also been associated with acute thyroiditis.

TABLE 37-1 Classification of Inflammatory Thyroid Disorders

Painful Thyroiditis

Infectious agents

- Pyogenic (bacterial) thyroiditis
- Subacute viral thyroiditis
- Opportunistic agents (e.g., *Pneumocystis carinii*, *Mycobacteriae*, *Aspergillus*)

Trauma

- Radiation thyroiditis

- Direct trauma (e.g., fine-needle aspiration, surgery, palpation)

Painless Thyroiditis

Spontaneous disorders

- Chronic autoimmune (Hashimoto) thyroiditis
- Subacute lymphocytic (postpartum) thyroiditis
- Subacute lymphocytic (sporadic) thyroiditis

Pharmacologic agents

- Cytokines (interferon-*α*, interleukin 2)
- Amiodarone-induced thyroiditis
- Lithium carbonate

Invasive fibrous (Riedel) thyroiditis

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TABLE 37-2 Differential Diagnosis of the Painful Neck Mass

Subacute viral thyroiditis
Hemorrhage into thyroid cyst or nodule
Acute bacterial thyroiditis
Infected thyroglossal duct cyst
Infected branchial cleft cyst
Rapidly enlarging thyroid cancer
Painful Hashimoto thyroiditis
Radioactive thyroiditis
Trauma-induced thyroiditis
Cellulitis of the anterior neck
Note that subacute viral thyroiditis and hemorrhage into a cyst or nodule constitute the overwhelming majority of painful thyroid lesions.

2. **Clinical features.** Fever, chills, and other systemic signs or symptoms of abscess formation are present. Rapid onset of anterior neck pain and swelling are usual, with pain occasionally radiating to the ear or mandible. The physical examination is notable for the presence of a tender, fluctuant mass, with erythema of the overlying skin.
3. **Laboratory tests.** Leukocytosis with a left shift is usually present. Thyroid hormone concentrations in blood are usually normal, although hyperthyroxinemia has been reported, probably

as a result of discharge of preformed hormone. The thyroid scan (which is indicated in any patient with a tender anterior neck mass) reveals an absence of isotope uptake in the involved area. If acute thyroiditis is suspected, fine-needle aspiration should be performed, and appropriate smears and cultures obtained.

4. **Differential diagnosis.** The differential diagnosis includes any disorder associated with an acutely tender, painful anterior neck mass, including subacute thyroiditis (SAT), cellulitis of the anterior neck, acute hemorrhage into a thyroid cyst, adenoma or carcinoma, anterior deep neck space infection, infected thyroglossal duct cyst, and infected branchial cleft cyst (Table 37-2).
5. **Treatment.** Parenteral antibiotics should be administered according to the specific pathogen identified. If fluctuance is present, incision and drainage are required. Bacterial thyroiditis must be managed early and aggressively because abscess formation can occasionally dissect downward into the mediastinum. Recurrences of the disorder are very rare, as is permanent thyroid dysfunction. If recurrence of acute thyroiditis occurs, an examination is indicated to facilitate discovery of an undiagnosed defect, such as an internal fistula or thyroglossal duct cyst.

B. SAT (viral thyroiditis, subacute granulomatous thyroiditis, de Quervain thyroiditis, and giant cell thyroiditis)

1. **Etiology.** SAT is most likely viral in origin. Viruses implicated to be responsible for the disorder include coxsackievirus, adenovirus, mumps virus, echovirus, influenza, and the Epstein-Barr virus. Clinical evidence suggesting a viral cause includes reports of outbreaks of infection, the common presence of a viral-like prodrome, and a summer and fall seasonal distribution of the illness. In addition, convalescent sera to viral antibodies are present in patients with SAT.
2. **Clinical features.** The most common symptom is unilateral anterior neck pain, often associated with radiation of pain to the ear or mandible. The pain is often preceded by a few weeks of myalgias, low-grade fever, malaise, and sore throat. Dysphagia is also common. Symptoms of thyrotoxicosis are common and include tachycardia, palpitations, weight loss, nervousness, and diaphoresis. As the disorder progresses, pain often migrates to the contralateral side.

Physical examination reveals a very tender, hard, ill-defined mass that is usually unilateral, although tenderness of the opposite lobe may be present. p. 502p. 503Tenderness is often so extreme that palpation is limited. Tachycardia, warm skin, and a fine tremor of the hands are also observed when hyperthyroidism is present.

3. **Laboratory tests**
   - **a.** The complete blood count usually reveals a mild normochromic-normocytic anemia and a normal total white blood cell count. However, mild leukocytosis may occur. The erythrocyte sedimentation rate is usually >50 mm/hour. The serum thyroxine (T_4) or free thyroxine (FT_4) and tri-iodothyronine (T_3) levels are often elevated, and the serum thyrotropin (thyroid-stimulating hormone or TSH) is suppressed. The severity of the thyrotoxicosis correlates with the degree of the destructive process. There tends to be a disproportionate elevation of serum T_4 relative to serum T_3, because the blood levels reflect proportional amounts of preformed hormones released into the circulation during the active inflammatory phase.
   - **b.** Thyroid autoantibodies (antimicrosomal [thyroid peroxidase antibody or TPO] and antithyroglobulin) may be mildly elevated several weeks after the onset of symptoms and then return to normal, usually within a few months. The transient antibody elevation is probably a response to the release of thyroglobulin into the circulation and not an autoimmune response. The serum thyroglobulin is significantly elevated during active inflammation.
   - **c.** The thyroid radioactive iodine uptake (RAIU) is always suppressed during the acute phase of the illness, usually to <2% at 24 hours. The suppressed uptake is a result of disruption of the iodine-trapping mechanism from the inflammation and cell destruction. The RAIU test is helpful to confirm the clinical diagnosis of SAT and exclude other disorders associated with a painful anterior neck mass.
4. **Differential diagnosis.** SAT must be differentiated from both euthyroid and hyperthyroid states associated with pain in the

anterior neck (Table 37-2).

5. **Clinical course and treatment.** SAT typically consists of four phases.
   - **a.** The initial, or acute, phase is associated with pain, tenderness, a suppressed RAIU, and hyperthyroidism. This phase lasts for anywhere from 4 to 12 weeks, during which treatment is directed toward relief of pain, inflammation, and symptoms of hyperthyroidism. **Prednisone**, 10 to 20 mg orally, 2 to 4 times a day, is virtually always effective in reducing pain, often within several hours of the initial dose. Indeed, if the pain does not abate quickly, the clinician should question the diagnosis of SAT. After 1 to 2 weeks, the prednisone can be tapered by 5 mg every 2 to 3 days. An increase in pain may occur during steroid tapering, at which time the prednisone dosage can be increased again and the tapering process resumed. Very mild bouts of SAT may be treated with nonsteroidal anti-inflammatory agents. Symptoms of thyrotoxicosis may be controlled with the use of β-adrenergic–blocking agents. **Antithyroid drugs are not indicated**, nor would they be of any benefit.
   - **b.** Following the acute painful thyrotoxic phase, euthyroidism is restored, because the thyroid becomes depleted of stored hormone. Patients may either remain euthyroid or, in more severe cases, progress to a hypothyroid phase.
   - **c.** The hypothyroid phase is characterized by biochemical and, at times, symptomatic hypothyroidism. The hypothyroid phase rarely lasts longer than 2 to 3 months, and during this interval, thyroid hormone replacement, in the form of sodium levothyroxine (L-T_4), 0.10 to 0.15 mg/day, should be given. After several months of treatment, L-T_4 can be discontinued and a serum TSH repeated in 6 to 8 weeks.
   - **d.** Following the hypothyroid phase, *recovery* occurs, and the normal histologic features and secretory capacity of the thyroid are restored. During this phase, plasma thyroid hormone levels are normal, but the RAIU can be temporarily elevated because of avid iodine trapping by the recovering thyroid. It should be emphasized that it is unnecessary to perform RAIU tests during the course of SAT, except initially to confirm the diagnosis. Although permanent hypothyroidism has been reported

following SAT, it is uncommon, and patients almost always return to euthyroidism. However, it has been shown that p. 503p. 504administration of exogenous iodides in patients with prior episodes of SAT may result in hypothyroidism. Thus, even though SAT is nearly always self-limiting, patients with a history of SAT who receive iodides should be evaluated for hypothyroidism with a serum TSH.

C. Radiation thyroiditis

Radiation thyroiditis is usually characterized by mild-to-moderate anterior neck pain and thyroid tenderness, and may occur approximately a week after receiving ^{131}I for thyrotoxic Graves disease. Symptoms may last for up to a month after ^{131}I administration.

Patients treated with ^{131}I for thyroid cancer may also develop radiation thyroiditis, especially if a significant amount of normal thyroid tissue was left remaining after thyroidectomy. If pain and tenderness is significant, short-term prednisone (20 to 40 mg/day) may be used.

D. Pneumocystis carinii thyroiditis

Pneumocystis carinii (PCC) thyroiditis has been reported by several authors, and its clinical characteristics are similar to those of SAT, including neck pain, either hyperthyroidism or hypothyroidism, and a suppressed RAIU. **PCC** should be considered in immunocompromised patients with neck pain. The diagnosis can be established only by performing a fine-needle aspiration and staining for **PCC** organisms with Gomori silver methenamine. This form of thyroiditis has become extremely rare, because aerosolized pentamidine is no longer used for PCC prophylaxis.

II. PAINLESS THYROIDITIS

A. Spontaneous disorders

1. Subacute lymphocytic thyroiditis (painless thyroiditis, lymphocytic thyroiditis, and silent thyroiditis)

a. Background. This disorder is characterized by symptoms of thyrotoxicosis, elevated serum T_4 and T_3 levels, a suppressed serum TSH, a low RAIU, and a painless nontender goiter.

Subacute lymphocytic thyroiditis (painless thyroiditis [PT] or lymphocytic thyroiditis [LT]) usually occurs in women, and most patients are seen postpartum. Sporadic cases are uncommon. The disorder is reported to occur in approximately 8% of postpartum women in North America.

b. Etiology. The subacute lymphocytic variant of PT is most likely autoimmune in origin and is probably a variant of chronic autoimmune (Hashimoto) thyroiditis (HT) (see later). Approximately 80% of patients have elevated levels of thyroid microsomal (TPO) antibodies. A genetic predisposition is also likely because there is a significant prevalence of human leukocyte antigen (HLA)-DRw3 and HLA-DRw5 histocompatibility antigens. Because of the similar clinical course that LT shares with SAT, a viral cause has also been suggested.

c. Clinical features

i. Hyperthyroid symptoms, such as nervousness, palpitations, anxiety, diaphoresis, heat intolerance, and weight loss, are common, varying from mild to marked, depending on the severity of the disorder. Postpartum cases occur anywhere from 6 weeks to 3 months after delivery.

ii. Physical examination often discloses a mildly enlarged, nontender goiter, although up to 50% of patients have been reported to have absence of palpable goiter.

iii. The clinical features of PT may also be very difficult to distinguish from those of Graves disease. Clinical and laboratory findings that may be helpful in differentiating the two disorders are listed in Table 37-3.

d. Laboratory tests

i. Serum total and free T_4 and T_3 levels are mildly to moderately elevated, and the serum TSH is suppressed. Serum T_3 levels are less elevated proportional to T_4 levels than is observed with Graves disease. The ratio of T_3 to T_4 has been suggested as being helpful in distinguishing LT from Graves thyrotoxicosis, in which T_3 levels are considerably higher because of preferential secretion of T_3 by thyroid-stimulating immunoglobulin.

TABLE 37-3 Differentiation between Painless Lymphocytic Thyroiditis and Graves Hyperthyroidism

Clinical feature	Lymphocytic thyroiditis	Graves thyroiditis
Onset	Abrupt	Gradual
Severity of symptoms	Mild to moderate	Moderate to marked
Duration of symptoms (usual)	<3 mo	>3 mo
Goiter	Firm, diffuse, mildly enlarged, or absent	Mildly to moderately firm, diffuse, large
Thyroid bruit	Absent	Often present
Exophthalmos, dermopathy	Absent	May be present
T_4/T_3 ratio	<20:1	>20:1
RAIU	Suppressed	Elevated

RAIU, radioactive iodine uptake; T_3, tri-iodothyronine; T_4, thyroxine.

ii. The RAIU is suppressed, usually to <3% at 24 hours, during the hyperthyroid phase of LT. It is essential to obtain an RAIU test unless the diagnosis of Graves disease is evident on clinical grounds.

e. Differential diagnosis. Once Graves disease has been excluded, the differential diagnosis of painless hyperthyroidism associated with a low RAIU must be considered (see Chapter 38). Most of the disorders can be readily distinguished from each other based on a careful history and physical examination.

f. Clinical course and treatment. The clinical course of PT is similar to that of SAT:

i. There is an initial hyperthyroid phase lasting from approximately 6 weeks to 3 or 4 months (rarely longer). Treatment during this phase is directed to relief of hyperthyroid symptoms, using β-blockers. Antithyroid drugs, such as methimazole and propylthiouracil, are ineffective and should be avoided.

ii. Following the hyperthyroid phase, there is a euthyroid interval of approximately 3 to 6 weeks, during which the

thyroid becomes depleted of hormone.

iii. This is followed in 25% to 40% of patients by a hypothyroid period, during which symptomatic and biochemical hypothyroidism may occur. Hypothyroidism usually lasts no longer than 2 to 3 months, and thyroid hormone supplementation with L-T_4 may be required.

iv. Following the hypothyroid phase, patients usually remain clinically euthyroid. Persistent thyroid abnormalities, such as goiter and/or frank hypothyroidism, occur in up to one third of patients. Thus, long-term follow-up of patients who have had an episode of PT is necessary. Patients who have had postpartum PT are at significant risk of experiencing a recurrence following a subsequent pregnancy. Postpartum thyroiditis occurs in approximately 25% of women with type 1 diabetes mellitus.

2. **HT (also known as chronic autoimmune thyroiditis, chronic LT, and chronic thyroiditis)**

   a. **Etiology.** HT is an organ-specific autoimmune disorder that is the most common thyroid inflammatory disease. The basic defect underlying this disorder likely is due to an abnormality in suppressor T lymphocytes that allows helper T lymphocytes to interact with specific antigens directed against the thyroid cell. A genetic predisposition is suggested because of the frequent occurrence of HLA-DR5 and HLA-B8 histocompatibility antigens in patients with HT. The disorder may be associated with other organ-specific autoimmune disorders (Table 37-4).

   b. **Clinical manifestations**

      i. HT may exhibit a wide spectrum of clinical features, ranging from an asymptomatic euthyroid individual with a goiter to frank myxedema. p. 505p. 506It is the principal cause of hypothyroidism in the iodine-sufficient world. The most common presentation is that of a middle-aged woman with a small, asymptomatic goiter. Approximately 95% of patients are women. Occasionally, patients may complain of mild anterior neck discomfort, especially if the thyroid is enlarging rapidly, although this is uncommon. In general, thyroid enlargement is insidious and

asymptomatic. Symptoms of hypothyroidism may be present, depending on the degree of hypothyroidism, if present. Hypothyroidism is the presenting manifestation in approximately 20% of patients.

TABLE 37-4 Differentiating Features of Amiodarone-Induced Hyperthyroidism

	Type 1 (Iodine excess)	Type 2 (Thyroiditis)
History of thyroid disease	Often	No
Goiter	Nodular	Small or absent
FT_4	↑, ↑↑	↑, ↑↑
FT_3	↑	↑
TSH	↓	↓
IL-6	N or slightly ↑	↑
Thyroid RAIU	↓, N, occasionally ↑	↓
Color Doppler ultrasound	Increased flow	Decreased flow

FT_3, free tri-iodothonine; FT_4, free thyroxine; IL-6, interleukin 6; N, normal; RAIU, radioactive iodine uptake; ↑, elevated; ↓, lowered.

ii. Physical examination usually discloses a symmetrically enlarged, very firm goiter; a pebbly or knobby consistency is common. Occasionally, patients present with a single thyroid nodule.

iii. Although hypothyroidism is the typical form of thyroid dysfunction associated with HT, a smaller subset of patients (probably 2% to 4%) present with hyperthyroidism and have "hashitoxicosis." Thyroid-stimulating immunoglobulin has been detected in the sera of some of these patients, suggesting commonality with Graves disease.

c. Laboratory tests

i. Approximately 80% of patients with HT have normal circulating T_4 and TSH levels at the time of diagnosis. Antimicrosomal (TPO) antibodies are elevated in >90% of patients. Although antithyroglobulin antibodies are also generally elevated, performing both tests is unnecessary.

ii. The presence of a rapidly enlarging, firm-to-hard goiter and strikingly elevated thyroid TPO antibodies, especially in

elderly patients, should alert the clinician to the possibility of primary thyroid lymphoma. However, HT is not felt to be etiologic in the development of lymphoma.

iii. The thyroid ultrasound (not recommended in routine evaluation) reveals a heterogeneous, micronodular pattern, often with increased blood flow on Doppler exam.

d. Treatment

i. L-T_4 is the treatment of choice for HT when hypothyroidism is present. Goiters tend to shrink with normalization of TSH levels. Thyroid hormone should be continued indefinitely in hypothyroid patients with HT. Patients with mild thyroid failure (i.e., normal serum T_4 levels and elevated TSH concentrations) have an approximately 5% per year likelihood of becoming overtly hypothyroid, so L-T_4 administration may be warranted in such patients.

ii. Pharmacologic doses of glucocorticoids have been reported to be effective in HT when there is a rapidly enlarging goiter associated with pressure symptoms. Such a presentation is rare, though, and if glucocorticoids are employed, their use should be brief.

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iii. Surgery is indicated in HT only if persistent significant symptoms of obstruction are present. Such a scenario is rare.

3. Riedel thyroiditis (Riedel struma)

Riedel thyroiditis is an extremely rare inflammatory disorder of uncertain etiology, and earlier suggestions that it might be a fibroid variant of HT have not been substantiated. Clinically, Riedel thyroiditis presents with pressure symptoms, and on examination an extremely hard, “woody,” immobile thyroid gland is palpated. Riedel thyroiditis has a female to male prevalence of 3:1 and usually occurs between 30 and 60 years of age. The disorder may be associated with other focal sclerosing syndromes, including retroperitoneal and mediastinal fibrosis, and ascending cholangitis, so patients with Riedel thyroiditis should be evaluated for the possibility of other sclerosing conditions. Thyroid function tests

reveal hypothyroidism in approximately 30% of patients. Thyroid antibody tests are usually negative. Ultrasound of the thyroid reveals an "invasive"-type picture, with obliteration of the normal thyroid margins.

Management of Riedel thyroiditis is surgical for patients in whom symptoms of obstruction occur. Recently, **tamoxifen** has been shown to be helpful in some patients, because of its inhibitory effects on growth factors. Glucocorticoids are rarely effective. L-T_4 is required for management of hypothyroidism but is not effective for goiter shrinkage.

B. PT due to pharmacologic agents

1. Cytokines

a. Interferon-*α* (IFN-*α*), which is used in the management of chronic hepatitis C (HCV), may be associated with a LT type of syndrome. Patients with IFN-*α*–induced thyroid dysfunction may present with hypothyroidism or hyperthyroidism. Predisposing factors for the development of IFN-*α*–associated thyroid dysfunction include female sex, older age, longer duration of IFN treatment, and the preexistence of anti-TPO antibodies. Thyroid abnormalities may occur in up to 60% of patients receiving IFN-*α* who have positive TPO antibodies prior to treatment, whereas only approximately 3% of patients who develop thyroid dysfunction have negative TPO antibodies.

The mechanism for IFN-*α*–induced thyroid dysfunction is likely related to the enhancement of the autoimmune process. Also, IFN-*α* therapy has been shown to induce TPO antibody production in patients with HCV.

i. Clinical features. IFN-*α*–induced thyroid dysfunction may present with either hypothyroidism or hyperthyroidism. Differentiating hypothyroidism from the fatigue normally associated with IFN-*α* therapy may be difficult, underscoring the importance of monitoring all patients receiving IFN-*α* with periodic serum TSH levels.

A small, painless, firm goiter may be present, especially in patients with underlying HT, although goiter may be absent.

ii. Laboratory findings. Thyroid function test results of IFN-*α*–associated thyroid dysfunction are similar to those

noted with painless LT. Patients who present with hyperthyroidism should be evaluated with an RAIU test to exclude the possibility of Graves thyrotoxicosis.

iii. **Treatment.** Management of IFN-*α*–induced thyroid dysfunction depends on the severity of clinical manifestations and the degree of the biochemical abnormality. Hypothyroidism should be treated with L-T_4 for the duration of IFN-*α* treatment, and patients should be monitored with periodic serum TSH levels. After IFN-*α* is discontinued, L-T_4 may be stopped and a serum TSH checked 4 to 6 weeks later. Hypothyroidism may persist for a number of months (or even permanently) in some patients.

The symptoms of hyperthyroidism associated with IFN-*α* therapy may be managed with *β*-blockers. Patients who have Graves disease (infrequent) should be treated with radioactive iodine rather than thionamide drugs because of the potential, albeit small, risk of liver damage from antithyroid drugs.

b. **Interleukin 2 (IL-2)** is used as an adjunctive therapy in the treatment of various malignancies, including metastatic solid tumors and leukemias, and may be p. 507p. 508associated with a painless LT type of syndrome. Prevalence rates have varied from 2% to 39% of IL-2–treated patients, and, as with IFN-*α*, female gender and preexistence of thyroid autoantibodies are risk factors for developing thyroid dysfunction. Like IFN-*α*, IL-2 probably activates the autoimmune process, because its administration is associated with the development of thyroid antibodies as well as an increase in titers of preexisting TPO antibodies. Of note is that combination immunotherapy with IFN-*α* and IL-2 results in an even greater prevalence of thyroid dysfunction than occurs with either agent alone.

The laboratory assessment, clinical features, and management of IL-2–associated thyroid dysfunction are the same as those associated with IFN-*α* therapy.

c. Sunitinib is a tyrosine kinase inhibitor, typically associated with hypothyroidism. It has been associated with a transient thyrotoxicosis in patients treated for metastatic renal cell carcinoma. Some of these patients went on to develop hypothyroidism.

2. Amiodarone-induced thyroiditis

a. Amiodarone, a potent antiarrhythmic agent containing 37% iodine, causes hyperthyroidism in approximately 3% of patients in the United States who take the medication. This contrasts with the approximately 10% of patients who develop amiodarone-associated hyperthyroidism who reside in iodine-deficient areas. Hyperthyroidism generally occurs within a few months after beginning the drug but may have its onset at any time after initiation of treatment. Symptoms of hyperthyroidism are often lacking, probably because of the β-blocker activity of amiodarone. However, patients are not protected from the tissue effects of thyrotoxicosis and may experience weight loss, worsening of arrhythmia, or development of congestive heart failure.

b. There are two types of amiodarone-induced hyperthyroidism: type 1 results from iodine excess and increased thyroid hormone synthesis, and type 2 is an inflammatory thyrodestructive process. It is important for the clinician to differentiate between the two types of amiodarone-induced hyperthyroidism because the treatment is different for each. The presence of a nodular goiter suggests iodine-induced hyperthyroidism, whereas the absence of thyroid enlargement suggests inflammatory thyroiditis. Table 37-4 outlines some diagnostic features of both types of disorders. The measurement of serum IL-6 levels may occasionally allow for differentiating between the two types of amiodarone-induced hyperthyroidism, although the amount of overlap limits its usefulness. Perhaps the most useful study is color flow on Doppler thyroid ultrasound; flow is increased in patients with type 1 and decreased in patients with type 2 amiodarone-induced thyrotoxicosis. RAIU is not as useful of a diagnostic test because the iodine in amiodarone interferes with uptake.

c. Treatment of type 2 amiodarone-induced hyperthyroidism consists of pharmacologic doses of glucocorticoids (e.g., as

prednisone, 40 mg/day) in divided doses. Thionamide agents are not helpful, although if the diagnosis is in question, a combination of glucocorticoids and thionamide drugs (which are usually reserved for type 1) may be indicated. Type 2 amiodarone-induced hyperthyroidism follows a course similar to that observed with other forms of PT or LT.

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38 Hypothyroidism and Hyperthyroidism

Jerome M. Hershman

I. HYPOTHYROIDISM

A. Definition

Hypothyroidism is a condition resulting from a lack of the effects of thyroid hormone on body tissues. Because thyroid hormone affects growth and development and regulates many cellular processes, the absence or deficiency of thyroid hormone has many detrimental consequences.

B. Causes of hypothyroidism

1. Infancy or childhood

- **a.** Maldevelopment—hypoplasia or aplasia
- **b.** Inborn deficiencies of biosynthesis or action of thyroid hormone
- **c.** Hashimoto thyroiditis
- **d.** Hypopituitarism or hypothalamic disease
- **e.** Severe iodine deficiency

2. Adults

- **a.** Hashimoto thyroiditis
- **b.** Lymphocytic thyroiditis following transient hyperthyroidism
- **c.** Thyroid ablation
  - **i.** Surgery
  - **ii.** Following ^{131}I therapy for hyperthyroidism
  - **iii.** Radiation of cervical neoplasms
- **d.** Hypopituitarism or hypothalamic disease
- **e.** Drugs
  - **i.** Iodine, inorganic or organic (e.g., amiodarone)
  - **ii.** Antithyroid: thionamides (methimazole and propylthiouracil [PTU]), potassium perchlorate, thiocyanate
  - **iii.** Lithium
  - **iv.** Interferon-α
  - **v.** Sunitinib
  - **vi.** Cytotoxic T-lymphocyte–associated antigen-4 and

programmed death receptor 1 immunotherapy

C. Incidence

1. Hypothyroidism is a common condition. Congenital hypothyroidism is diagnosed by screening methods in 1 of every 3 000 newborns. In adults > 65 years of age, the incidence is approximately 10%. The overall incidence in the population is 4.6%; 4.3% is subclinical, and 0.3% is overt.

D. Symptoms, signs, and pathophysiology

1. **Nervous system.** Patients with hypothyroidism may complain of forgetfulness, reduced memory, mental slowing, depression, paresthesia (sometimes associated with compression of nerves, such as carpal tunnel syndrome), ataxia, and reduced hearing. Tendon jerks show slowed or “hung-up” relaxation.
2. **Cardiovascular system.** There may be bradycardia, diastolic hypertension, reduced cardiac output, quiet heart sounds, a flabby myocardium, pericardial effusion, reduced voltage on the electrocardiogram and flat T waves, endothelial dysfunction, arterial stiffness, and dependent edema. Cardiomegaly seen on plain film is usually shown by echocardiography to be attributable to effusion.

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3. **Gastrointestinal system.** Constipation is common in hypothyroidism. Achlorhydria occurs, often associated with pernicious anemia. Ascitic fluid, like other serous effusions in myxedema, has a high-protein content.
4. **Renal system.** Reduced excretion of a water load may be associated with hyponatremia. Renal blood flow and glomerular filtration rate are reduced, but serum creatinine is normal.
5. **Pulmonary system.** Ventilatory responses to hypoxia and hypercapnia are reduced. Severe hypothyroidism may cause carbon dioxide retention. Pleural effusions have a high-protein content.
6. **Musculoskeletal system.** Arthralgia, joint effusions, muscle cramps, and stiff muscles occur. Serum creatinine phosphokinase may be very high.
7. **Hemopoiesis.** Anemia may occur, usually of the normocytic type. Megaloblastic anemia suggests coexisting pernicious anemia.
8. **Skin and hair.** The presence of dry, cool skin is common. Glycosaminoglycans, mainly hyaluronic acid, accumulate in skin

and subcutaneous tissues, causing retention of sodium and water. The face is puffy, and features are coarse. The skin has a sallow appearance and can be flaky. The skin may also be orange because of accumulation of carotene. The hair lacks luster. Lateral eyebrows thin out, and body hair is scanty.

9. **Reproductive system.** Menorrhagia from anovulatory cycles may occur, or the menses may become scanty and even cease completely because of deficient secretion of gonadotropins. In adolescents, there may be primary amenorrhea. Hyperprolactinemia occurs because of the absence of the inhibitory effect of thyroid hormone on prolactin secretion, resulting in galactorrhea and amenorrhea.
10. **Development.** Growth and development of children are retarded. Epiphyses remain open. Thyroid hormone plays an essential role in the synthesis, secretion, and action of growth hormone. Untreated hypothyroidism in pregnant women can result in reduced intellectual function of the progeny.
11. **Metabolic system.** Hypothermia is common. Intolerance of cold temperature is a specific finding. Hypercholesterolemia with increase in serum low-density lipoprotein (LDL) cholesterol occurs because of reduced number of LDL receptors. Hypertriglyceridemia may occur because of reduced degradation of lipoproteins and reduced lipoprotein lipase activity. Hereditary hyperlipidemic conditions are exacerbated by hypothyroidism. Weight gain is common despite reduced food intake, but severe obesity is rarely caused by hypothyroidism.
12. **Thyroid gland.** Enlargement of the thyroid gland in young children with hypothyroidism suggests a biosynthetic defect. Goitrous hypothyroidism in adults is caused by Hashimoto thyroiditis.

E. Diagnostic tests

1. Serum thyrotropin (thyroid-stimulating hormone or TSH) concentration and serum free thyroxine (T_4) concentration or free T_4 index are an excellent battery for diagnosis of hypothyroidism.
2. Serum **TSH** concentration (normal range, 0.4 to 4.0 mU/L) may be modestly elevated in the range of 4 to 10 mU/L in patients with normal free T_4 concentration and indicates subclinical hypothyroidism. Serum TSH values of 10 to 20 mU/L indicate

more severe impairment of thyroid function although the serum T_4 may still be normal. When serum TSH concentration exceeds 20 mU/L, it is likely that frank hypothyroidism is present. Because of the sensitivity of the serum TSH level as an indicator of primary hypothyroidism, serum TSH is the best method to screen for the disorder.

3. **Central hypothyroidism** is usually associated with other evidence of pituitary or hypothalamic dysfunction. Serum free T_4 and TSH concentrations are low. In some patients, especially those with hypothalamic lesions, serum TSH is in the normal range, but the TSH probably has reduced biologic activity. Magnetic resonance imaging may show the lesion, most commonly, a pituitary tumor. Enlargement of the pituitary also occurs in primary hypothyroidism as a result of hyperplasia of the thyrotropes. In response to thyroid hormone therapy, restoration of normal pituitary size occurs.

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F. Diagnosis of hypothyroidism in patients taking thyroid hormone

Many patients take thyroid hormone without an adequate diagnosis of hypothyroidism having been established. Typical faulty indications include fatigue, weight gain, and irregular menses. If both the patient and the doctor agree that the diagnosis was never adequately established, then the best approach to diagnosis involves **stopping the replacement therapy for 5 weeks**. At this time, the serum T_4 and TSH concentrations will indicate either a euthyroid state or primary hypothyroidism. If the tests are carried out 10 to 14 days after withdrawal of therapy, they may reflect physiologic hypothyroidism from the suppression of the pituitary-thyroid axis by the exogenous hormone. An alternative approach is reduction of the T_4 dose by half and then assessing thyroid function after 5 weeks. If the TSH is elevated above normal on the reduced dose, the patient has primary hypothyroidism.

G. Thyroid function and nonthyroid illness

1. **Tri-iodothyronine (T_3).** Severe systemic illness will reduce serum T_3 concentrations by blocking the extrathyroidal production

of T_3 from T_4. Inhibition of 5′-monodeiodination occurs in many illnesses, including liver disease, uremia, severe infections, diabetic ketoacidosis, general surgery, starvation, burns, and severe myocardial infarction.

2. **T_4.** With more severe illness, serum T_4 concentration falls to subnormal levels, and free T_4 concentration may be normal or low. Serum TSH is usually normal, or sometimes low. This condition may be interpreted as a transient form of central hypothyroidism that is an adaptation to severe catabolic illness. During recovery, serum TSH rises, sometimes to levels of 10 to 20 mU/mL, and T_3 and T_4 concentrations return to normal.

H. Therapy

1. Preparations

a. **Sodium levothyroxine.** The preparation of choice is synthetic sodium levothyroxine because it produces stable serum levels of both T_4 and T_3. The absorption is approximately 75%.

b. **Desiccated thyroid extract, United States Pharmacopeia (USP)** is an extract of pig thyroid glands, which is standardized based on its iodine content, although assays of the hormone content are also performed by the leading pharmaceutical manufacturers. It contains a T_4/T_3 ratio of about 4:1. Approximately 4 to 8 hours after ingestion, T_3 levels may rise to the supranormal range. The relative potency of desiccated thyroid to T_4 is 1:1 000 (1 mg desiccated thyroid is equivalent to 1 μg of synthetic T_4).

c. **Synthetic T_3 (liothyronine, Cytomel).** There are really no indications for chronic therapy with synthetic T_3. It is used only when rapid withdrawal of thyroid hormone therapy is planned and for some diagnostic tests. Absorption is approximately 90%. Patients taking T_3 therapy have elevated T_3 concentrations for several hours after ingestion, which gradually fall to much lower levels 24 hours later. Substitution of 12.5 μg of T_3 for 50 μg of T_4 as a component of therapy was reported to improve mood and psychometric parameters. However, several carefully performed studies could not confirm any psychological or

metabolic benefit from using T_3 together with T_4 for therapy of hypothyroidism.

d. Synthetic T_4-T_3 combination (Liotrix). This preparation was developed before it was appreciated that T_4 is converted to T_3 outside the thyroid. It has a synthetic T_4/T_3 molar ratio of 4:1 and is available in various doses.

2. **Young adults.** The usual replacement dose of T_4 is 1.5 to 1.7 μg/kg ideal body weight. The full replacement dose may be prescribed from the inception of therapy. In following patients, it is important to explain to the patient that clinical improvement occurs gradually over several weeks and that the full effect of therapy in restoring the euthyroid state is likely to take 2 to 3 months. Laboratory indices of response show a rise in serum free T_4 to the normal range within 2 weeks, but serum TSH concentrations require about 6 weeks to fall to normal. After this time, adjustment of the dose by 12.5 to 25 μg of T_4 is made to optimize the clinical response and bring the serum TSH into the mid-normal range. There are p. 512p. 513no worthwhile laboratory indices of the action of thyroid hormone, so reliance is placed mainly on serum TSH because it is more sensitive than clinical evaluation.
3. **Middle-aged patients.** Hypothyroid individuals in this age group who are otherwise healthy may be treated with approximately 1.5 μg T_4 per kilogram. If there is coexisting ischemic heart disease or chronic pulmonary disease, then it is best to initiate therapy with a small dose of T_4, such as 25 μg a day, and increase the dose by 25 μg each subsequent month depending on the clinical response. The basis for this "low and slow" approach is the fear that **(a)** restoration of the euthyroid state will increase demands and worsen angina, and **(b)** the heart is particularly susceptible to the chronotropic action of thyroid hormone, so fatal tachycardia may be induced in susceptible patients. This fear tends to be exaggerated and overemphasized. The "low and slow" approach leads to prolongation of the hypothyroid state, so the justification for it must be clearly apparent.
4. **Elderly patients.** In the elderly, it is best to assume that ischemic

heart disease may exist, possibly subclinically, and to initiate replacement therapy with a low dose of T_4, such as 25 μg/day. The dose may be increased every 4 to 6 weeks by 25 μg until the serum TSH is in the normal range.

5. **Pregnancy.** In pregnant women with preexisting hypothyroidism, the dose of thyroid hormone must be increased by 25% to 50% in pregnancy to maintain a normal serum TSH, preferably in the range of 0.5 to 2.5 mU/L. The increased requirement for thyroid hormone, based on elevation of serum TSH above normal, occurs early in pregnancy, usually by 8 weeks. Increasing the weekly dose by adding two extra tablets of the daily dose each week (9 tablets/week) is recommended as soon as pregnancy is detected. In the first trimester, the normal range for TSH is 0.1 to 2.5 mU/L. After delivery, the patient may return to the prepregnancy dose of T_4.

I. Subclinical hypothyroidism

Subclinical hypothyroidism is usually defined as an asymptomatic state in which free T_4 is normal, but serum TSH is elevated. If serum TSH is >10 mU/L, there is consensus that the patient should be treated with T_4 because of the likelihood that the patient will develop overt hypothyroidism with subnormal free T_4 and because this degree of subclinical hypothyroidism predisposes to cardiovascular disease. When the serum TSH is in the range of 4.5 to 10 mU/L, there is controversy about the efficacy of T_4 therapy. Many endocrinologists will treat such patients with T_4, especially if hypercholesterolemia or depression is present. Even in the absence of hyperlipidemia, a trial of therapy may be warranted to determine whether the patient experiences improvement (i.e., the therapy may provide the patient with more energy, a feeling of well-being, desirable weight reduction, improved bowel function, or other signs of better health even though the patient is not aware of these symptoms before therapy). Presumably, the normal serum free T_4 concentration before therapy did not reflect adequate tissue effects of thyroid hormone in such a patient. Unfortunately, it is difficult to differentiate this type of response from a placebo effect. Therefore, it is also reasonable to follow these patients without T_4 therapy by surveying thyroid function at 6-month intervals to determine whether thyroid failure has occurred, as indicated by

further increase in serum TSH and fall of the serum T_4 to subnormal level along with the appearance of clear-cut symptomatology. However, I prefer to treat anyone in whom the serum TSH is persistently and clearly elevated, because even minimal hypothyroidism may be a risk factor for atherosclerosis.

J. Coronary artery disease, elective surgery, and hypothyroidism

Occasionally, patients have both severe coronary artery disease and coexisting untreated hypothyroidism. In such patients, arteriography and coronary artery bypass procedures should be performed, if indicated, prior to initiation of therapy with thyroid hormone. Afterward, the patient will have better tolerance of the inotropic and chronotropic effects of thyroid hormone. Untreated hypothyroidism is probably not a major risk factor for general surgery, as was once believed. Nevertheless, in the absence of severe coronary artery disease, it is preferable to restore a euthyroid state before elective surgery. Urgent surgery need not be postponed because of hypothyroidism.

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K. Myxedema coma as the end result of long-standing untreated hypothyroidism

These patients have hypothermia, bradycardia, alveolar hypoventilation, typical myxedematous facies and skin, and severe obtundation or coma. Usually, the condition is precipitated by an intercurrent illness, such as an infection or stroke, or a sedative drug state from which the patient does not awaken. If untreated, mortality approaches 100%. This mortality is prevented with aggressive therapy, which consists of giving 300 to 500 μg sodium levothyroxine intravenously (IV). Subsequent parenteral dosages may be about 100 μg T_4 daily. Some authorities prefer to use IV T_3 in a dose of 10 to 20 μg every 4 to 8 hours for the first few days because of reduced conversion of T_4 to T_3 in myxedema. Therapy consisting of both T_4 and T_3 IV has also been advocated. The initial therapy is 250 μg T_4 plus 25 μg T_3 IV, followed by 10 μg T_3 every 8 hours until the patient responds. Supportive therapy and treatment of underlying diseases are essential. Rewarming the patient can be harmful because it can cause peripheral vasodilatation and consequent hypotension.

II. HYPERTHYROIDISM

A. Definition

Hyperthyroidism is the condition resulting from the effect of excessive amounts of thyroid hormones on body tissues. Thyrotoxicosis is a synonym. Some prefer to use the term "hyperthyroidism" in a narrower sense to denote the state in which the thyroid gland is producing too much thyroid hormone, in contrast to excessive ingestion of thyroid hormone medication or release of thyroid hormone in thyroiditis.

B. Causes (Table 38-1)

1. **Graves disease** is the most common cause of hyperthyroidism.
2. **Toxic multinodular** goiter is found mainly in the elderly and the middle-aged patients.
3. Administration of inorganic iodine, such as potassium iodide, or organic iodine compounds, such as **amiodarone**, to patients with multinodular goiter or a tendency p. 514p. 515for Graves disease may cause iodine-induced hyperthyroidism. Amiodarone also causes thyroiditis, resulting in thyrotoxicosis.

TABLE 38-1 Causes of Hyperthyroidism

Cause	Thyroid activator
Overproduction of Thyroid Hormone	
Graves disease	TSI
Toxic multinodular goiter	Autonomy or TSI
Autonomous hyperfunctioning adenoma	Activating TSH-R mutation
TSH-secreting pituitary adenoma	TSH
TSH overproduction due to pituitary resistance to the suppressive effect of thyroid hormone	TSH
Hydatidiform mole or choriocarcinoma	hCG
Hyperemesis gravidarum	hCG
Thyroid Destruction Resulting in Leakage of Thyroid Hormone	None
Lymphocytic thyroiditis	
Granulomatous (subacute) thyroiditis	
Other	
Thyrotoxicosis medicamentosa (or factitia)	
Struma ovarii	

Metastatic thyroid carcinoma
hCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin.

4. Iodine-induced thyrotoxicosis (the **Jod-Basedow phenomenon**) may also occur in <1% of those receiving iodine supplementation in regions of endemic goiter.
5. Most autonomous hyperfunctioning adenomas do not produce hyperthyroidism, but when the adenoma ("hot" nodule) exceeds 3 cm in diameter, this outcome is more likely. Activating mutations of the TSH receptor have been found in many of these adenomas.
6. The TSH-secreting pituitary adenoma is rare and usually relatively large, but TSH-secreting microadenomas have also been reported in 15% of the cases. The condition may be a part of another functioning pituitary tumor, such as one causing acromegaly or hyperprolactinemia; the serum TSH is elevated or inappropriately normal and does not suppress with administration of T_3.
7. The *pituitary may be resistant* to the suppressive effect of thyroid hormone, whereas other tissues are more sensitive to thyroid hormone; serum T_4 and T_3 concentrations in these patients are elevated, whereas serum TSH is inappropriately normal. The patients do not have neuroradiologic evidence of a pituitary tumor. These patients usually have mutations of the T_3 β-receptor that are responsible for the pituitary resistance.
8. Hydatidiform moles and choriocarcinomas secrete large amounts of human chorionic gonadotropin (hCG). When serum hCG concentrations exceed 200 IU/mL (several times the peak levels of normal pregnancy), hyperthyroidism may be present. hCG is a weak thyroid stimulator, triggers the TSH receptor, and causes hyperthyroidism in these patients. Removal of the mole or effective chemotherapy of the choriocarcinoma is curative. In hyperemesis gravidarum, hCG secretion is increased, and hyperthyroidism (gestational thyrotoxicosis) may occur.
9. **Thyroiditis.** See Chapter 37.
10. Excessive ingestion of thyroid hormone may cause thyrotoxicosis. Some patients are given excessive doses of thyroid hormone by their physicians, with poor rationale. Other patients take excessive

amounts surreptitiously, sometimes to achieve weight loss. These patients have small thyroid glands, low thyroid uptake of radioiodine, and low serum thyroglobulin levels, whereas patients with thyroiditis and low thyroid uptake have elevated serum thyroglobulin levels.

11. Ovarian teratomas with thyroid elements (struma ovarii) and large metastatic functioning follicular thyroid carcinomas are very rare causes of hyperthyroidism.

C. Frequency

Graves disease is the most common cause of hyperthyroidism and is fairly common in the population. Based on the National Health and Nutrition Examination Survery (NHANES) 3 survey, approximately 1% of the population suffers from hyperthyroidism, either overt or subclinical.

D. Symptoms, signs, and pathophysiology

The manifestations depend on the duration and severity of the disorder.

1. **Nervous system.** Nervousness and a feeling of inner tension are common symptoms in hyperthyroid patients. Inability to get along with others, depression, emotional lability, poor concentration, and reduced performance in school and work may also occur. Tremor is common, and reflexes are brisk.
2. **Cardiac system.** There is tachycardia, usually supraventricular, because of direct effects of thyroid hormone on the conduction system. Atrial fibrillation may be superimposed on the underlying heart disease or may be due to hyperthyroidism alone. Long-standing thyrotoxicosis can cause cardiomegaly and result in heart failure despite a high cardiac output. Flow murmurs are common. Extracardiac sounds are because of the banging hyperdynamic heart.
3. **Musculoskeletal system.** Muscles become atrophic and weak because of excessive muscle catabolism. There is reduced muscle performance in walking, climbing, rising from a knee bend, or weight lifting. **Myasthenia gravis** or **hypokalemic periodic paralysis** (see Chapter 49) may accompany hyperthyroidism. The patient appears gaunt. Bone resorption exceeds bone formation, resulting in hypercalciuria and sometimes hypercalcemia. Long-standing hyperthyroidism may cause osteopenia.

4. **Gastrointestinal system.** Food intake increases, and some patients have insatiable appetites. Despite this, weight loss is common. Hyperdefecation occurs because of more rapid motility, but diarrhea is uncommon. Abnormal liver function tests reflect the malnutrition of far-advanced hyperthyroidism.
5. **Eyes.** Retraction of the upper lid as a result of increased sympathetic tone gives some patients a wide-eyed stare. Infiltrative ophthalmopathy is part of Graves disease, but only a minority of Graves patients have clinical evidence of ophthalmopathy. There may be proptosis, extraocular muscle swelling, and fibrosis causing restriction of ocular motility and diplopia. The exposed eyes become red. Pressure on the optic nerve or keratitis can cause blindness. Graves eye disease usually parallels hyperthyroidism but may run an independent course. The disorder is attributed to an autoimmune retro-orbital inflammation. Rarely, this ophthalmopathy occurs in patients with Hashimoto thyroiditis and in euthyroid patients without any history or evidence of thyroid disease (euthyroid Graves disease).
6. **Skin.** The patient's skin is warm, moist, and velvety, giving it a youthful appearance. The sweaty palms are hot rather than cool. Onycholysis (retraction of the nail from its bed) indicates a long duration of hyperthyroidism. Dermopathy of Graves disease, an orange-peel thickening of the pretibial areas, is rare.
7. **Reproductive system.** Hyperthyroidism impairs fertility in women and may cause oligomenorrhea. In men, the sperm count is reduced, and impotence may occur. Gynecomastia occurs because of **increased peripheral conversion of androgen to estrogen** despite high testosterone levels, so that the ratio of estrogen and testosterone is increased, leading to increased estrogen action on the breast. Thyroid hormone increases sex hormone–binding globulin and thus raises total testosterone and estradiol levels, whereas serum luteinizing hormone and follicle-stimulating hormone may be increased or normal.
8. **Metabolic system.** Weight loss is a common finding, especially in older patients who develop anorexia. Some teenagers and young adults lose control of their appetite, "pig out," and gain weight. The increased heat production caused by thyroid hormones is dissipated by increased sweating accompanied by mild polydipsia. Many patients describe an aversion to heat and a preference for

cold temperatures. The insulin requirement of diabetic patients usually increases.

9. **Thyroid gland.** The thyroid is usually enlarged. Its size and consistency depend on the underlying pathology. The enlarged hyperfunctioning gland has increased blood flow causing a thyroid bruit.

E. Graves disease

Graves disease is an **autoimmune disorder** responsible for >80% of cases of hyperthyroidism. In this condition, there is an antibody to the thyrotropin receptor on the thyroid follicular cell that results in stimulation of this receptor and is thus given the name thyroid-stimulating immunoglobulin (TSI) or TSH receptor antibody. The concentration of TSI in the serum bears a rough correlation with the severity of the hyperthyroidism. The cause of production of TSI is unclear. Antibodies to other thyroid constituents, especially antiperoxidase antibody, are also present.

Graves disease is familial, but the genetics are not well established. HLA-DR3 confers a fivefold increased risk for developing the disease.

F. Thyroid function tests

Thyroid function tests may be categorized into **(a)** those needed to establish whether there is hyperthyroidism and **(b)** those that show the cause of hyperthyroidism.

1. Tests of thyroid function

a. Serum free T_4 concentration or free T_4 index is increased in nearly all hyperthyroid patients.

b. Serum T_3 concentration, free T_3 concentration, and free T_3 index are also elevated. In a small fraction of patients (<5%), serum T_3 concentration or free T_3 is elevated when serum free T_4 is not; this entity is termed T_3 thyrotoxicosis.

c. Serum TSH, measured by the sensitive methods now commonly available, is undetectable or subnormal. About 2% of euthyroid elderly individuals will have a slightly suppressed serum TSH. A normal or elevated TSH in a hyperthyroid patient indicates TSH-induced hyperthyroidism, which is rare (see Table 38-1).

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d. Thyroid uptake of radioiodine (^{123}I or ^{131}I) at 4, 6, or 24 hours

is increased in patients with increased production of thyroid hormone and reduced when the gland is leaking thyroid hormone (granulomatous or lymphocytic thyroiditis).

2. **Tests for etiology**
   - **a.** TSI is now available commercially as a marker for active Graves disease. If positive, it confirms that the hyperthyroidism is a result of Graves disease.
   - **b. TSH receptor antibody** measures the binding of the patient's immunoglobulin G to a TSH receptor. It is positive in approximately 90% of patients with active Graves disease and is technically easier to measure than TSI.
   - **c.** The antiperoxidase (antimicrosomal) antibody test is usually positive in Graves disease (and in Hashimoto lymphocytic thyroiditis), thus helping to differentiate Graves disease from other causes of hyperthyroidism.
   - **d.** Thyroid scans are useful in patients with nodular goiter and hyperthyroidism to determine **(a)** whether there is an autonomous hyperfunctioning nodule that concentrates all the radioiodine and suppresses the normal glandular tissue, **(b)** whether multiple nodules concentrate radioiodine, or **(c)** whether the nodules are cold, and the hyperfunctioning tissue is between the palpable nodules. This differentiation may be important with regard to therapy (see Section VIII).
   - **e.** Thyroid ultrasonography shows increased blood flow and diffuse hypoechogenicity in Graves disease. Ultrasonography will also reveal multinodular goiter that may not be readily palpable.

G. Differential diagnosis

1. **Establishment of diagnosis of hyperthyroidism.** In patients with weight loss and features of hypermetabolism, the thyroid function tests are very sensitive, so the diagnosis of hyperthyroidism is straightforward. Milder cases may be difficult to diagnose. The serum TSH is subnormal in patients with minimal hyperthyroidism. Therefore, a discussion of differential diagnosis based on subtle clinical features is superfluous.
2. **Thyroiditis.** Subacute granulomatous thyroiditis is an uncommon disorder in which there are signs of an inflammatory viral illness with fever and malaise associated with thyroid pain and tenderness. The sore throat is unusually severe; there is pain on swallowing

that radiates to the ears. The thyroid gland is irregular and very firm. The process may begin in one lobe and progress to involve the other lobe in a few days. The sedimentation rate is elevated; antithyroid antibodies are usually negative; and the thyroid uptake of radioiodine is very low. A **hyperthyroid phase** lasts for several weeks, followed by a transition to a hypothyroid phase of several weeks and then recovery. Thyroid tenderness is the hallmark of the disorder. Cases of "silent subacute thyroiditis" in which thyroid tenderness is absent probably represent lymphocytic thyroiditis.

The features of hyperthyroidism usually respond well to β-adrenergic blockers. Propranolol, atenolol, or metoprolol may be used to reduce the tachycardia. Nonsteroidal anti-inflammatory drugs or aspirin may be sufficient for the pain and discomfort and will reduce the inflammation and fever. In patients who do not improve in a few days, prednisone is given, 15 to 40 mg/day for 10 to 14 days, then tapered and discontinued in 2 to 3 weeks.

3. **Lymphocytic thyroiditis.** Lymphocytic thyroiditis is currently responsible for a small percentage of new cases. It is a variant of Hashimoto thyroiditis. Usually, a small firm goiter is present, but the thyroid may not be enlarged or may be up to three times the normal size. There is usually no thyroid tenderness. The differentiation from Graves disease is based on the **low thyroid uptake** in lymphocytic thyroiditis. The increased T_4 blood levels occur because the gland is "leaking" thyroid hormone. The T_3/T_4 ratio is lower than in Graves disease because the stimulated Graves thyroid secretes more T_3, but this is not invariable. Thyroid antiperoxidase antibodies are positive.

   Lymphocytic thyroiditis with hyperthyroidism occurs commonly in the postpartum state. The hyperthyroid phase may last 4 to 12 weeks and is followed by a hypothyroid phase that lasts for several months. A mild subclinical form occurs in 8% of postpartum women. Recovery, rather than persistent hypothyroidism, p. 517p. 518is the rule. Nearly three fourths of postpartum women with the disorder will have a recurrence after a subsequent pregnancy.

   For the hyperthyroid phase, β-adrenergic blockers may be

given to control symptoms. The **use of antithyroid drugs that block the synthesis of thyroid hormone is not appropriate**.

4. **Acute psychosis.** In many patients hospitalized with acute psychosis, transient elevation of serum T_4 and free T_4 index has been reported. About half of these patients also have elevation of serum T_3 concentration. The abnormality is self-limiting. Tests repeated 2 weeks later are generally normal. Whether this is due to central release of TSH by the process underlying the psychosis is unclear. Measurements of serum TSH performed after recognition of the disorder have usually shown suppressed rather than elevated levels, but in an earlier phase of the disorder, serum TSH levels may be elevated or inappropriately normal rather than suppressed. A few patients with amphetamine abuse have had inappropriately normal serum TSH levels when the serum T_4 was elevated.
5. **Hyperthyroidism in the elderly.** Elderly patients with hyperthyroidism may not have typical clinical features. The presenting features of their "apathetic" hyperthyroidism may be weight loss, weakness, and depression or apathy. In one study, 20% of elderly hyperthyroid patients did not have a goiter. Atrial fibrillation and heart failure are more common than in the young. Proptosis and Graves ophthalmopathy are unusual in the elderly.

H. Therapy

1. Drugs

a. **Antithyroid drugs of the thionamide series** remain the backbone of therapy. The effectiveness of the therapy has been established by >60 years of experience with PTU and methimazole (Tapazole). Both PTU and methimazole block the biosynthesis of thyroid hormones by inhibiting thyroid peroxidase. In addition, PTU (but not methimazole) blocks the peripheral production of T_3 from T_4 by inhibiting the type 1 deiodinase.

i. **Dosage.** The usual daily therapeutic dose is 20 to 40 mg of methimazole given in divided dose twice daily (BID) or 300 to 600 mg of PTU given in divided doses every 8 hours. Both drugs are concentrated in the thyroid gland. For the forgetful patient, methimazole may be given once daily, if necessary, because it has a longer action than PTU, but

initiation of therapy with BID dosing is probably more effective.

ii. **Follow-up.** Patients should be followed at monthly intervals initially to assess the response to therapy and to adjust the dose of drug. When the patient responds well, the dose can be reduced to one half to two thirds of the initial dose. I prefer to maintain the therapy for 1.5 to 2 years because there is evidence that long-term remission is more likely to occur in patients who receive the therapy for at least 18 months, in contrast to patients treated for only the few months necessary to control the hyperthyroidism.

iii. **Adverse effects.** Side effects of these drugs include skin rash, urticaria, arthralgia, serum sickness, abnormal liver function tests, vasculitis, and, rarely, agranulocytosis. I warn patients to contact me if an unusual infection occurs, but I do not perform routine white cell counts and differentials unless there is an infection. Analysis of the Food and Drug Administration database showed that PTU, but not methimazole, caused severe liver failure in children and young adults. Because of this, there is a "black box" warning for use of PTU, and its use has been discouraged in patients less than 40 years of age.

iv. **Prognosis.** In my experience, about one third of patients undergo long-term remission when the course of therapy is completed. Relapses usually occur within the first year after stopping therapy. Long-term follow-up of patients treated with antithyroid drugs 20 to 25 years earlier showed that some had become hypothyroid, suggesting that thyroid destruction occurs spontaneously in Graves patients, probably as a result of autoimmune thyroiditis.

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b. *β*-Adrenergic blockers

i. Propranolol causes rapid improvement by **blocking the excessive adrenergic activity** of hyperthyroidism. It also causes a modest **reduction in serum T_3 concentration by blocking T_4 to T_3 conversion**, which is probably independent of its effect on *β* receptors.

The usual dose is 20 to 40 mg every 4 to 6 hours. The dose is adjusted to lower resting heart rate to about 70 to 80 beats/minute. As the hyperthyroidism is controlled, the dose is tapered, and the drug is discontinued when a euthyroid state is achieved.

ii. Effective β-adrenergic blockade will eliminate the tachycardia, tremor, anxiety, nervousness, and sweating, thus masking the condition and making clinical evaluation more difficult.

iii. Other β-adrenergic blockers are equally effective. **Atenolol** is longer acting and less likely to cause depression. Reduction of serum T_3 concentration does not occur with the more selective β_1 agents.

iv. β-Adrenergic blockers are especially indicated for tachycardia, even in the presence of heart failure, if the tachycardia is a result of thyrotoxicosis and if the cardiac failure is due to the tachycardia. Asthma and obstructive pulmonary disease are relative contraindications to the use of β-adrenergic blockers.

v. Hyperthyroid patients should not be treated with β-blockers alone, because these agents have no direct effect on the thyroid.

c. Other agents

i. **Inorganic iodine.** Saturated solution of potassium iodine, 250 mg (5 drops) BID, is effective for most patients, but escape from its effect usually occurs in about 10 days. Its principal use is to prepare patients for surgery, because iodine firms up the thyroid and reduces its vascularity. Nowadays, it is seldom used for definitive therapy. Sodium iodide may be given IV if necessary.

ii. **Sodium ipodate (Oragrafin) and iopanoic acid (Telepaque).** The radiographic contrast agents sodium ipodate and iopanoic acid are very potent **inhibitors of peripheral conversion of T_4 to T_3**. In addition, the iodine in these drugs is deiodinated, taken up by the thyroid, and inhibits the release of hormone from the gland. A dose of 1 g of sodium ipodate daily usually results in a dramatic fall of serum T_3 within 24 to 48 hours and may be

continued for 7 to 14 days. Unfortunately, these drugs are not currently available.

iii. **Corticosteroids.** Large doses of corticosteroids, such as 8 mg/day of dexamethasone, reduce the secretion of thyroid hormone by an unknown mechanism and also inhibit peripheral conversion of T_4 to T_3. Thus, steroid therapy for 2 to 3 weeks may be indicated for severe hyperthyroidism.

2. **Radioiodine-131.** ^{131}I has been used for >60 years for definitive therapy of hyperthyroidism. It is efficacious and simple to administer. The usual doses are 5 to 15 mCi (185 to 555 MBq) to deliver approximately 80 to 160 mCi/g thyroid estimated weight, corrected for the 24-hour thyroid uptake. Such doses deliver 5 000 to 15 000 rad (50 to 150 Gy) to the thyroid. There has been a trend in recent years to use doses at the upper end of this range to achieve greater certainty that the hyperthyroidism is eliminated. ^{131}I therapy results in gradual restoration of a euthyroid state in most patients over a period of 6 months. Doses should be increased by approximately 25% in patients who have taken antithyroid drugs within the previous 10 days.

   a. In some patients, ^{131}I causes little improvement, and in others, permanent hypothyroidism may develop. The hypothyroidism may be transient in some who become hypothyroid in the first few months after therapy, but permanent hypothyroidism is the rule with the larger dose of ^{131}I currently used. Because the patients are usually very symptomatic when they undergo a rapid transition from hyperthyroidism to hypothyroidism, I prescribe T_4 therapy for all hypothyroid patients in the usual replacement dose for about 1 year and then give a short trial of a reduced dose in this group to determine whether the hypothyroidism is permanent. Hypothyroidism that develops >6 months after therapy is nearly always permanent. To prevent ophthalmopathy induced by ^{131}I therapy, it is important to initiate T_4 therapy within several weeks after p. 519p. 520radioiodine treatment. Patients receiving ^{131}I therapy require permanent annual evaluations for hypothyroidism. Some

patients require a second dose of ^{131}I, but only a few require three or more doses. Such patients have resistance to the radiation for reasons that are not clear.

b. ^{131}I therapy may cause an acute release of hormone from the gland, resulting in significantly increased serum concentrations of T_4 and T_3 in about one fifth of patients, usually about 5 to 10 days after the ^{131}I is given. This may be associated with exacerbation of symptoms. Because of the potential for worsening of the condition by ^{131}I, I do not administer it to severely hyperthyroid patients until the disease has been controlled with antithyroid drugs. The thionamide must be stopped for at least 2 days before giving ^{131}I so that it will not interfere with the retention of the therapeutic dose; it can be restarted 2 or 3 days later.

c. Because of the uncertain control of the hyperthyroidism with ^{131}I, I prefer to administer antithyroid drugs afterward for a period of 3 to 12 months to control the condition with greater certainty in most middle-aged and elderly patients. I discontinue the thionamide when the patient is euthyroid on a small daily dose of the drug, such as 5 mg of methimazole or 50 mg of PTU. In younger patients, I do not give a second dose of ^{131}I until 1 year after the first dose in order to allow the full effect of the ^{131}I to occur and to reduce the possibility of hypothyroidism from unnecessary administration of a second dose of ^{131}I. However, others will retreat patients after 3 months if the hyperthyroidism persists. In older patients with complicating illnesses, I recommend additional doses of ^{131}I, 3 months or more after the first dose, if the hyperthyroidism has not been cured. There is reluctance to use ^{131}I in young adults and children because of the potential carcinogenic effect of the radiation. Careful follow-up of patients for >30 years has shown **no increase in thyroid carcinoma, leukemia, or birth defects** in the progeny of those who received this therapy for hyperthyroidism, so skepticism regarding treatment of patients <25 years of age does not appear to be justified. ^{131}I is now used as the treatment of choice for children with hyperthyroidism in some referral centers.

3. **Surgical thyroidectomy**
   a. **Preparation for surgery.** Subtotal thyroidectomy has been used for >80 years as effective therapy of hyperthyroidism. It is preferable to perform it after patients have regained their weight and are in good condition. Thus, these patients should be treated with methimazole for several months starting with a dose of 15 mg BID. Inorganic iodine is added for 7 to 10 days prior to surgery to reduce the vascularity of the gland. Alternatively, patients may be treated for a short period with high doses of β-blockers, such as atenolol 50 mg BID or metoprolol 50 mg BID, alone as preparation for surgery. This controls some symptoms and cardiovascular effects of hyperthyroidism, such as tachycardia, but does not reverse the catabolic state. It may be justifiable under circumstances in which patients cannot take thionamide drugs or have mild hyperthyroidism.
   b. **Complications.** Thyroidectomy has an appreciable incidence of complications. Instead of subtotal thyroidectomy, near complete thyroidectomy is the current preferred operation for Graves disease. Complications include hypothyroidism, persistent or recurrent hyperthyroidism in 10% after subtotal thyroidectomy, hypoparathyroidism in 1%, recurrent laryngeal nerve palsy in 1%, wound infections, and keloids. Because of these complications, surgical therapy should be reserved for special situations, such as side effects to antithyroid drugs, a patient's unwillingness to take ^{131}I, multinodular toxic goiter that is also causing obstruction of the airway or esophagus, or coexisting hyperparathyroidism. In addition, the financial cost is probably greater than that of definitive drug therapy or ^{131}I at the present time.
4. **Choice of therapy.** I prefer to use antithyroid drugs as the definitive therapy for most patients, especially young and middle-aged adults. Its main advantage is that the therapy is reversible and does not destroy the thyroid gland. For older patients and those with cardiovascular disease or complicating disorders, ^{131}I is the preferred therapy because it is more likely to produce a permanent cure of hyperthyroidism; its main drawback is that it causes a high incidence of hypothyroidism. ^{131}I p. 520p.

administration has become the most commonly used treatment for hyperthyroidism in the United States. Surgery is reserved for special situations as stated previously.

I. Hyperthyroidism in pregnancy

1. **Incidence.** Graves disease occurs commonly in women of child-bearing age, complicating approximately 0.1% of pregnancies. Because severe hyperthyroidism tends to reduce fertility, it is unusual to have this combination. More commonly, drug treatment of patients with hyperthyroidism improves fertility, and a pregnancy may then ensue. To avoid this complication, hyperthyroid young women on methimazole should be urged to practice contraception. Hyperemesis gravidarum is associated with mild hyperthyroidism in a high proportion of cases. This is a result of high hCG concentrations; the disorder is self-limiting and disappears when the hyperemesis remits.
2. **Management.** Antithyroid drugs and surgery are the alternatives.
   a. ^{131}I is never used in women known to be pregnant because it crosses the placenta and is **concentrated in the fetal thyroid after 10 weeks of gestation**, resulting in cretinism. PTU is preferable to methimazole in the first trimester because methimazole has been associated rarely with aplasia cutis and more severe embryopathy. The patient can be switched to methimazole after the first trimester. To avoid fetal hypothyroidism, the dose of thionamide should be adjusted to the smallest necessary to maintain a near-euthyroid state, with serum T_4 in the upper-normal to slightly elevated range for pregnancy. Young pregnant women tolerate mild hyperthyroidism very well.
   b. If necessary, surgical thyroidectomy is best performed in the second trimester because general surgery in the third trimester may induce premature labor.
3. **Outcome.** About 80% to 90% of adequately treated hyperthyroid women have a normal outcome of pregnancy. The incidence of prematurity and spontaneous abortion is no greater than that found in pregnancies without hyperthyroidism.
4. **Newborn.** Hyperthyroidism may occur in the newborn as a result of transmission of the Graves TSI across the placenta to the fetus.

The antithyroid drug given to the mother may control the hyperthyroidism in utero, but it may also cause goiter and hypothyroidism. Therefore, the newborn of a Graves mother requires special attention for these possibilities. Measurement of TSH receptor antibody in the pregnant woman with Graves disease is currently recommended at the onset of the third trimester as an indicator of the need for therapy of hyperthyroidism in the newborn (see Chapter 32).

J. Thyroid storm

1. **Clinical.** Thyroid storm is a dangerous condition of decompensated thyrotoxicosis. The patient has tachycardia, fever, agitation, restlessness or psychosis, nausea, vomiting, and/or diarrhea. It usually results from long-neglected severe hyperthyroidism to which there is added a complicating intercurrent illness, such as gastroenteritis or pneumonia, or emergency surgery.
2. **Treatment.** Therapy is multifactorial and includes appropriate supportive measures such as fluids and electrolytes, and management of an underlying infection with appropriate antibiotics. Specific treatment directed at the hyperthyroidism includes:
   - **a.** Antithyroid drugs in large doses (600 mg of PTU or 60 mg of methimazole stat and half this dose every 6 hours) given by gavage if necessary.
   - **b.** Iodine orally (0.5 mL saturated solution of potassium iodide BID) or IV (1 g sodium iodide) or iopanoic acid, 1 g/day for 2 weeks, if available starting 2 hours after the antithyroid drug.
   - **c.** Propranolol in large oral doses (40 to 80 mg every 4 to 6 hours) or small doses IV approximately 1 mg every 5 minutes, up to 10 mg) to reduce heart rate based on cardiac monitoring, or esmolol IV approximately 250 to 500 μg/kg/min loading dose followed by 50 μg/kg/min for 4 minutes with cardiac monitoring. A maintenance infusion at this dose can be used with cardiac monitoring. β-Blockers are continued until thyroid hormone levels fall to the normal range.
   - **d.** Dexamethasone, 4 to 8 mg/day, unless contraindicated by a severe infection. As a result of receiving all or several of the preceding drug therapies concurrently, patients usually experience significant improvement in a few days.

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e. In patients who do not respond to these measures, plasmapheresis has been used with success.

K. Graves eye disease

1. **Clinical.** Graves eye disease (orbitopathy) affects approximately 25% of patients with Graves hyperthyroidism and also occurs rarely in patients with Hashimoto thyroiditis or in those without overt autoimmune thyroid disease. Only 1% to 5% of patients with Graves disease have significant eye disease. The main findings are proptosis, redness of the conjunctiva, ocular discomfort, diplopia, and periorbital edema. Computed tomography or magnetic resonance imaging scans of the orbit show thickened eye muscles that may impinge on the optic nerve and impair vision. The pathogenesis is a result of retro-orbital inflammation induced by cytokines. There is evidence that the TSH receptor may be the orbital antigen that has a role in triggering the disorder.
2. **Treatment.** There is no entirely satisfactory therapy. Fortunately, the condition improves spontaneously in the majority of patients, even though complete resolution does not occur. In patients with severe manifestations, corticosteroid therapy in high doses is sometimes effective in reducing the inflammation. Patients should be followed in consultation with an ophthalmologist. Orbital decompression by an experienced eye surgeon can be performed after the condition stabilizes, which may take 6 to 24 months. Complete thyroidectomy may improve the condition. ^{131}I therapy may worsen Graves eye disease, so it should not be used until the eye condition is stable. Selenium has been used for prevention of orbitopathy.

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39 Thyroid Tumors in Adults

Jerome M. Hershman

I. GENERAL PRINCIPLES

A. Prevalence of thyroid nodules

1. In the Framingham population study, the lifetime risk of developing a palpable thyroid nodule was estimated to be 5% to 10% based on prospective follow-up of >5 000 patients with a female/male ratio of 5/1. In an ultrasound survey of people in Germany without apparent thyroid disease, nodules were detected in approximately 60% of those over age 40 and in 25% of those under age 40. Three fourths of the nodules were <10 mm in size. In middle age, nodules were more common in women, but men over age 60 had nodules almost as commonly as women. In a large autopsy series in the United States, 50% of the population with no known history of thyroid disease had discrete nodules, 35% of whom had nodules >2 cm in diameter. Older studies reported a higher incidence of thyroid cancer in single nodules than in multinodular goiter. However, a study of almost 2 000 patients in Boston found the same thyroid cancer incidence of 15% in patients with a single nodule and in those with multinodular goiter when all nodules >1 cm were biopsied.
2. There are approximately **64 000 new cases of thyroid cancer in the United States each year**, accounting for 3.7% of all new cancers. Mortality from thyroid cancer is 0.3% of all cancer deaths. The increased incidence of thyroid cancer during the last two decades is mainly attributed to improved diagnosis, but undiscovered environmental factors may also play a role.

II. CLASSIFICATION.

Almost any pathologic process involving the thyroid gland (benign and malignant neoplasms, colloid goiter, inflammatory processes, developmental abnormalities, intrinsic metabolic defects, or hemorrhage) can present as a thyroid nodule. Table 39-1 lists the pathologic classification of thyroid tumors.

TABLE 39-1 Pathologic Classification of Thyroid Tumors

Epithelial Tumors

Benign

- Follicular adenoma
- Hürthle cell adenoma
- Adenomatous hyperplasia in colloid goiter

Malignant

- Papillary carcinoma
- Follicular carcinoma
- Hürthle cell carcinoma
- Undifferentiated (anaplastic) carcinoma
- Medullary carcinoma

Malignant Nonepithelial Tumors

Lymphoma

Metastatic carcinoma

Squamous cell carcinoma

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III. EVALUATION OF THYROID NODULES

A. Clinical evaluation. Although thyroid nodules are found **more frequently in women**, the likelihood of a thyroid nodule being **malignant is higher in men than in women**. A history of radiation exposure is important, because a thyroid adenoma or carcinoma can develop many years later in those who received radiation therapy for treatment of benign conditions or, more commonly currently, malignancies such as lymphoma. A family history of thyroid cancer suggests familial papillary thyroid cancer or familial medullary thyroid cancer as a component of multiple endocrine neoplasia type 2 (MEN2). Papillary thyroid cancer is familial in 5% to 10% of cases and much more common than familial medullary thyroid cancer. A history of goiter in the family suggests a benign disorder.

The distinction between solitary and multiple nodules by neck examination may be limited. In approximately 50% of patients with a clinically solitary nodule on palpation, the lesion was subsequently found to be a dominant nodule in a multinodular goiter on ultrasound or pathologic examination.

Most thyroid nodules do not cause symptoms. Pain may occur with a hemorrhage into a preexisting cyst or colloid nodule. Currently, a large majority of nodules are found incidentally during carotid ultrasonography, computed tomography (CT) scan, positron emission tomography (PET) scan, or magnetic resonance imaging (MRI) of the neck.

The following clinical features are highly suggestive of the presence of a malignant thyroid lesion:

1. Rapid expansion of an existing nodule
2. Firm texture of the lesion
3. Pressure on adjacent structures
4. Fixation of the nodule to surrounding structures
5. Obstructive symptoms
6. Dysphagia
7. Vocal cord paralysis manifested as hoarseness
8. Presence of enlarged cervical lymph nodes (especially suspicious in children)

   Nearly all these symptoms or signs have also been associated with proven benign lesions, so they are only suggestive but indicate the need for a pathologic diagnosis.

B. Diagnostic procedures. Laboratory evaluation of thyroid function is useful to assist in determining whether a nodule is benign or malignant. Figure 39-1 illustrates a recommended approach to management of a thyroid nodule.

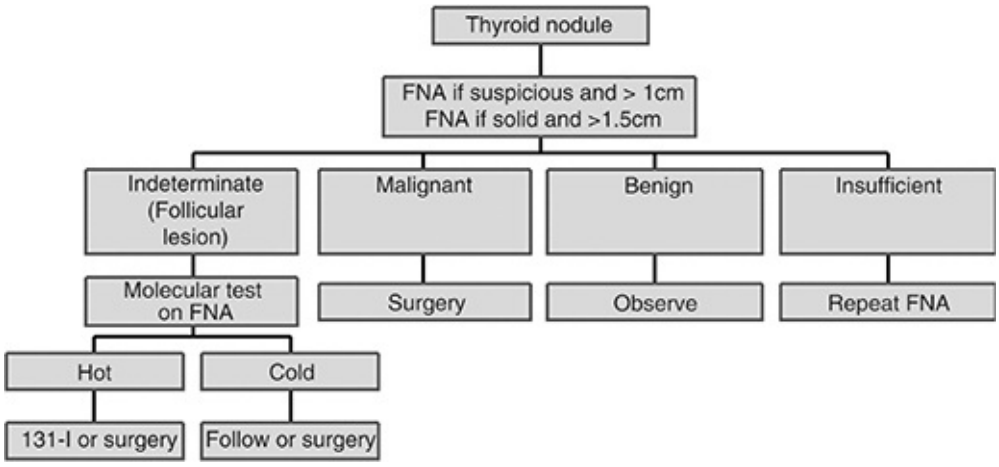

Figure 39-1. Decision tree for the management of a thyroid nodule based on fine-needle aspiration (FNA).

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1. **Thyroid function tests.** Nearly all patients with either thyroid carcinoma or benign nodules are euthyroid. An abnormal thyroid function test in a patient with a thyroid nodule does not rule out thyroid cancer, but may make thyroid carcinoma a less likely possibility. Low serum thyroid-stimulating hormone (TSH) concentration in the setting of a thyroid nodule suggests the presence of either an autonomously functioning adenoma or a toxic multinodular goiter. There is a positive correlation between serum TSH and the frequency of thyroid cancer, extending to TSH that is slightly elevated. Elevated antiperoxidase and antithyroglobulin antibody titers indicate lymphocytic thyroiditis that may present as a nodule. The serum thyroglobulin level is not a useful test to distinguish benign from malignant nodules because it is increased with any goitrous process.
2. **Thyroid ultrasound** is a noninvasive test that distinguishes cystic from solid lesions. It is routinely used to guide fine-needle aspiration (FNA) biopsy. Thyroid ultrasonography is capable of identifying impalpable solid and cystic nodules as small as 0.2 mm. The ultrasonographic features that suggest the diagnosis of malignancy are hypoechogenicity in a solid nodule, fine stippled calcifications, irregular margins, taller than wide, and intranodular vascularity.
3. **FNA biopsy.** FNA biopsy is the most important diagnostic technique. This technique consists of removal of cells from the thyroid gland via a fine needle (25 to 27 gauge). There are many variations of this technique. It is usually performed under ultrasound guidance. FNA reliably identifies thyroid nodule cytology and is the most effective method to diagnose malignancy. In experienced hands, the procedure is safe, with accuracy, sensitivity, and specificity of approximately 90%. With common use of FNA, the number of patients requiring surgery has declined by >40%. FNA biopsy should be performed on solid nodules >1 cm that are suspicious based on ultrasound characteristics, on nodules >1.5 cm that are minimally suspicious, on nodules with both a solid and cystic component >2.0 cm, on the solid component of large cystic nodules, and on nodules with evidence of recent growth.

FNA biopsy results are divided into six categories based on the Bethesda classification: **(a)** nondiagnostic due to insufficient material, **(b)** benign, **(c)** atypia of undetermined significance or follicular lesion of undetermined significance, **(d)** follicular neoplasm or suspicious for follicular neoplasm, **(e)** suspicious for malignancy (includes aspirates with some features of thyroid carcinoma but not conclusively malignant), and **(f)** malignant. Categories c and d are indeterminate. Several molecular methods have been used to clarify the diagnosis of the indeterminate results. These consist of detection of oncogenes that are mutations or gene fusions, microRNAs that correlate with cancer or benign lesions, or a complex mRNA analysis that identifies benign lesions. This is an area of active research, and it is likely that new molecular methods will be developed to clarify the diagnosis of cancer on FNA material and possibly to predict the biologic aggressiveness of the cancer as a guide to therapy. Those patients with a nondiagnostic cytologic diagnosis should have a repeat biopsy.

4. **Radioiodine scans with ^{123}I or ^{131}I.** Nodules may be classified into hyperfunctional (“hot”) nodules, nonfunctional (“cold”) nodules, or normal functioning (“warm”) nodules by radioiodine scan. Most studies show that a **hot nodule is rarely malignant**. The finding of a cold nodule has relatively low sensitivity because the majority of both benign and malignant solitary thyroid nodules appears hypofunctional relative to adjacent normal thyroid tissue. Therefore, a **radioiodine scan is not recommended** in the initial evaluation of a thyroid nodule.
5. **Serum calcitonin** measurement represents an excellent marker in the preoperative diagnosis of medullary carcinoma of the thyroid, especially if a calcitonin rise can be demonstrated 3 to 5 minutes after the administration of pentagastrin (not currently available in the United States), 0.5 μg/kg IV push, or after a calcium infusion. Serum calcitonin should be ordered in all subjects belonging to a kindred with familial MEN2. However, calcitonin levels may be somewhat elevated in patients with Hashimoto thyroiditis and other benign thyroid conditions; neuroendocrine tumors; lung, colon, breast, and prostate cancers; sepsis; and generalized inflammation. In several studies of the

routine measurement of serum p. 525p. 526calcitonin in patients with nodular thyroid disease, medullary carcinoma was found in 0.3% to 1.4%. False positives occur in about one half of those with an elevated baseline calcitonin. Currently the test is not routinely performed in the evaluation of a thyroid nodule in the United States.

6. **PET scan.** PET scans with fluorodeoxyglucose are useful to localize metastatic thyroid cancers, but are probably not useful to differentiate between benign and malignant thyroid nodules. Although nodules detected by focal uptake in the thyroid were believed to confer a 30% chance of malignancy, ultrasound features should be considered in determining the need to perform FNA on nodules detected by focal uptake on PET scan. Diffuse uptake of the tracer in the thyroid is not indicative of thyroid cancer.

IV. MANAGEMENT OF THYROID NODULES

A. Nonsurgical management.

The vast majority of thyroid nodules is benign and can be followed with observation alone. Spontaneous regression of thyroid nodules may occur. Thyroid hormone suppression therapy is based on the assumption that TSH is a growth factor for the nodule. The aim of therapy is to reduce serum TSH to the low-normal range. This therapy for the treatment of benign thyroid nodules has been challenged by failure of some studies to show a significant decrease in nodule size and concern about decreasing mineral bone density or triggering atrial fibrillation, especially in the elderly. Generally, patients with benign nodules are followed by ultrasonography at intervals of 6 to 12 months to assess growth or shrinkage of the nodule. One study showed that 99% of nodules that did not increase in size at 1-year follow-up and did not grow during the next 3 years.

B. Operative management

1. The extent of thyroidectomy varies from a lobectomy to a near-total thyroidectomy. Indications for thyroid nodule resection are
   - **a.** The presence of a malignant or suspicious for malignant lesion
   - **b.** Indeterminate lesions classified as malignant by molecular methods
   - **c.** Some follicular neoplasms and Hürthle cell neoplasms

(Bethesda category d)

d. When the nodule or goiter causes compression of the surrounding structures, causing dysphagia, dysphonia, or breathing problems

e. Cosmetic reasons

C. Postoperative management of benign nodules. In the postoperative period after lobectomy, thyroxine (T_4) is often given to the patients to prevent recurrent nodule or goiter formation in those who had a lobectomy. I prescribe a dose of levothyroxine that brings the serum TSH to the low-normal range.

V. THYROID CANCER

A. Classification and features. Thyroid carcinoma is classified into five major types: papillary, follicular, medullary, anaplastic, and thyroid lymphoma (Table 39-1). Most thyroid cancers grow slowly over years, but a few are more aggressive and have high mortality rates. Thyroid carcinomas tend to be more aggressive clinically in older patients compared with younger individuals. This is reflected in the TNM classification of differentiated thyroid cancers (papillary and follicular) (Table 39-2).

1. **Papillary thyroid carcinoma** accounts for 80% to 90% of all thyroid cancers. The stage depends on the age of the patient at the time of initial diagnosis, the size of the primary lesion, local invasion, and the degree of metastases, as noted in Table 39-2. The tumor tends to invade lymphatics and metastasize to the regional lymph nodes and lungs. About 50% of classic papillary thyroid cancers contain an activating oncogene: the *BRAF V600E* mutation. The follicular variant of papillary thyroid cancer is more likely to have mutations in *N-RAS*, *H-RAS*, or *K-RAS* than *BRAF V600E*. *BRAF V600E* is associated with a worse prognosis. Recently, the encapsulated follicular variant of papillary thyroid cancer has been reclassified as a neoplasm rather than a cancer because it does not recur.
2. **Follicular thyroid carcinoma** accounts for approximately 6% of all thyroid cancers in the United States and is relatively more common in countries with iodine deficiency. Follicular thyroid carcinoma is slightly more aggressive than

papillary carcinoma. Cervical lymph node involvement is less common, but distant metastasis is more frequent compared with papillary thyroid cancer. Hürthle cell carcinoma and insular thyroid carcinoma are more lethal variants of follicular carcinoma.

TABLE 39-2 Staging of Differentiated Thyroid Cancer Using the TNM Classification

Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor diameter 2 cm or less
T2	Tumor diameter 2–4 cm
T3	Tumor >4 cm in greatest dimension limited to the thyroid or with minimal extrathyroid extension
T4a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous tissue, larynx, trachea, esophagus, recurrent laryngeal nerve
T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels

Regional lymph nodes (N)

(Regional lymph nodes are the cervical and upper mediastinal lymph nodes.)

NX	Regional lymph nodes cannot be assessed
N0	No metastatic nodes
N1	Regional lymph node metastasis
N1a	Metastasis to level VI or VII (pretracheal, paratracheal, and prelaryngeal lymph nodes or upper mediastinal nodes), unilateral or bilateral
N1b	Metastasis to unilateral, bilateral, or contralateral cervical, or retropharyngeal lymph nodes

Distant metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Stage grouping

	Papillary or follicular	
	<55 years old	**55 years and older**
Stage I	Any T, any N, M0	T1, N0/NX, M0
Stage II	Any T, any N, M1	T2, N1, M0; T3, any N, M0
Stage III		T3, N0, M0; T1-3, N1a, M0
Stage IVA		Any T4b, any N, M0
Stage IVB		Any T, any N, M1

3. **Medullary thyroid carcinoma** accounts for 2% to 4% of thyroid cancers and is derived from the calcitonin-secreting cells or parafollicular cells. Elevated serum calcitonin levels establish the diagnosis and correlate with tumor mass. Approximately 20% are familial tumors and are associated with other endocrine neoplasias (MEN type 2A or 2B). The recognition of point mutations in the *ret* proto-oncogene on chromosome 10 has enhanced the ability to detect these neoplasms at an early and potentially curable stage in suspected family members. The treatment is total thyroidectomy with dissection of central compartment nodes.

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4. **Anaplastic thyroid carcinoma,** the most aggressive and lethal neoplasm, makes up only 1% of all thyroid cancers. Anaplastic thyroid cancer is often derived from a well-differentiated thyroid carcinoma. Three quarters of patients are >60 years of age. Examination of the neck usually reveals a fixed, large, firm mass. Surgical resection is usually contraindicated unless the tumor is in its initial stage. A tracheostomy can be performed to prevent suffocation by these rapidly growing tumors. The patient is usually treated with external irradiation beam therapy or chemotherapy or both. The mortality exceeds 80% at 12 months.
5. **Thyroid lymphoma** accounts for approximately 1% of thyroid malignancies and is often engrafted on a background of chronic lymphocytic thyroiditis. The tumor arises from B-cell lymphocytes. Patients are usually women >60 years of age with a long history of Hashimoto thyroiditis and present with a rapidly enlarging thyroid mass. The patient may complain of neck pressure, local swelling of the thyroid gland, hoarseness, and dysphagia. FNA may suggest the diagnosis, but definitive diagnosis generally requires an open biopsy. Treatment with external radiation and four to six courses of chemotherapy usually produces a permanent remission.

B. Management of Papillary and Follicular Thyroid Cancer

1. **Surgical resection.** For differentiated carcinoma, a near-total or total thyroidectomy is performed. Total thyroidectomy can be associated with complications, such as recurrent laryngeal nerve damage and hypoparathyroidism. Lymph node dissection is based on surgical findings.
2. **Radioiodine-131 remnant ablation.** Ablation of thyroid remnants following surgery improves the prognosis in patients with more extensive disease. However, there is no benefit in patients with minimal disease such as 1 to 4-cm papillary carcinomas confined to the thyroid. The treatment is given 1.5 to 3 months postoperatively, after the patient has been withdrawn from thyroid hormone or after two consecutive daily injections of 0.9 mg recombinant human TSH while the patient is on replacement dose of levothyroxine. For the withdrawal protocol, the patient is treated with tri-iodothyronine (T_3) (Cytomel, 25 μg twice a day) for 4 to 8 weeks; then, T_3 is discontinued for 2 weeks during which the patient follows a low-iodine diet. **The routine use of a diagnostic scan before an ablative dose has been discontinued** because the large diagnostic dose can impair the uptake of the therapy dose. The ablative dose varies from 30 to 100 mCi; studies have shown that 30 mCi is as effective as 100 mCi for ablation of remnants. Seven to 10 days after the ablative dose, the patient undergoes a posttherapy scan, which sometimes reveals extrathyroid disease.
3. **Levothyroxine suppression of TSH.** A suppressive dose of thyroid hormone is given after thyroidectomy to reduce thyroid cancer recurrence rates. TSH stimulates thyroid tumors that contain TSH receptors. The dose of thyroxine should be adjusted to keep the TSH suppressed without causing clinical thyrotoxicosis. The degree of suppression should be based on the stage of the patient. In patients with a good prognosis, TSH should be suppressed to the slightly subnormal range. In patients with poor prognosis, TSH should be suppressed to <0.1 mU/L without causing clinical thyrotoxicosis, provided that this can be done safely.
4. **Metastatic or recurrent tumors.** Surgical removal is preferable for metastases or recurrence that is accessible to surgery. Radioiodine-131 is the principal treatment of distant metastatic

tumors. If the tumor does not concentrate the isotope, external radiation may be effective. For metastatic differentiated thyroid cancer that is radioresistant and progressive, two tyrosine kinase inhibitors have been approved for use: lenvatinib and sorafenib. Both have been shown to improve progression-free survival, but neither is yet believed to improve overall survival.

5. **Routine follow-up**
   a. **Serum thyroglobulin.** Patients are followed at intervals of 3 to 6 months by clinical evaluation, measurements of TSH and serum thyroglobulin, and neck ultrasonography. In the absence of the thyroid gland, thyroglobulin should be undetectable in serum; measurable thyroglobulin signifies persistent thyroid tissue, either differentiated thyroid cancer or persistent normal tissue. On p. 528p. 529levothyroxine suppression therapy, a thyroglobulin level >1 to 2 ng/mL is regarded as abnormal. TSH-stimulated serum thyroglobulin is a more sensitive assessment of recurrence than the radioiodine scan. Unfortunately, antibodies to thyroglobulin, found in 10% to 20% of patients, interfere with the measurement and make it uninterpretable. In these patients, radioiodine scans may be helpful.
   b. **^{131}I scanning with recombinant TSH injection.** Recombinant TSH (Thyrogen) permits performance of ^{131}I scans while patients remain on their levothyroxine therapy. The current protocol consists of the intramuscular injection of 0.9 mg of Thyrogen on Monday and Tuesday; on Wednesday the patient is given 4 mCi of ^{131}I; and on Friday the patient's serum Tg level is obtained and a total body scan is performed. If the scan is negative and the patient's serum Tg level remains low after Thyrogen stimulation, the patient is considered free of disease. The cost of Thyrogen is substantial, but its use avoids symptoms of hypothyroidism.
   c. **Ultrasound.** Annual ultrasound of the neck is very useful for detection of metastases to lymph nodes. Abnormal nodes or masses can be biopsied by FNA under ultrasound. Measurement of thyroglobulin in the aspirate is a useful addition to histologic evaluation.

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40 Newborn Thyroid Disorders and Screening

Stephen A. Huang and Stephen LaFranchi

In addition to thyroid hormone's importance for regulating body metabolism throughout life, it is crucial for growth and development of the fetal central nervous system and during the first 3 years of life. Lack of sufficient thyroid hormone during this period results in mental retardation and other neurologic sequelae. For the most part, congenital hypothyroidism is **not a heritable disorder**. Thus, it is not possible to identify a population of high-risk pregnant women who might deliver an infant with congenital hypothyroidism. To date, no reliable prenatal test for fetal hypothyroidism short of fetal blood sampling (cordocentesis) has been developed. Furthermore, the clinical manifestations of congenital hypothyroidism are often subtle or even absent in newborns, so that the condition is usually not suspected or diagnosed in the neonatal period. Yet few disorders respond so dramatically to treatment. For these reasons, **newborn screening** programs were developed for congenital hypothyroidism. These screening programs were made possible by the application of precise radioimmunoassays for thyroid hormones to mass screening techniques, allowing for the diagnosis and treatment of hypothyroidism in the first few weeks of life, before clinical manifestations are apparent. Newborn thyroid screening is an effective method to prevent the neurologic injury caused by in adequately treated congenital hypothyroidism and has expanded our understanding of thyroid disease in infancy.

I. FETAL THYROID PHYSIOLOGY

A. Fetal thyroid development. The fetal thyroid develops from an outpouching of the foregut at the base of the tongue and migrates to its normal location in the thyroid bed in the first 4 to 8 weeks of gestation. Its bilobed shape is recognizable at 7 weeks of gestation. Thyroglobulin (TG) production is apparent by the 8th week of gestation, and the thyroid is capable of trapping iodine at the 10th week. By the 12th week of gestation, thyroid hormone production occurs and colloid storage is apparent histologically. Fetal thyroid-

stimulating hormone (TSH), thyroxine-binding globulin (TBG), and total and free thyroxine (T_4) concentrations gradually rise from week 12 of gestation and reach mean adult levels by 36 weeks of gestation. The rise in fetal serum tri-iodothyronine (T_3) is smaller, most likely the result of placental and fetal 5-deiodinases that catalyze T_3 inactivation.

B. Maternal–fetal thyroid relationship

1. A portion of maternal thyroid hormones crosses the placenta, sufficient to result in serum T_4 concentrations that are 25% to 33% that of full-term infants. Thus, maternal thyroid hormones may have a role in normal fetal development prior to the maturation of the fetal hypothalamic–pituitary–thyroid axis. Evidence suggests that maternal thyroid hormones can partially protect a hypothyroid fetus until delivery but will not normalize fetal serum T_4 concentrations. Additional protection is afforded by more efficient fetal brain 5′-deiodinase activity, which increases T_4-to-T_3 conversion.
2. **Hypothyroid women** tend to have decreased fertility and, if they conceive, they have an increased rate of pregnancy loss; this can be prevented by T_4 replacement. Maternal hypothyroidism during pregnancy may adversely affect neurologic development in offspring. In one study, offspring born to mothers with TSH elevations (occurring at a frequency of 1 in 400) had an IQ of 103 compared with a control group at 107. In a second study, offspring born to mothers with p. 531p. 532T_4 concentrations in the lowest 5th percentile had a psychomotor developmental index 14 points lower (PDI = 86) compared with the remainder of the group (PDI = 100). These issues are compounded by the fact that normal pregnancy increases thyroid hormone requirements. Thus, frequent monitoring of serum thyroid function tests is recommended for all hypothyroid women during pregnancy, to carefully titrate their levothyroxine regimen.

C. Treatment of fetal hypothyroidism. Rarely, a fetus is discovered to be hypothyroid during pregnancy. This can occur with familial dyshormonogenesis, maternal autoimmune thyroid disease with transfer of thyrotropin receptor–blocking antibodies, overtreatment with antithyroid drugs for maternal Graves disease, or inadvertent

radioactive iodine (RAI) treatment of a pregnant woman. Fetal hypothyroidism can be proven by fetal blood sampling. Fetal hypothyroidism resulting from overtreatment of a mother with Graves disease can be managed by reducing or discontinuing the dose of maternal antithyroid medication with or without enteral levothyroxine administration. In severe cases, especially those detected late in gestation, **intra-amniotic injections of levothyroxine, 250 to 500 μg weekly until term**, have been shown to rapidly reduce fetal goiter size and normalize cord-blood T_4 and TSH concentrations.

II. NEONATAL THYROID PHYSIOLOGY

A. Term infant

1. **Thyroid changes at birth.** There are dramatic changes in thyroid function shortly after birth. Within 30 minutes of delivery, there is a sharp increase in the serum TSH concentration up to 80 μU/mL, most likely a result of the stresses of the birth process and clamping of the cord. The serum TSH concentration gradually falls to <10 μU/mL during the first week of life.
2. **Thyroid function over the next 6 weeks.** This sharp rise in TSH stimulates rapid increases in serum T_4, free T_4, and T_3 concentrations into the hyperthyroid range (see Table 40-6 for normal values with age). Serum T_4 and T_3 concentrations gradually decrease over several weeks.

B. Preterm infant

1. **Thyroid changes at birth.** Preterm infants have a reduced TSH surge, up to 50 mU/L. Cord-blood T_4, free T_4, and T_3 concentrations are reduced in comparison with term infants and directly proportional to gestational age and birth weight.
2. **Thyroid function after birth.** Thyroid changes in preterm infants after birth are qualitatively similar to but quantitatively smaller than that of term infants. In very-low-birth-weight infants, serum T_4 and T_3 concentrations may actually fall to below birth levels in the first week of life. This drop is a result of multiple factors, including immaturity of the hypothalamic–pituitary–thyroid axis, lack of the maternal contribution of thyroxine, and nonthyroidal illness–like changes.
3. **Hypothyroxinemia of prematurity, morbidity, and neurologic outcome.** Several studies correlate measures of

morbidity and mortality with reduced serum T_4 concentrations, but they do not establish cause and effect. While some studies show improvement in some of these measures with thyroxine treatment, most controlled trials show no effect. Overall, thyroxine treatment does not appear to affect IQ, although evidence from a Dutch study suggested that the subgroup of premature infants younger than 27 weeks may benefit from thyroxine treatment.

C. Neurologic consequences of congenital hypothyroidism

1. **Pathophysiology.** Thyroid hormone is required for normal fetal neuroblast proliferation and migration, axonal and dendritic outgrowth, oligodendrocyte differentiation, and myelination. Animal studies have shown nuclear thyroid receptor and thyroid hormone deiodinase expression in both neuronal and glial components of the brain. This expression predates the onset of fetal thyroid function and supports that transplacentally transferred maternal thyroid hormone is important for early embryonic development.
2. **IQ.** Several studies document an inverse correlation between the age of diagnosis and treatment and intellectual prognosis (Table 40-1). Data from the prescreening era show that treatment delay beyond 6 months of age results in severe mental p. 532p. 533retardation (mean IQ 54). Mean IQ improves to 71 in patients who initiate treatment between 3 and 6 months of age, and to 89 in those treated by 3 months of age. This illustrates that the timing of diagnosis and the rapid restoration of euthyroidism are crucial to best neurologic outcome. The early initiation of **optimal levothyroxine therapy within the first 2 weeks of life** is associated with normal intellectual outcome of affected children, and this best outcome is only possible through newborn screening.

TABLE 40-1 Age Treatment for Congenital Hypothyroidism Started and Intellectual Outcome Prior to Newborn Screening[a]

Age (mo)	IQ ($\bar{X}$)	Range
0–3	89	64–107
3–6	71	35–96
>6	54	25–80

$\overline{X}$, mean.
[a]Other neurologic sequelae include the following: (a) ataxia, (b) gross and fine motor incoordination, (c) hypotonia and spasticity, (d) speech disorder, (e) sensorineural hearing loss, (f) strabismus, and (g) short attention span.
Adapted from Klein AH, Meltzer S, Kenny FM. Improved prognosis in congenital hypothyroidism treated before age 3 months. *J Pediatr* 1972;81:912.

3. **Other neurologic sequelae.** Besides abnormal cognitive function, abnormalities of muscle tone, gait, coordination, speech, hearing, and vision can be present (Table 40-1). Recent consensus guidelines recommend close monitoring of psychomotor and language development and screening for delays in speech acquisition by 3 years of age.

III. SCREENING PROGRAMS FOR CONGENITAL HYPOTHYROIDISM

Since the introduction of newborn screening for congenital hypothyroidism in the 1970s, programs have been developed in the Americas, Europe, Asia, and Africa. It is now estimated that over 37 million births are screened per year worldwide, corresponds to approximately 29% of the world's birth population. This indicates both continued advancement and the need for further growth because most (71%) infants are still born in areas that lack newborn screening.

A. Screening strategies

1. **Primary T_4-follow-up TSH.** Historically, early screening programs relied upon T_4 tests, given the technical challenges of large-scale TSH measurements from filter paper. In this approach, a filter-paper T_4 measurement is carried out on all infants; in those infants with a T_4 level below a prescribed cutoff (usually 10%), a TSH determination is performed. As TSH assays have improved, many screening programs have transitioned to a primary TSH test. However, almost half the programs in the USA still employ a primary T_4-follow-up TSH strategy.

   This strategy will detect overt primary hypothyroidism. In addition, if low T_4 nonelevated TSH screening tests are followed up, this approach has the potential to detect infants with hypothyroidism and a delayed TSH rise, hypothalamic–pituitary hypothyroidism, and TBG deficiency. Primary T_4-follow-up TSH

strategies will miss infants with subclinical hypothyroidism (normal T_4, elevated TSH).

2. **Primary TSH.** Worldwide, most screening programs now employ a primary TSH strategy (exceptions include some programs in the United States, Israel, the Netherlands, and Japan). A primary TSH screening approach may not identify infants with hypothalamic–pituitary hypothyroidism or TBG deficiency. However, it can identify infants with subclinical hypothyroidism and transient hyperthyrotropinemia. In countries that promote early discharge of infants <24 hours old (when the normal TSH level can extend above 50 μU/mL), age-adjusted TSH cutoffs should be implemented. Overall, the worldwide shift toward primary TSH

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strategies has facilitated the detection of milder forms of primary hypothyroidism in the newborn period.
3. **Simultaneous T_4 and TSH.** A minority of programs perform simultaneous T_4 (or free T_4) and TSH testing. This screening approach can diagnose all the thyroid disorders described earlier.
4. **Specimen collection at two time periods.** Ten programs in the United States collect a routine second specimen on all newborns and several other programs collect a "discretionary" second specimen in babies at-risk for delayed TSH rise. Data from programs that collect two routine specimens indicate that **up to 10% of infants with primary hypothyroidism are detected by their second test**, indicating the need for further study of this strategy and the outcome of infants with delayed TSH rise. It is universally recognized that a second specimen for testing should be considered in all newborns at-risk for delayed TSH elevation, including those with premature birth, critical newborn illness, congenital anomalies, same-sex twins, and drug exposures (steroids, dopamine, iodine) that could suppress TSH secretion (Table 40-2).

IV. EPIDEMIOLOGY

A. Incidence. Changes in newborn screening have expanded our understanding of neonatal thyroid disease and contributed to recent changes in the reported epidemiology of congenital hypothyroidism. Until recently, the incidence of congenital hypothyroidism was

commonly cited to be **1:3 000 to 1:4 000**, with the vast majority of cases (85%) attributed to dysgenesis and the remainder largely attributed to dyshormonogenesis. In contrast, several reports from the past decade have reported much higher rates of congenital hypothyroidism, ranging from **1:1 030 to 1:2 450**. This marked increase is due in part to changing demographics, including a relative increase in the screening of Asian, Native American, and Hispanic populations (where congenital hypothyroidism is more common) and of infants who are born prematurely or to older mothers (both risk factors for congenital hypothyroidism).

However, several analyses support that changes in screening practices themselves have increased the incidence of congenital hypothyroidism by detecting milder forms of hypothyroidism. As mentioned above, the worldwide shift toward primary TSH screening strategies now permits the detection of subclinical hypothyroidism (high TSH, normal T_4) and this has been compounded in several programs by modifications to lower TSH cutoffs (to prevent missed cases) and to obtain earlier specimens (when the neonatal TSH surge is still ongoing) to compensate for the practice of earlier infant discharge. In studies of etiology, most children with these milder forms of hypothyroidism have anatomically normal, eutopic thyroid glands ("thyroid-in-situ") and one study that screened known dyshormonogenesis genes found likely disease-causing mutations in 59% of subjects in a cohort enriched for familial cases. This has in turn increased the fraction of congenital hypothyroidism attributed to dyshormonogenesis.

TABLE 40-2 Potential Indications for a Second or Discretionary Screening Test

A. Very-low-birth-weight infants: <1 500 g
B. Perinatal complications, including the following:
  1. NICU admission
  2. Transfusion
  3. Congenital heart disease
  4. Other severe congenital anomalies
  5. Same-sex twins
  6. Dopamine administration
  7. Steroid administration
  8. Iodine exposure

NICU, neonatal intensive care unit.

V. ETIOLOGY

Congenital hypothyroidism is not the result of a single disorder; rather there is a spectrum of thyroid dysfunction, as listed in Table 40-3.

A. Permanent primary hypothyroidism

1. **Thyroid dysgenesis,** defined as defective development of the embryonic thyroid, accounts for approximately 80% of permanent congenital hypothyroidism. The most common form is ectopy (usually with ectopic glandular tissue in the sublingual region or elsewhere along the normal migration path of the fetal thyroid), followed by athyreosis (failure of the thyroid gland to form) and hypoplasia (a normally located but small thyroid gland). Although most thyroid dysgenesis occurs without a positive family history, analysis of a French registry has shown that approximately **2% of cases are familial**. This indicates that dysgenesis may be genetically mediated in certain cases—a concept that has been further supported by the specific association of thyroid dysgenesis with rare germline mutations in transcription factors important for normal thyroid embryonic development, including TTF1 (also called NKX2-1), TTF2, PAX8, and NKX2-5, and with loss of function mutations in the TSH receptor (TSHR), which can cause severe hypoplasia by disrupting TSH-dependent glandular growth.
2. **Dyshormonogenesis,** defined as defective thyroid hormone biosynthesis, is an important cause of permanent congenital hypothyroidism. It has long been recognized that loss of function mutations in several genes that encode proteins required for normal thyroid hormone production can cause congenital hypothyroidism in humans. This includes mutations in the sodium-iodine symporter (*SLC5A5*, required for iodine uptake into thyroid follicular cells), thyroid peroxidase (required for iodide oxidation and organification), and TG genes, which usually transmit congenitally hypothyroidism in autosomal recessive pattern of inheritance. More recently, human mutations in the thyroid oxidase (THOX2 and THOX2A) and iodotyrosine deiodinases (DEHAL1) genes have also been shown to impair thyroid hormone biosynthesis and present variably in patients as either congenital hypothyroidism (transient, permanent, or delayed onset) or as

euthyroid goiter.

3. **Maternal RAI treatment.** If a woman inadvertently receives ^{131}I iodine therapy for hyperthyroidism or thyroid cancer beyond the eighth week of gestation, the radioiodine can cross the placenta and ablate the fetal thyroid.

TABLE 40-3 Causes of Congenital Hypothyroidism

- **A.** Permanent primary hypothyroidism
  - **1.** Thyroid dysgenesis
    - **a.** Ectopy
    - **b.** Athyreosis
    - **c.** Hypoplasia
  - **2.** Dyshormonogenesis
  - **3.** Maternal radioactive iodine treatment
- **B.** Transient primary hypothyroidism
  - **1.** Maternal transfer of TSH receptor–blocking antibodies
  - **2.** Maternal Graves disease and transplacental passage of antithyroid drug
  - **3.** Maternal iodine deficiency
  - **4.** Excessive iodine exposure
- **C.** Subclinical primary hypothyroidism
- **D.** Transient central hypothyroidism
  - **1.** Nonthyroidal illness syndrome
  - **2.** Transient hypothyroxinemia of prematurity
  - **3.** Delayed TSH rise
- **E.** Permanent central hypothyroidism

TSH, thyroid-stimulating hormone.

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B. Transient primary hypothyroidism

1. **Maternal transfer of TSH receptor blocking antibodies (TBAb).** Maternal antibody-mediated congenital hypothyroidism resulting from transplacental passage of TBAb is reported to occur in approximately 1 in 100 000 newborns. Some mothers who have autoimmune thyroiditis can produce an IgG TBAb that crosses the placenta and blocks fetal TSH binding to the thyroid receptor. Affected infants are born with primary hypothyroidism. Thyroid scintigraphy may be interpreted as athyreosis (due to the lack of TSH-dependent radionuclide uptake), but an ultrasound examination shows a eutopic thyroid gland. With disappearance of maternal TBAb over the first months of life, the infant's thyroid

function normalizes. Thus, when there is a history of maternal autoimmune thyroid disease or of transient congenital hypothyroidism in an older sibling, it is recommended that mothers and infants be tested for TBAb. If present, an early trial of decreased thyroxine replacement should be considered.

2. **Maternal Graves disease** and transplacental passage of antithyroid medication. The thionamide drugs (methimazole or propylthiouracil) used to treat maternal hyperthyroidism can cross the placenta and block fetal thyroid hormone production. This form of hypothyroidism is transient and usually resolves within 2 weeks because the drug is cleared from the newborn's circulation.
3. **Maternal iodine deficiency.** Iodine is an obligate nutritional precursor for thyroid hormone synthesis. In geographic areas of iodine deficiency, associated with endemic goiter, maternal and therefore fetal iodine deficiency can result in neonatal thyroid hormone deficiency and overt hypothyroidism. The main areas of endemic goiter are the South Pacific, China, and Africa, but parts of Europe are also affected. **Worldwide, iodine deficiency is the most common etiology of combined maternal and fetal hypothyroidism**, which represents a unique mechanism of *in utero* injury as neither thyroid axis is normal and able to compensate for thyroid hormone deficiency. The resultant morbidity of endemic cretinism, which includes both growth failure and neurologic injury, is completely **preventable** by the correction of dietary iodine deficiency through either iodine supplementation or food fortification.
4. **Excessive iodine exposure.** Although adequate dietary iodine intake is required for normal thyroid function, exposure to excessive amounts of iodine has potent antithyroid action, both through the **Wolff–Chaikoff effect** and through the inhibition of thyroid hormone release. Congenital hypothyroidism can occur secondary to excessive maternal iodine exposure (from iodine-containing antiseptics used in obstetric care or the ingestion of certain nutritional supplements) or to excessive neonatal exposure (from iodine-containing antiseptics or contrast media). After the excessive iodine exposure has passed, thyroid function will eventually normalize. However, recovery from iodine's antithyroid effects can be prolonged in prematurely born infants. Given the critical dependence of neonatal neurodevelopment on thyroid

hormone, levothyroxine therapy should be offered if necessary to avoid prolonged hypothyroidism.

C. Subclinical primary hypothyroidism

1. As described above in Section IV, the worldwide shift toward primary TSH screening strategies has increased the detection of subclinical hypothyroidism (**high TSH, normal T_4**) in newborns, and a large number of infants with mild primary hypothyroidism are now identified by newborn screening programs. Most have anatomically normal, eutopic thyroid glands ("thyroid-in-situ").
2. Several recent studies document a high rate of transient hypothyroidism, with spontaneous normalization of thyroid function in about a quarter of neonates diagnosed with mild congenital hypothyroidism and "thyroid-in-situ." This argues that a trial of decreased therapy should be offered to such patients after 2 to 3 years of age (to assess hypothyroidism permanence) and that future clinical research related to etiology should take care to phenotype subjects by hypothyroidism permanence (vs. transience).

D. Transient central hypothyroidism. When persistent, the pattern of low total and free T_4 concentrations but normal TSH can be interpreted as central (secondary) p. 536p. 537hypothyroidism. However, isolated central hypothyroidism is extremely rare, and this same pattern can be transiently displayed in individuals without true hypothalamic or pituitary disease. Awareness of conditions associated with such transient hypothyroxinemia is helpful to avoid misdiagnoses.

1. **Nonthyroidal illness syndrome** refers to the transient derangement of serum thyroid function tests that is observed in most hospitalized patients. Critical illness decreases both TSH secretion and the peripheral activation of secreted T_4. In addition, thyroid hormone degradation is increased. Collectively, these mechanisms produce hypothyroxinemia with an inappropriately normal TSH concentration in patients who are ill. With resolution of the intercurrent sickness, thyroid function tests eventually normalize. Thus, in patients who develop hypothyroxinemia during hospitalization or other critical illness, the possibility that

nonthyroidal illness (rather than permanent central hypothyroidism) should be considered to avoid unnecessary evaluations for hypopituitarism.

2. **Transient hypothyroxinemia of prematurity.** As described above in Section II, premature and other low-birth-weight infants have lower serum T_4 concentrations and attenuated neonatal TSH surges when compared with full-term infants. These changes are attributed to immaturity of the thyroid axis and are **most pronounced in extreme prematurity (before 28 weeks gestation)**. This same population requires intensive medical care so their hypothyroxinemia is further compounded by the nonthyroidal illness syndrome. As a result, preterm infants commonly develop temporary postnatal reductions in serum T_4 and free T_4 (compared to cord values) without hyperthyrotropinemia, a pattern that is commonly termed **transient hypothyroxinemia of infancy**. Although the hypothyroxinemia in this population has been associated with worse neurodevelopmental outcome, the causality has not been established and, despite intensive study, a **definitive benefit of thyroid hormone replacement in this population has not been established**.
3. **Delayed TSH rise.** Some infants initially have a low T_4 and nonelevated TSH concentration, but on a second screening test have a low T_4 and elevated TSH concentration, confirmed by serum studies. These cases are uncommon, but occur more frequently in preterm or acutely ill infants (as would be expected from continued maturation of the hypothalamic–pituitary–thyroid axis and recovery from the nonthyroidal illness syndrome).
4. **Thyroxine-binding** artifacts, such as X-linked TBG deficiency, that decrease circulating thyroxine-binding proteins are associated with low serum total T_4 measurements, but normal free T_4 and TSH concentrations. Such individuals are **euthyroid and require no treatment**. If a binding artifact is suspected, a normal free T_4 concentration should be documented by a dialysis or ultrafiltration method that separates free from bound T_4 (as these reference tests are least subject to assay artifact from aberrant binding proteins).

E. Permanent central hypothyroidism accounts for approximately

5% of cases of congenital hypothyroidism detected by screening programs. These defects are usually associated with multiple pituitary hormone deficiency and about half will have pituitary malformations on MRI. Sporadic congenital hypopituitarism from birth trauma or asphyxia with pituitary stalk transection has been described. In addition, genetic research has identified a growing number of driver mutations. Central hypothyroidism may also develop as a component of combined pituitary deficiency from *HESX1; LHX3; LHX4; SOX3; PROP-1;* or *POU1FI* mutations. Isolated central hypothyroidism is rare, but can occur from germline mutations in *TRHR; TSHB; or IGSF1 (X-linked).*

VI. CLINICAL MANIFESTATIONS

At the time, infants with hypothyroidism are detected by newborn screening programs, their clinical manifestations are usually subtle, nonspecific, or absent. **Fewer than 5% are suspected of having hypothyroidism on clinical grounds** prior to notification by the screening laboratory. This absence of initial clinical features is partly explained by the protective effects of maternal thyroid hormones. In the few infants who are so p. 537p. 538affected that they have obvious clinical manifestations in the first week of life, one can surmise that they have had more severe, long-lasting hypothyroidism in utero. In general, mean birth weight and length are near the 50th percentile; head circumference is slightly increased, approximately at the 70th percentile, owing to **cerebral myxedema**. Despite normal somatic growth, there may be evidence of in utero hypothyroidism based on retarded skeletal maturation at birth. There is also a tendency to prolonged gestation, with **one third of the pregnancies lasting 42 weeks or longer**. The most common symptoms and signs of congenital hypothyroidism are listed in Table 40-4.

A. Symptoms.

Common symptoms include lethargy, delayed stooling and constipation, poor suck and feeding problems, and hypothermia. However, fewer than a third of infants with congenital hypothyroidism detected by screening programs manifest any of these symptoms at the time of detection.

B. Signs

1. **On physical examination** at the time of detection, the majority of infants have few if any of the signs listed in Table 40-4. A small

number of infants present with the classic physical appearance, including puffy, myxedematous facies, depressed nasal bridge with pseudohypertelorism, large fontanels (particularly the posterior fontanel), wide sutures, a large protruding tongue with an open mouth (macroglossia), a hoarse cry, an umbilical hernia with distended abdomen, cold mottled skin (cutis marmorata), jaundice (secondary to delayed maturation of the hepatic enzyme glucuronyl transferase), hypotonia, and delayed deep tendon reflexes. Galactorrhea associated with elevated prolactin levels has also been reported. A goiter may be palpable in infants with one of the inborn errors of thyroid hormone biosynthesis or in infants born to mothers overtreated with thionamides.

2. **If the diagnosis is delayed** or not made, infants manifest a subnormal growth rate and delayed development. These can be apparent by 3 to 6 months of age. Mental retardation along with neurologic damage, including incoordination, ataxia, hyper- or hypotonia, neurosensory hearing loss, and strabismus, is also likely to develop.
3. **Hypothalamic–pituitary hypothyroidism.** In these infants, TSH deficiency in general produces milder hypothyroidism, so that clinical manifestations are less obvious than with primary hypothyroidism. However, one should be suspicious of secondary hypothyroidism in infants with midline defects such as cleft lip or palate, infants with ocular signs such as wandering eye movements or nystagmus, and infants with signs of other pituitary hormone deficiencies. These include hypoglycemia, which can be secondary to growth hormone and/or adrenocorticotropic hormone (and cortisol) deficiency, and males with microgenitalia, p. 538p. 539including micropenis, hypoplastic scrotum, and undescended testes. Diabetes insipidus resulting from antidiuretic hormone deficiency is seen uncommonly with congenital hypopituitarism.

TABLE 40-4 Clinical Manifestations of Congenital Hypothyroidism

Symptoms	Signs
Prolonged jaundice	Skin mottling

Lethargy	Umbilical hernia
Constipation	Jaundice
Feeding problems	Macroglossia
Cold to touch	Large fontanels, wide sutures
	Distended abdomen
	Hoarse cry
	Hypotonia
	Dry skin
	Slow reflexes
	Goiter

Adapted from LaFranchi SH, Murphey WH, Foley TP Jr, et al. Neonatal hypothyroidism detected by the Northwest Regional Screening Program. *Pediatrics* 1979;63:180.

C. Associated congenital anomalies. Infants with congenital hypothyroidism appear to be at increased risk for other congenital anomalies. One study showed a fourfold higher prevalence of congenital anomalies (8.4%) compared with a control infant population (2%). Cardiovascular anomalies are the most commonly associated, including pulmonary stenosis, atrial septal defect, and ventricular septal defect. It is unclear whether these anomalies are secondary to an underlying genetic abnormality or teratogen, or whether the increased medical testing in this population increases the detection of thyroid dysfunction. **Congenital hypothyroidism occurs more commonly with trisomy 21 and trisomy 18.** Rare syndromic forms of thyroid dysgenesis can be associated with other inherited extrathyroidal pathology, including pulmonary disease (from germline *TTF1* mutation) and cleft palate and choanal atresia (from germline *TTF2* mutation).

VII. DIAGNOSTIC TESTS

Although screening tests identify infants who are likely to have congenital hypothyroidism, formal laboratory tests should always be obtained to confirm the diagnosis (Table 40-5).

A. Routine tests. The simplest tests to confirm the diagnosis of primary hypothyroidism are serum-free T_4 and TSH measurements. If preferred, a free T_4 index (FT_4I) may be calculated from the serum total T_4 measurement and thyroid hormone binding ratio (THBR) (also called the T_3 resin uptake [T_3RU]) to substitute for a free T_4

measurement. **Serum T_3 is not useful to diagnosis hypothyroidism**, as it is often maintained in the normal range during early disease. It is important to keep in mind that the normal range of serum thyroid hormone concentrations is higher in the first few weeks and months of life, so that abnormal results can be determined only by comparison to age-related normative date. The normal ranges for serum-free T_4, T_4, free T_3, T_3, TBG, and TSH through infancy and childhood are presented in Table 40-6. Measurement of serum-free T_4, total T_4, THBR, and TSH separates out the common neonatal thyroid disorders, as summarized in Table 40-7.

1. The biochemical hallmarks of **primary hypothyroidism** are a low–serum-free T_4 (or FT_4I) and elevated TSH levels. Infants with subclinical hypothyroidism have elevated TSH levels but normal free T_4. Infants with transient hypothyroidism have abnormal screening results that revert to normal, usually in the first few months of life, depending on the underlying etiologic factor (see Section V.B).
2. **With central hypothyroidism,** the serum-free T_4 is low, and TSH is usually inappropriately normal or low TSH. **Of note, while certain patients with TRH deficiency may present with a high TSH** (related to impaired TRH-dependent TSH glycosylation and bioactivity), this pattern is extremely rare.

TABLE 40-5 Diagnostic Tests in Congenital Hypothyroidism

A. Routine (required to confirm diagnosis)
  1. Serum-free T_4 (or free T_4 index calculated from total T_4 and THBR)
  2. Serum TSH
B. Optional
  1. Thyroid ultrasound
  2. Serum thyroglobulin
  3. Thyroid scintigraphy using ^{123}I or ^{99m}Tc
  4. TSH receptor–blocking antibodies
  5. Urinary iodine
  6. Radiograph of knee and foot for bone age

T_3, tri-iodothyronine; T_4, thyroxine; TSH, thyroid-stimulating hormone; THBR, thyroid hormone binding ratio.
[a]Commercial assays currently available measure thyrotropin-binding inhibitor immunoglobulin.

TABLE 40-6 **Normal Mean and Range (±SD) for Total Thyroxine, Free Thyroxine, Tri-iodothyronine, Free Tri-iodothyronine, TBG, and TSH in Infancy and Childhood**

Age	T_4 (μg/dL)[a]	Free T_4 (ng/dL)[a]	T_3 (ng/dL)[a]	Free T_3 (pg/dL)[a]	TBG (mg/dL)[a]	TSH (μU/mL)[a]
Premature infant	4.0 (2.0–6.5)	1.2 (0.5–1.6)	32 (14–50)	—	—	2.0 (0.8–5.2)
Cord blood	10.2 (7.4–13.0)	1.5 (0.9–2.2)	45 (15–75)	—	5.6 —	9.0 (1.0–17.4)
1–3 d	17.2 (11.8–22.6)	3.7 (2.2–5.3)	124 (32–216)	470 (180–760)	5.0 —	8.0 (1.0–17.4)
1–2 wk	13.2 (9.8–16.6)	2.7 (1.6–3.8)	250 —	—	—	4.0 (1.7–9.1)
2 wk–4 mo	10.7 (7.0–15.0)	1.5 (0.9–2.2)	180 (120–240)	480 (185–770)	—	2.3 (1.7–9.1)
4–12 mo	11.0 (0.7–1.9)	1.3 (0.7–1.9)	176 (110–280)	465 (215–720)	4.4 (3.1–5.6)	2.0 (0.8–8.2)
1–5 y	10.5 (7.3–15.0)	1.5 (0.8–2.3)	168 (105–269)	460 (215–700)	4.2 (2.9–5.4)	2.0 (0.8–8.2)
5–10 y	9.3 (6.4–13.3)	1.4 (0.7–2.1)	150 (94–241)	440 (230–650)	3.8 (2.5–5.0)	2.0 (0.7–7.0)
10–15 y	8.1 (5.6–11.7)	1.3 (0.6–2.0)	113 (83–213)	440 (230–650)	3.3 (2.1–4.6)	1.9 (0.7–5.7)

SD, standard deviation; T_3, tri-iodothyronine; T_4, thyroxine; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone.

[a]Conversion factors:

- T_4: 1 ng/dL = 12.87 pmol/L
- Free T_4: 1 μg/dL = 12.87 nmol/L
- T_3: 1 ng/dL = 15.36 pmol/L
- Free T_3: 1 pg/dL = 0.1563 pmol/L
- TBG: 1 mg/dL = 10 mg/L
- TSH: 1 μU/mL = 1 mU/L

Adapted from LaFranchi SH. Hypothyroidism, congenital and acquired. In: Kaplan SA, ed. *Clinical Pediatric and Adolescent Endocrinology*. Philadelphia: WB Saunders; 1982:87; and Nichol's Institute and Esoterix normal reference range.

B. Optional studies. The below tests have historically been used to establish specific etiologies of congenital hypothyroidism in individual patients. They are important research tools and so warrant discussion. However, as their diagnostic accuracy is limited and their results rarely alter clinical care, the authors do not recommend their routine use in the management of patients (considered optional). When ancillary tests are desired to assess the etiology of congenital hypothyroidism, the combination of serum TG and neck ultrasonography is favored to avoid exposing the infant to radiation.

1. **Thyroid ultrasound examination** is a convenient first-line imaging test. A large eutopic gland suggests dyshormonogeneses. Ultrasonography may also diagnose hypoplasia (a small thyroid gland) or hemiagenesis. If no glandular tissue is visualized in the thyroid bed, athyreosis is possible but imaging should be extended superiorly to look for ectopic thyroid tissue, recognizing that very superior/lingual foci may not be well visualized.
2. **Serum TG concentrations** roughly correlate with the amount of functioning thyroid tissue. TG levels are extremely low or undetectable in thyroid agenesis. p. 540p. 541Intermediate or elevated TG concentrations suggest thyroid ectopy or dyshormonogenesis (with the exception of TG synthetic defects). These possibilities can be differentiated by neck ultrasonography.

TABLE 40-7 Interpretation of Screening and Confirmatory Thyroid Blood Tests

Disorder	Screening		Confirmatory			
	T_4	TSH	Free T_4	T_4	THBR	TSH
Primary hypothyroidism	↓	↑	↓	↓	↓ –N	↑
Subclinical hypothyroidism	↓ –N	↑	N	N	N	↑
Transient hypothyroidism	↓	↑	N	N	N	N
Hypothalamic–pituitary hypothyroidism	↓	"N"	↓	↓	↓ –N	↓ –N
TBG deficiency	↓	N	N	↓	↑	N

N, normal; "N", below the level of sensitivity of the screening assay (i.e., <25 μU/mL); T_4, thyroxine; T_3RU, tri-iodothyronine resin uptake; TSH, thyroid-stimulating hormone; ↓, decreased; ↑, increased.

3. **Thyroid scintigraphy** with RAI (^{123}I) or sodium pertechnetate (^{99m}Tc) can identify the location and shape of functional thyroid tissue. Sensitivity is best before euthyroidism is fully restored because hyperthyrotropinemia stimulates the thyroidal uptake of ^{123}I and ^{99m}Tc. **^{131}I delivers** a much higher dose of radioactivity to the patient and **should not be used in infants**. If scintigraphy shows an ectopic thyroid tissue, the cause of the hypothyroidism is established and no additional tests are necessary. If ^{123}I uptake is elevated with a eutopic location, dyshormonogenesis is likely and a **perchlorate discharge test**

(if available) may be considered to diagnosis defective iodide oxidation or organification. If radionuclide uptake is absent, an ultrasound examination should be performed to distinguish thyroid aplasia from TSHR and sodium-iodine symporter defects. Of note, prior to scintigraphy, a medication and dietary history should be performed to rule out occult iodine exposures that may artifactually decrease radionuclide uptake (measurement of urinary iodine in the infant can confirm this if suspected).

4. **TBAb.** Measurement of TBAb in the infant and mother is recommended when transient hypothyroidism from maternal autoimmune thyroid disease is suspected. Affected infants typically have decreased/absent radionuclide uptake by scintigraphy but a eutopic gland by ultrasound examination. Documentation of elevated TBAb titers in such patients may be used to justify a near term trial of decreased levothyroxine therapy (to test for hypothyroidism resolution).
5. **Urinary iodine.** When excess iodine exposure (in utero or postnatal) is suspected as a cause of transient congenital hypothyroidism, urinary iodine can be directly measured to look for abnormal elevation. Conversely, low urinary iodine measurements may also be used to document iodine deficiency.
6. **Bone age evaluation.** An evaluation of skeletal maturation through radiography of the knee and foot can be used to estimate the onset of hypothyroidism. Most newborn infants show ossification of the distal femur, proximal tibia, and cuboid bone of the foot. Delayed maturation of these ossification centers indicates more prolonged hypothyroidism prior to birth.

VIII. TREATMENT

It is important to start thyroid hormone as **early as possible** and to pick a starting dose that will rapidly restore euthyroidism to avoid the untoward effects of hypothyroidism on the developing nervous system. Once this is accomplished, the long-term goal is **to maintain serum T_4 concentrations in the upper half of the normal range** along with a normalized TSH to ensure normal growth and development, including maximal p. 541p. 542intellectual potential without neurologic sequelae. Because central nervous system development is dependent on normal thyroid levels for at **least the first 2 or 3 years of life**, this is a

crucial treatment period.

A. T_4 administration and dosage. Sodium levothyroxine is the treatment of choice; only tablets should be used because there are no FDA-approved liquid preparations. We instruct parents to crush the tablets (with a pill crusher or between two spoons), then dissolve the powder in a small volume of expressed breast milk or water. This mixture, prepared daily, can be placed in the cheek pad using a syringe or placed in an open nipple and given before a feeding. It should not be placed in a full bottle. Levothyroxine **should not be given with any food or nutrient supplement that contains soy protein, iron, or concentrated calcium preparations** because these have the potential to bind thyroxine and interfere with its absorption. Increasing the levothyroxine dose might be acceptable, but the concern is that the binding and inhibition of absorption is variable, so one might see variable serum T_4 levels. If **soy protein formula** must be used, the more common recommendation is to space the thyroid hormone treatment halfway between feedings. The recommended L-T_4 starting dose is 10 to 15 μg/kg/day (see Table 40-8). This dose can be tailored to the severity of hypothyroidism, with patients who have athyreosis and/or more severe hypothyroidism (serum T_4 < 5 μg/dL [<65 nmol/L]) started at the higher end of this dosage range. In selected mild cases of congenital hypothyroidism, lower starting doses in the 6 to 10 μg/kg/day range may be considered.

IX. MONITORING AND FOLLOW-UP MANAGEMENT

Careful follow-up management with proper titration of levothyroxine therapy is crucial in ensuring normal growth and neurocognitive development. Guidelines from the American Academy of Pediatrics and the European Society for Pediatric Endocrinology are available (Table 40-9), but it should be emphasized that management must be individualized in each case.

A. Clinical follow-up. The aim of treatment is to achieve normal growth and development within the context of the family's genetic potential. At each visit, the child's length, weight, and head circumference should be measured and plotted. Developmental milestones, including gross and fine motor skills, language, and social development, may be assessed at each visit, using a tool such as the Denver Developmental Screen.

B. Laboratory follow-up. Serum thyroid function tests should be determined approximately 2 and 4 weeks after onset of therapy, every 1 to 2 months in the first 6 months of life, and then every 2 to 4 months up to 3 years of age. More frequent monitoring should be performed, if serum thyroid tests are abnormal or noncompliance is suspected. Commonly recommended targets are to **keep the serum-free T_4 in the upper half of age-specific normal ranges and aim for a serum TSH <5 mU/mL**. Both undertreatment and overtreatment have been associated with poorer neurodevelopmental outcome and should be avoided.

C. Psychometric follow-up. Psychomotor development and school performance should be carefully monitored and recorded in children with congenital hypothyroidism. Some consensus groups have recommended screening for speech delay by 3 years of age and repeated hearing testing before school age.

TABLE 40-8 Recommended Daily Dose of Sodium Levothyroxine (Na l-T_4) in the Management of Hypothyroidism

Age	Na l-T_4 (μg/kg/d)
Initial starting dose	10–15
0–3 mo	8–12
3–6 mo	7–10
6–12 mo	6–8
1–5 yr	4–6
6–12 yr	3–5
>12 yr	2–4

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TABLE 40-9 Follow-up Monitoring and Management of Congenital Hypothyroidism

A. Biochemical (T_4 or free T_4 and TSH) evaluation
1. Two and 4 weeks after starting treatment
2. Every 1–2 mo in first year
3. Every 3–4 mo in second and third years
4. Goals:
   a. Serum-free T_4 in the upper half of normal range

b. Serum TSH normal (ideally <5 mU/L) **B.** Clinical evaluation of growth and development **C.** Monitor psychometric development and school performance. **D.** Consider screening for speech delay by 3 years of age and repeat hearing testing before school age
TSH, thyroid-stimulating hormone.

D. Documentation of permanent hypothyroidism. If imaging studies were carried out and definitively diagnosed a permanent form of congenital hypothyroidism (i.e., athyreosis or complete ectopy), parents may be counseled that treatment will be lifelong. In addition, if an infant has a **"secondary rise" of TSH above 10 μU/mL after 6 months of age while on therapy, it can be assumed that he or she has permanent hypothyroidism. If this does not occur by age 3, it is recommended that a trial of decreased levothyroxine therapy be performed** to test for hypothyroidism permanence.

X. PROGNOSIS

A. Growth and pubertal development. Essentially all programs report that infants detected by screening and adequately treated grow at normal percentiles. Onset and progression of puberty are normal, and adult heights are within the range expected for genetic potential.

B. Intellectual and neurologic outcome. Many screening programs have reported that infants started on early treatment and treated appropriately through the first 3 years of life have normal IQs similar to those in control groups. The New England Collaborative Group reported a mean verbal IQ of 109, a performance IQ of 107, and a full-scale IQ of 109 at 6 years, essentially identical to sibling and classmate control groups. Some long-term follow-up studies have reported subtle differences in neurocognition and correlated these deficits with later onset of treatment and lower starting doses of levothyroxine. Future research will determine if current management (which is characterized by earlier treatment and higher starting doses) will resolve these subtle deficits.

XI. MISSED CASES

As a public health measure, newborn screening was initiated to identify infants with primary hypothyroidism. After >40 years of experience, it is

apparent that newborn screening has been extremely successful; approximately one case is missed for every 120 cases detected. Factors responsible for cases being missed include the following: no specimen collected (a concern with home deliveries and infants transferred from one hospital to another), collection of an inadequate specimen, failure to transport the specimen to the screening laboratory, errors in laboratory procedures, which include technical assay errors or human errors in recording abnormal results, and lack of follow-up of infants with abnormal screening results (especially when families transfer care to another physician or relocate). Finally, some infants with milder forms of hypothyroidism pass an initial screen yet develop more overt hypothyroidism in the first months of life (see Sections III.A.4 and III.C.1.c). Thus, physicians caring for infants should not assume that in cases with compatible clinical features, hypothyroidism has been excluded on the basis of a normal newborn screening test. Physicians need to stay alert to the possibility of undiagnosed congenital hypothyroidism and should perform their own serum thyroid function test when infants manifest suspicious symptoms and signs.

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XII. NEONATAL HYPERTHYROIDISM

Neonatal hyperthyroidism (from neonatal Graves disease) is an uncommon disorder observed in a minority **(<3%) of infants born to mothers with Graves disease**. It is caused by the transplacental transfer of maternal thyrotropin receptor–stimulating antibodies (TSAb) that hyperstimulate the fetal/neonatal thyroid. As expected from this mechanism of disease, hyperthyroidism is transient and usually remits by 3 months of age as maternal TSAb clear from the infant's circulation. The persistence of neonatal hyperthyroidism beyond 3 months of age should prompt consideration of permanent hyperthyroidism from an **activating mutation of the TSHR** or from **McCune–Albright syndrome (**caused by an **activating mutation in the *α* subunit of the G protein)**.

A. Clinical manifestations

1. **Fetal tachycardia** exceeding 160 beats/minute after midgestation is a sign of fetal thyrotoxicosis in the at-risk fetus.
2. **Infants with neonatal hyperthyroidism** can be born prematurely (although the thyrotoxic state can influence estimates

of fetal maturity), and there is often intrauterine growth retardation with birth weights of 2.0 to 2.5 kg in full-term infants.

3. **Microcephaly and ventricular enlargement** may be present.
4. **Exophthalmos** is often present.
5. **A goiter is palpable** in about half the cases, and this can enlarge and cause upper airway obstruction.
6. Affected **infants are irritable**, sweaty, hyperactive, and tend to have an increased appetite (although some feed poorly). Nevertheless, they manifest poor weight gain or even weight loss, which can be exacerbated by vomiting and diarrhea.
7. **Hepatosplenomegaly and jaundice** may be present.
8. **Tachycardia** is usually present, and arrhythmias and cardiac failure have been described.
9. The **onset, severity, and duration** of symptoms are variable. In some infants, the **onset of neonatal hyperthyroidism can be delayed for weeks** because of the transplacental transfer of maternal antithyroid medications or TBAb.

B. Diagnosis

1. Pregnant women with a history of Graves' disease should be screened for elevated **TSH receptor antibodies (TRAb) titers in mid gestation** (20 to 24 weeks gestation). Elevated TRAb titers indicate a significant risk of fetal/neonatal thyroid dysfunction and warrant increased fetal surveillance with serial ultrasonography (to monitor fetal growth, thyroid size, and heart rate). Of note, as elevated TSAb titers can persist for years after successful thyroid ablation, women who are euthyroid on levothyroxine after thyroidectomy or I-131 ablation for Graves' must also be screened. Even without elevated TRAb titers, active maternal hyperthyroidism (that requires treatment with antithyroid medication) or the history of a previously affected offspring warrant increased surveillance for fetal Graves.
2. **Serum** thyroid tests (free T_4, T_3, and TSH) should be measured in at-risk infants upon birth, keeping in mind the higher range of normal thyroid function tests during infancy (Table 40-7). Infants with significant neonatal Graves disease manifest abnormally elevated T_4 and T_3 concentrations with a suppressed TSH concentration. Because the appearance of neonatal thyrotoxicosis can be delayed by the presence of maternal thionamide drugs,

serum thyroid function tests should be repeated at 1 week of age if antithyroid medications were administered during the last month of pregnancy. Similarly, because cotransfer of maternal TBAb can sometimes delay the presentation of neonatal thyrotoxicosis for weeks, the **possibility of late hyperthyroidism** should be considered in high-risk infants.

3. **Thyroid uptake or scanning** is usually unnecessary. If performed, RAI uptake is elevated.
4. **Radiographic films of the skeleton** may show advanced bony maturation if severe fetal hyperthyroidism was present and inadequately treated. Later on, they may show craniosynostosis.
5. **Serial serum T_4 and T_3** concentrations are an indication of the effectiveness of treatment.

C. Treatment. In moderate or severe cases, treatment should be immediate and vigorous because this disease can be life-threatening. Medical therapy consists p. 544p. 545of a thionamide drug. Inorganic iodine and beta-blockade should be offered in severe cases.

1. **Methimazole,** 0.5 to 1.0 mg/kg/day, is given in divided doses every 8 hours. **Propylthiouracil should be avoided** as first-line treatment given its association with liver toxicity.
2. **Propranolol, 2 mg/kg/day,** is an important adjunct in reducing sympathetic overstimulation. If no clinical improvement is seen in 2 to 4 days, the dose can be increased by 50% to 100%.
3. **Inorganic iodide** can be used to inhibit thyroid hormone synthesis and release; using saturated solution of potassium iodide (SSKI) (48 mg iodide/drop) at the dose of 1 drop/day. Once a euthyroid state is reached, iodides should be discontinued.
4. **Adjunctive therapy.** In severe cases, airway obstruction (from severe thyromegaly) or heart failure (from thyrotoxicosis) may warrant intensive care. In rare cases, adding corticosteroids can acutely inhibit thyroid hormone secretion.
5. **In mild cases,** in which the infant manifests minimal clinical problems, observation alone or short-term propranolol treatment may be all that is necessary. Overtreatment and hypothyroidism should be avoided.

D. Prognosis

1. **Improvement** is often seen in 7 to 10 days, with remission by 3 to 6 weeks. However, 20% of cases are prolonged up to 3 to 6 months. Mortality in the range of 15% to 20% has been reported in the past, but is now rare, presumably due to earlier detection (from maternal screening) and increased access to neonatal intensive care.
2. **Craniosynostosis** can be a long-term sequela.
3. **Intellectual impairment** is observed in some infants and has been reported even in cases when antithyroid therapy was started early, suggesting that intrauterine thyrotoxicosis affects the developing brain and skeleton. Of note, with appropriate maternal screening and maternal thyroid care coordinated between a thyroidologist and high-risk obstetrician, fetal hyperthyroidism can be treated during pregnancy to normalize the thyroid status and neurodevelopment of the fetus.
4. **Pituitary hypothyroidism,** which can be secondary to prenatal exposure of the pituitary to excessive thyroid hormone levels during a critical stage of development, has been reported to follow neonatal thyrotoxicosis.

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41 Thyroid Nodules and Thyroid Cancer in Children and Adolescents

Harvey K. Chiu and Andrew J. Bauer

Thyroid cancer is uncommon during childhood. Older children and adolescents are more likely to be diagnosed. Despite this fact, the incidence is increasing. This could be due to increased surveillance (sequelae of treatment for childhood cancer); improved detection methods; effects of radiation or other pollutants in the environment; incidental detection of nodules during imaging for other reasons; and previous radiation exposure. In 2015, the American Thyroid Association (ATA) published the first guidelines on the evaluation and management of thyroid nodules and differentiated thyroid cancer (DTC) in children and adolescents, as well as an update of the medullary thyroid carcinoma (MTC) guidelines (www.thyroid.org).

The DTC guidelines emphasize differences between the clinical behavior of DTC in pediatrics compared with adults and provide recommendations highlighting the importance of complete and accurate preoperative assessment of thyroid nodules to optimize the surgical approach, providing care in a high-volume pediatric thyroid center to reduce complications of medical and surgical care, and novel risk categories designed to identify patients that may not benefit from postsurgical radioiodine therapy.

DTC is the most common form of thyroid cancer in children and adolescents with papillary thyroid cancer (PTC) comprising over 90% of DTC tumors and follicular thyroid cancer (FTC) and MTC comprising the remainder. The majority of the chapter will focus on DTC with MTC briefly addressed at the end of the chapter.

I. OVERVIEW

A. Thyroid cancer, the most common pediatric endocrine neoplasm, represents 1% to 1.5% of all pediatric malignancies and 5% to 5.7% of malignancies in the head and neck. PTC is the second most common cancer in adolescent girls (after Hodgkin lymphoma).

B. Pediatric thyroid nodules are two to four times more likely to be malignant compared with thyroid nodules in adults.

C. There is a strong tendency for PTC to metastasize to cervical lymph nodes. Even in patients without a palpable thyroid nodule, a thyroid ultrasound (US), with US imaging of the lateral neck lymph nodes, should be performed prior to excisional biopsy of a lymph node. The lungs are the most common site of distant metastasis.

D. In spite of a high risk of metastasis, there is excellent overall survival and prognosis with appropriate treatment.

E. Referral to a high-volume pediatric thyroid center reduces the risk of medical and surgical complications.

F. Risk factors for thyroid nodules and DTC

1. Female gender
2. Pubertal age
3. Family history of thyroid nodules and thyroid cancer (familial tumor predisposition syndromes).
4. Radiation exposure
5. After exposure to ionizing radiation, younger age (children under age 10 years) and female gender are associated with an increased risk and shorter latency to develop thyroid nodules and thyroid cancer.
6. There is a linear and increasing risk of developing thyroid nodules and thyroid cancer up to exposures of 10 Gray (Gy). Between 10 and 30 Gy the risk continues p. 547p. 548to have an upward trend and above 30 Gy the risk is still higher compared with no exposure, but, the risk begins to decrease secondary to radiation-induced thyroid gland sclerosis.
7. Childhood cancer survivors (2% annual risk of nodules, peaking after 15 to 25 years).
8. Environmental; nuclear accident exposure (such as Chernobyl or Fukushima Daiichi). **Iodine prophylaxis at the time of the accident is essential** and associated with reduced risk of developing thyroid cancer (https://www.remm.nlm.gov/potassiumiodide.htm).

G. Autoimmune thyroid disease, either hypothyroidism (Hashimoto thyroiditis) or hyperthyroidism (Graves disease), is associated with an increased risk of thyroid nodules and DTC. The etiology is unknown but may be related to overstimulation of thyroid follicular cells

secondary to elevated thyroid stimulating hormone (TSH) levels or antibody mediated (thyroid stimulating immunoglobulin in Graves disease).

II. PATHOGENESIS

A. DTC (PTC and FTC) originates from follicular cells of the thyroid and most retain the ability to absorb iodine (maintain differentiation). The nuclear features and histologic pattern of the tumors distinguishes PTC from FTC. In addition, these tumors appear to derive from different driver mutations and display a difference in regard to the likelihood and path for metastasis.

B. PTC variants include classic, solid, diffuse sclerosing, and follicular variant. The same tumor may harbor different variants of PTC. The most common driver mutations for PTC include *BRAF*, *RET/PTC* rearrangements, and *NTRK*-gene fusions. PTC has a high propensity to metastasize via the lymph system to regional lymph nodes. For patients with lateral neck metastasis, there is an approximate 15% to 20% risk of metastasis to the lungs.

C. FTC is less common, and the majority of FTCs in children and adolescent are minimally invasive. FTC is more frequently associated with iodine deficiency. The most common driver mutations for FTC include *RAS* and *PAX8/PPARγ*. FTC typically metastases hematogenously to distant sites (bone and lung).

D. In general, PTC metastasizes via the lymphatics and FTC metastasizes hematogenously.

E. Common oncogenes in PTC include point mutations in *BRAF* (20% to 40%) and the *RET/PTC* gene rearrangements. Less frequent genetic abnormalities include mutations in *RAS* and *NTRK* fusions. In FTC, *RAS* and *PAX8/PPARγ* mutations are more common. In pediatrics, there is limited data on the clinical correlation between the genetic abnormality and clinical behavior.

F. The majority of patients do not have an identifiable risk factor for developing a thyroid nodule or thyroid cancer; however, there are familial patterns of inheritance.

1. Two or more first-degree relatives define a familial predisposition to thyroid nodules or DTC. Currently, there is no test or molecular marker to explain the pattern or identify family members at risk.
2. Thyroid nodules and DTC may also be associated with several tumor syndromes, the majority following an autosomal dominant

pattern of inheritance;

a. PTEN hamartoma syndrome (gene—*PTEN*; formally known as Cowden syndrome)—macrocephaly, multinodular goiter (MNG), DTC, breast cancer, endometrial cancer, and gastrointestinal (GI) polyps. For additional information, see https://www.ncbi.nlm.nih.gov/books/NBK1488/.

b. Familial Adenomatous Polyposis (gene—*APC*; formally known as Gardner syndrome)—mucocutaneous lentigines, GI polyps, and cancer, PTC. For additional information, see https://www.ncbi.nlm.nih.gov/books/NBK1345/.

c. DICER1 pleuropulmonary blastoma (PPB) syndrome (gene—*DICER1*)—PPB, MNG and DTC, sertoli-leydig cell tumors, and cystic nephroma. For additional information, see https://www.ncbi.nlm.nih.gov/books/NBK196157/.

d. Carney complex (gene—*PRKAR1A*)—lentigines, Cushing syndrome, cardiac and skin myxomas, pituitary tumors, and gonadal tumors. For additional information, see https://www.ncbi.nlm.nih.gov/books/NBK1286/.

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III. CLINICAL PRESENTATION

A. A painless thyroid nodule or persistent, asymptomatic lateral neck lymphadenopathy is the presenting sign in the majority of pediatric patients.

B. The thyroid nodule may also be diagnosed during nonthyroid head and neck imaging.

C. Approximately 15% to 20% of patients with metastasis to lateral neck lymph nodes will have asymptomatic pulmonary metastasis.

IV. DIAGNOSIS

A. History

1. Review family history and past medical history to screen for risk factors (see Section I.F).

B. Physical

1. Examination of the thyroid should be a part of every annual physical examination (PE). Similar to other portions of the PE, there are three parts: inspection, auscultation (can be reserved only for patients suspected to have hyperthyroidism), and palpation.

Inspection should include chin neutral as well as neck extension with swallowing. If the thyroid is enlarged (visible), asymmetric (one side larger than the other) or a nodule is visualized, then palpation for abnormal cervical lymph nodes should be completed. See the following video that highlights normal and abnormal PE and findings: https://www.youtube.com/watch?v=Z9norsLPKfU.

2. Pain and/or tenderness with rapid increase in size of a nodule suggests hemorrhage into a nodule or an infectious process.
3. Persistent asymmetric lateral neck lymphadenopathy (levels III, IV, or V) increases the likelihood of thyroid malignancy.
4. A firm, diffusely enlarged thyroid associated with lateral neck lymphadenopathy may represent diffuse sclerosing variant PTC. This variant is more common in pediatrics and young adults. This infiltrative form of PTC is not associated with a nodule by PE or US, but on US there are an increased number of microcalcifications, often described as a "snow-storm" appearance.

C. Laboratory studies

1. TSH and T_4 are usually normal. A low or suppressed TSH suggests an autonomously functioning thyroid nodule, previously referred to as "warm" or "hot" on thyroid scintigraphy. Depending on the US appearance, autonomously functioning nodules are typically considered to be at a lower risk of malignancy, but fine needle aspiration (FNA) may be required to determine the actual level of risk.
2. Antithyroid antibodies (antithyroglobulin and antithyroid peroxidase) are helpful in diagnosing chronic lymphocytic thyroiditis that is associated with an increased risk of a thyroid nodule and thyroid cancer. However, for patients with a thyroid nodule, the US features and results from FNA are more important in determining appropriate management.
3. Calcitonin may be helpful to screen for the potential for MTC; however, due to the rarity of sporadic MTC in pediatrics, assessment of calcitonin is not routinely performed in the evaluation of a thyroid nodule. For patients diagnosed with multiple endocrine neoplasia type 2 (MEN2), calcitonin is important for preoperative and postoperative surveillance (see Section VIII).

D. Imaging studies

1. Ultrasonography
   a. First-line imaging test in all pediatric patients with thyroid nodules.
   b. A solid nodule is more likely to be malignant; however, up to 50% of malignant lesions may have a cystic component, and approximately 8% of cystic lesions represent malignancies. Imaging characteristics may be helpful to direct which nodules are more likely to harbor a malignancy. Increased risk factors include nodules that harbor microcalcifications, that are hypoechoic, have infiltrative margins, demonstrate increased vascularity, or are taller than wide on transverse imaging (see Figs. 41-1 and 41-2).
   c. For patients with a thyroid nodule, a complete US examination includes assessment of the lateral neck lymph nodes (see Association for Medical Ultrasound guidelines; http://www.aium.org/resources/guidelines/thyroid.pdf).

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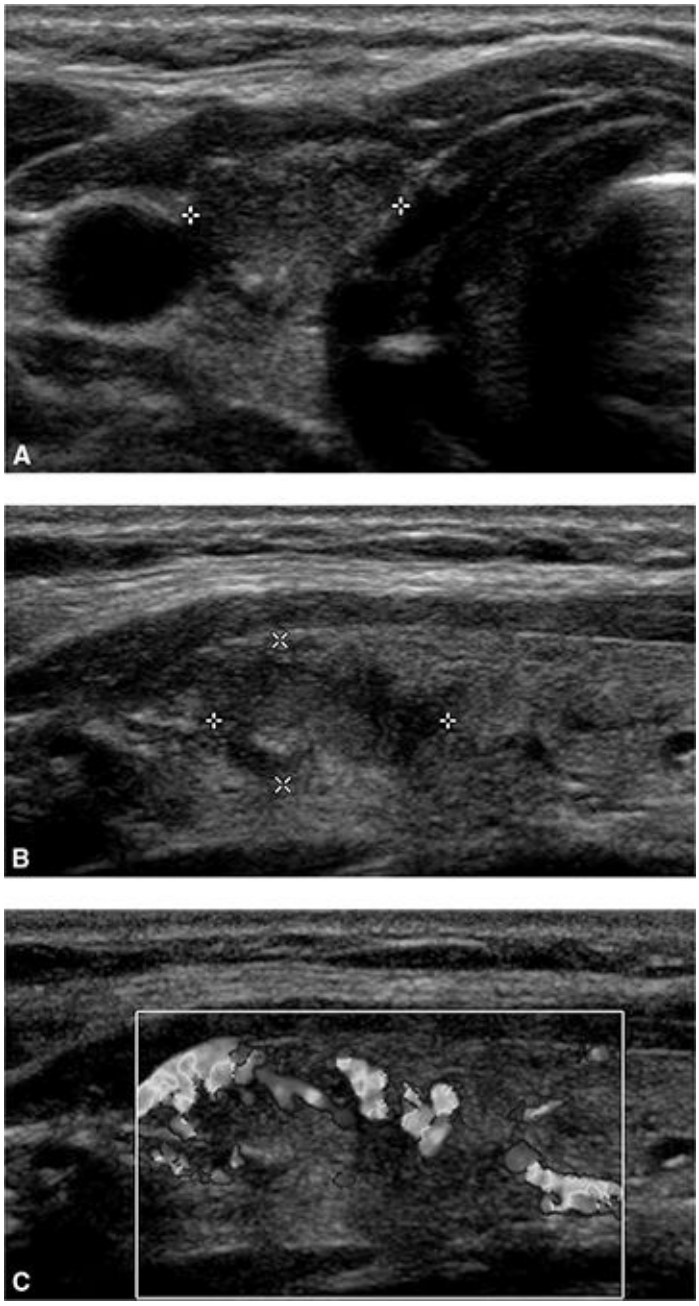

Figure 41-1. **A.** 17-Year-old female with a history of anaplastic ependymoma of the posterior fossa with a specific risk factor of cranial irradiation at the age of 2 to 3 years. Notice the worrisome right hypoechoic thyroid nodule with irregular margins. **B.** As well as hypervascularity on Doppler examination. **C.** This nodule eventually proved to represent a classic variant of papillary thyroid carcinoma.

d. For nodules followed by serial US imaging, nodule enlargement is defined as a 50% increase in volume, comparable with a 20% increase in two dimensions.

e. Thyroid US may be used as a method of surveillance for

children at increased risk of malignancy based on family or personal history. When to initiate US screening, as well as the frequency of surveillance, is not well established for any of the risk factors. Referral to a pediatric endocrinologist that is skilled

p. 550p. 551in reading US images will help reduce unnecessary procedures and anxiety for benign disease as well as identification of patients at increased risk of thyroid malignancy.

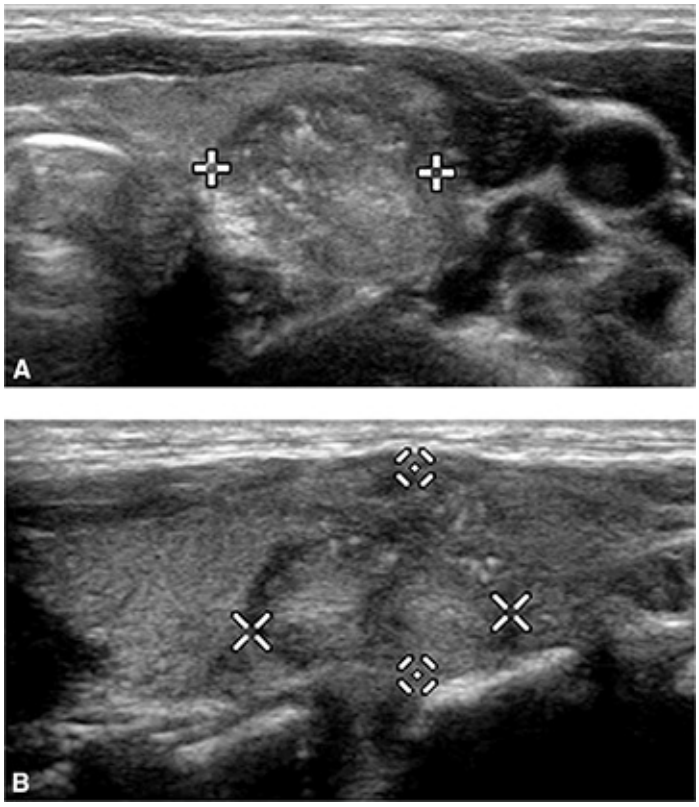

Figure 41-2. 11-Year-old male without any significant risk factors. **A.** Ultrasound demonstrates a left thyroid nodule with worrisome microcalcifications. **B.** Fine needle biopsy eventually demonstrated papillary thyroid carcinoma.

2. Anatomic imaging (computed tomography [CT] scan or magnetic resonance imaging [MRI])
   a. For patients with PTC and metastasis to the lateral neck lymph nodes, CT or MRI can be helpful to identify abnormal lymph nodes in areas not well visualized by US, including, para- and retropharyngeal, subclavicular, and upper mediastinum. This

information can be critical to ensure complete surgical resection. The use of iodinated contrast is acceptable, and typically not associated with a need to delay radioactive iodine (RAI) treatment. A 24-hour urine iodine level may be performed prior to administration of RAI to ensure complete clearance after preparation on a low-iodine diet for 2 weeks.

3. Chest/pulmonary imaging
   a. Routine chest X-ray or anatomic imaging is not typically recommended even for patients with an increased risk of pulmonary metastasis as the information does not alter the approach to care.
   b. For patients at increased risk of pulmonary metastasis, those with lateral lymph node metastasis, chest X-ray is less sensitive than CT or MRI secondary to an increased likelihood of micronodular rather than macronodular pulmonary metastasis.
4. Radionucleotide scan (scintigraphy)
   a. Thyroid scintigraphy (^{99}Tc Pertechnetate or ^{123}I) has not proven worthwhile in distinguishing malignant from benign thyroid nodule disease. Thyroid malignancy may be found in “cold,” “warm,” and “hot” lesions and because of this, scintigrapy is not a routine part of the assessment.

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   b. For patients with a suppressed TSH, increased uptake with scintigraphy confirms autonomous function; however, the US features and FNA are still more accurate in identifying malignancy potential.
5. Positron emission tomography (PET) scan
   a. There is no indication or utility to PET–CT in the initial evaluation of a patient with a thyroid nodule.
   b. PET–CT may be considered for patients with refractory, non-RAI avid DTC.

V. TREATMENT

The goals of treatment are to eliminate the disease and to reduce the chance of recurrence. Sometimes the disease cannot be entirely eradicated, and therefore, another therapeutic goal is to achieve stable disease and no symptoms of disease. With low-disease specific mortality, every effort must be made to reduce the potential risks of complications.

This is best achieved by referral to a high-volume pediatric thyroid center.

A. Surgical care

1. Total thyroidectomy is recommended for pediatric patients with PTC as multifocal disease is present in 65% and bilateral disease in 30%.
    a. This approach is associated with decreased risk of persistent and recurrent disease when compared with lobectomy (6% vs. 35% over 40 years in a large study).
2. FTC is usually unifocal with rare cervical lymph node metastases, but with the potential for hematogenous distant metastases.
3. Lymph node metastasis—all lymph node dissections must be compartment based. The removal of individual lymph nodes that appear suspicious. “Berry picking” is associated with an increased risk of persistent and recurrent disease.
    a. Central neck lymph node dissection—prophylactic central neck lymph node dissection should be considered for all patients with FNA consistent with PTC as up to 70% will have micrometastasis. This approach may afford for better assessment of the invasive behavior of disease and be used to stratify patients into a low-risk of benefit from RAI (if found to have less than five lymph nodes with micrometastasis).
    b. Lateral neck lymph node dissection—FNA of one suspicious LN from each lateral neck compartment should be performed to guide the operative plan. A prophylactic lateral neck dissection should not be performed as the risk of surgery outweighs the potential benefit without cytologic evidence of lateral neck metastasis.
4. Surgical risks include permanent hypoparathyroidism and recurrent laryngeal nerve (RLN) injury. Risks are reduced by ensuring complete and accurate preoperative staging with US and FNA as well as referral to a high-volume thyroid surgeon, defined as a surgeon that performs at least 30 or more thyroidectomies per year.
    a. Hypoparathyroidism
        i. Serum calcium levels are measured daily for the first 2 to 4 postoperative days in all patients who have undergone a total or subtotal thyroidectomy. The calcium level may decrease slightly as the parathyroid tissue recovers from surgical trauma. Intra- or postoperative PTH levels <10 to 15 pg/mL and/or hyperphosphatemia are predictive of

hypoparathyroidism and an increased risk of symptomatic hypocalcemia.

ii. Mild symptoms include perioral or hand tingling. More significant signs/symptoms include a positive Trousseau or Chvostek sign or cardiac arrhythmia.

iii. Institutional-specific guidelines should be created to direct when and how calcium and calcitriol treatment should be initiated. In general, if the PTH is <10 pg/mL or serum phosphorous is >6 mg/dL, calcitriol and calcium replacement should be initiated.

iv. The oral route of administration ensures more stable serum levels. Intravenous calcium gluconate is used for temporary treatment of arrhythmia and tetany.

b. RLN damage

i. There are no monitoring devices that are associated with a decreased risk of RLN damage

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B. Medical care

1. Postsurgical

a. Previously, the majority of pediatric patients with PTC were administered RAI therapy to ablate residual normal thyroid and to treat functioning metastases in differentiated thyroid tumors. The rational for this approach was to decrease the risk of recurrent disease as well as ease follow-up by improving the predictive value of postsurgical and RAI thyroglobulin levels.

b. The ATA pediatric DTC guidelines recommend a stratified approach to RAI administration, attempting to eliminate the use of RAI in patients at low risk of persistent disease (www.thyroid.org). For patients at intermediate and high risk of persistent disease, a stimulated thyroglobulin level (Tg) and 123-I (I^{123}) diagnostic whole body scan (DxWBS) are used to assess if RAI is indicated as well as to help guide selection of RAI activity. SPECT/CT can be added to the I^{123}-DxWBS to more accurately identify persistent disease from nonspecific uptake.

c. Preparation for DxWBS and potential RAI treatment includes two maneuvers to improve iodine uptake;

i. Low-iodine diet to establish an iodine insufficient or deficient state (see; www.thyca.org).
ii. TSH stimulation to a goal of >30 mIU/L. This may be accomplished by withdrawal from levothyroxine for 14 days (most common) or by administration of recombinant human TSH, which may decrease radiation exposure by one third.
iii. A blood draw to obtain a TSH-stimulated Tg should be obtained prior to administration of RAI to ensure adequate TSH levels (>30 mIU/L) and to evaluate the Tg level as a data point to determine biochemical evidence of persistent disease.

Administered RAI activities are in the range of 1.0 to 1.5 mCi/kg or 37 to 56 MBq/kg are commonly used as therapy for thyroid cancer. The presence of pulmonary metastatic disease or repeat RAI treatments suggests benefit from dosimetry-based treatment to minimize toxicity to nontarget organs. Dosimetry to calculate delivery of a maximum of 80 mCi to the lungs is indicated in known pulmonary metastasis to avoid pulmonary fibrosis.

a) Sufficient fluid intake is paramount to effect excretion of ^{131}I. Antiemetics such as ondansetron should be available for the frequent nausea and vomiting that ensue immediately after administration of RAI.
b) Regular bowel movements are necessary to effect clearance of ^{131}I and may be problematic especially if the patient has been prepared for RAI by withdrawal from levothyroxine, with resultant hypothyroidism-induced constipation. Vigilance for this scenario should be maintained, and laxative or stool softeners should be used as indicated.
c) Sour hard candies to stimulate salivary flow and reduce risk of sialadenitis are somewhat controversial because some studies suggest a theoretical increased risk of radioactivity exposure to the salivary gland by promoting increased glandular blood flow.
d) Gonadal function is usually preserved, though transient lower spermatogenesis and menstrual irregularities have

been observed. More recent studies also raise concern for long-term decrements in ovarian reserve with lower anti-Müllerian hormone levels 3 months after RAI without rising to baseline 1 year after RAI therapy. Avoidance of pregnancy (fathering or childbearing) for at least 6 months is recommended for men and women who receive RAI.

iv. Post-RAI treatment whole body scan (RxWBS) is performed 5 to 7 days after RAI therapy and may be discordant, revealing additional disease, when compared to the DxWBS.

DxWBS is a pretreatment scan using low dose I-123 (2 mCi), whereas RxWBS is a post–I-131 scan that has improved sensitivity as I-131 has a longer half-life compared with I-123. The administered activity is between 30 and 200 mCi (the amount determined by the age). TSH stimulates Tg and p. 553p. 554DxWBS images. For the majority of patients, this additional information will not require immediate treatment but is important for surveillance.

v. Postoperative suppression of TSH with thyroid hormone is utilized to decrease growth of residual thyroid cancer. The degree of TSH suppression is stratified based on the risk of disease recurrence and progression (Table 41-1).

a) Low-risk (disease limited to the thyroid or with microscopic metastatic disease to less than five central lymph nodes)—TSH 0.5 to 1.0 mIU/L

b) Intermediate-risk (extensive central but minimal lateral cervical lymph node involvement)—TSH 0.1 to 0.5 mIU/L

c) High risk (extensive cervical lymph node metastases, locally invasive disease, or distal metastases)—TSH < 0.1 mIU/L

vi. External beam radiation is not recommended in children.

VI. FOLLOW-UP AND SURVEILLANCE

A. Persistent disease is relatively common in children and adolescents secondary to several factors:

1. Cervical
    a. Incomplete surgery due to incomplete preoperative evaluation or secondary to incomplete surgical dissection
    b. Decreased efficiency of lymph node metastasis to absorb RAI
2. Pulmonary
    a. Up to one third of pediatric patients with pulmonary metastasis will not achieve remission from disease. However, the majority of these patients develop stable, nonprogressive disease.

B. Additional RAI treatment should be considered when the thyroglobulin (Tg) level plateaus or is increasing, and there is evidence of persistent, nonsurgical disease. A one time repeat RAI treatment can also be considered for patients without anatomic evidence of disease that have persistent Tg.
1. Similar to the initial RAI treatment, a TSH-stimulated Tg and DxWBS should be performed to help optimize the administered RAI activity.
2. Dosimetry should be considered for patients undergoing repeat RAI.
3. With rare exception, repeat RAI should not be administered within 12 months of the previous treatment.
4. This paradigm is based on studies that have demonstrated that Tg levels may decrease over years after a single RAI treatment even in the absence of a specific intervention.

C. Recurrent disease may present three to four decades after initial treatment. Factors associated with recurrence include:
1. Younger age
2. Male gender
3. Large tumors (>4 cm in diameter)
4. Multifocal disease
5. Regional lymph node involvement
6. Distant metastasis

D. Surveillance
1. Serum thyroglobulin (Tg) levels during thyroid hormone suppression (TSH-suppressed Tg)
    a. TSH-suppressed Tg levels are assessed every 3 to 6 months until remission is achieved.
    b. Undetectable Tg levels suggest remission from disease.
    c. TSH-stimulated Tg levels over 10 ng/mL are suggestive of potential persistent or recurrent disease, although the

therapeutic implications are dependent on other indications of disease progression.

d. Tg levels are not reliable if patient is positive for anti-Tg antibodies (TgAb), a confounder in up to 30% of cases. For these patients, TgAb titers may be used as a surrogate for tumor burden.

i. TgAb have lower interference on RIA versus Immunochemiluminometric assay (ICMA) Tg assays.

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TABLE 41-1 Risk of Persistent Disease in Pediatric Differentiated Thyroid Cancer with Recommended Management (American Thyroid Association Pediatric Risk Levels)

Risk	Clinical presentation	Initial evaluation following thyroidectomy	TSH target (mIU/L)	Ultrasound Follow-up	Tg follow-up	Stimulated-TSH ^{123}I scan
Low	Cancer largely limited to the thyroid or with microscopic spread to a few central neck lymph nodes	Tg	0.5–1.0	6 mo following thyroidectomy, then annually for 5 yr	Every 3–6 mo for 2 yr then annually	Not indicated unless other clinical suggestion of disease progression
Intermediate	Large central neck lymph node or minimal lateral neck lymph node spread	Stimulated-TSH Tg and ^{123}I scan	0.1–0.5	6 mo following thyroidectomy, then every 6–12 mo for 5 yr, then individualized based on clinical course	Every 3–6 mo for 3 yr then annually	1–2 yr following treatment with ^{131}I
High	Large lateral lymph node spread, locally invasive growth, or distant (i.e., pulmonary) spread	Stimulated-TSH Tg and ^{123}I scan	<0.1	6 mo following thyroidectomy, then every 6–12 mo for 5 yr, then individualized based on clinical course	Every 3–6 mo for 3 yr then annually	1–2 yr following treatment with ^{131}I

Tg, thyroglobulin; TSH, thyroid-stimulating hormone.

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ii. Tg via LC/MS/MS has been proposed as a means to circumvent the confounder of anti-Tg antibodies in the immunoassay methodologies of Tg, though concerns of perhaps a decreased sensitivity of Tg via LC/MS/MS dampen the value of an undetectable value and hence limit the utility to trending detectable values.

iii. Irrespective of the assay, ensuring that the same assay method, preferably from the same laboratory, affords the greatest accuracy to determine the status of disease.

iv. The trend in Tg or TgAb is the most useful predictor of disease status with measurements obtained every 3 to 6 months.

v. The disappearance of anti-Tg antibodies in a previously positive patient is a good prognostic sign and increasing TgAb levels should raise concern for disease progression.

2. Neck US—The initial surveillance US is performed approximately 6 months after thyroidectomy and then at 6- to 12-month intervals (depending on the Tg trend and risk of recurrence) thereafter. Increasing intervals are pursued once the patient achieves biochemical (Tg) and anatomic remission from disease or has a Tg level near the lower end of detection without anatomic evidence of disease.
3. Recombinant human TSH stimulated whole body RAI scan may be considered 1 to 2 years after initial treatment to confirm remission in a patient identified to be a high risk of persistent or recurrent disease. Similar to the initial DxWBS, a low-iodine diet for 1 to 2 weeks prior to such a scan is essential for adequate sensitivity. Otherwise, in the absence of other indication of disease relapse or progression, such repeat scans provide little clinical impression beyond that established by serial Tg/TgAb levels and neck USs.
4. ^{18}F-fluorodeoxyglucose PET scanning may be helpful in identifying non-RAI avid disease. This is less common in pediatrics compared with adults. PET/CT should be considered in patients with a significantly elevated Tg without identifiable disease by US, anatomic imaging, and whole body scan.
5. Serial Pulmonary Function Testing is indicated in patients with pulmonary metastasis because of concerns of RAI-induced pulmonary fibrosis, especially in the context of repeat RAI courses. The approach of delaying additional RAI until a plateau in Tg is observed, using chest CT to assess anatomic response to therapy, and dosimetry to calculate RAI decreases the risk of developing pulmonary fibrosis.
6. Although more than half of recurrences occur within 7 years of diagnosis, lifelong follow-up is required because recurrent disease has been documented up to 20 to 40 years after diagnosis.

VII. PROGRESSIVE THYROID CANCER THAT BECOMES REFRACTORY TO RAI

A. Although uncommon, there are adolescent patients that develop non-RAI avid disease.

B. The most common systemic agents are the tyrosine kinase inhibitors, although several other classes of medications, to include BRAF inhibitors, MEK inhibitors, and mTOR inhibitors are under investigation in adult patients.

C. To date, these agents show great promise to transiently slow progression, but there are no agents that have displayed tumorcidal effect.

D. All of these agents have significant side effects and potential adverse events.

VIII. MEDULLARY THYROID CANCER

A. MTC arises from the thyroid parafollicular or C cells, which secrete calcitonin. The disease follows anatomic progression from a normal state to C-cell hyperplasia to MTC.

B. With rare exception, MTC in pediatrics is typically associated with MEN2. Sporadic MTC is very uncommon in children and adolescents.

1. MEN2 consists of MTC and pheochromocytoma and either hyperparathyroidism (2A) or mucosal neuromas (2B) of the tongue, palpebral conjunctiva, and lips with marfanoid body habitus. Both are inherited in an autosomal dominant fashion.
2. MTC associated with MEN2B is highly aggressive with the potential for development prior to 1 year of age and early metastasis prior to 5 years of age. Early p. 556p. 557 clinical features of MEN2B are alacrima (lack of producing tears) and constipation from pseudo-Hirschsprung disease (GI ganglioneuromatosis). The constipation may be extremely difficult to treat and is associated with an increased risk of toxic megacolon.
3. MTC associated with MEN2A is less penetrant and less aggressive with the timing of prophylactic surgery based on the specific RET proto-oncogene mutation (see ATA guidelines for MTC; www.thyroid.org). Certain codons are also associated with an increased risk of Hirschsprung disease and cutaneous lichen amyloidosis (pruritic, plaque-like rash that develops on the upper back).

C. Once the index case is identified, all family members should undergo

mutation analysis for the specific mutation in the RET proto-oncogene. A genetic counselor and an oncology social worker are important members of the team to help the family navigate through the process of disclosure and testing.

D. Treatment

1. Total thyroidectomy is the treatment of choice. The timing of thyroidectomy, as well as surveillance for other tumors, is determined by the RET mutation and designated by the ATA risk categories; Highest, High, and Moderate (www.thyroid.org).
   - **a.** Highest—Children with MEN2B (RET codon M918T mutation) should undergo thyroidectomy by age 1 year.
   - **b.** High—Children with MEN2A (RET codon C634 or A883F mutation) should undergo a prophylactic thyroidectomy by age 5 years.
   - **c.** Moderate—Children with MEN2A and any other RET codon identified to be associated with disease may pursue thyroidectomy during childhood or pursue delayed thyroidectomy if they are compliant with obtaining annual surveillance neck US and calcitonin levels. Families need to be counseled and understand that if MTC demonstrates metastasis, there is no cure for disease. The best approach is to remove the thyroid before MTC has metastasized. Calcitonin is physiologically elevated up to age 3 years, decreasing to adult values thereafter.
2. Post-thyroidectomy patients are placed on thyroid hormone replacement (TSH targeted between 1 and 3 mIU/L) not TSH suppression because C-cell-derived tumors are not responsive to TSH and do not absorb RAI (no role for RAI in treatment metastatic MTC).

E. Surveillance

1. MTC
   - **a.** Neck US and annual calcitonin should be pursued after thyroidectomy to confirm remission. Thereafter, one can pursue surveillance with decreasing frequency based on the codon and initial presentation of disease.
   - **b.** Serum carcinoembryonic antigen (CEA) should be used to follow patients with metastatic MTC. A rising CEA out of proportion to calcitonin indicates progressive, poorly differentiated disease.

2. Pheochromocytoma
    a. Patients designated in the ATA Highest (M918T) and High (A883F and C634F) categories should initiate annual screening by 11 years of age. All others should initiate screening at 16 years of age.
    b. A spot plasma free metanephrine/normetanephrine panel or 24-hour urinary metanephrine/normetanephrines are the screening labs of choice. Adrenal imaging with CT or MRI should be performed for patients with a positive biochemical screen. Pheochromocytoma screening should also be considered for MEN2 patients undergoing surgery at any age.
3. Hyperparathyroidism
    a. Patients designated in the ATA High (A883F and C634F) and Moderate categories should be screened for hyperparathyroidism at the same time as being screened for pheochromocytoma, by 11 years of age (High) and 16 years of age (Moderate), respectively.
    b. An albumin-corrected calcium with or without a serum intact-PTH is adequate for screening.

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4. Systemic therapy with tyrosine kinase inhibitors, specifically the oral agents vandetanib and cabozantinib, has recently been studied and approved for advanced and progressing MTC.

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42 Thyroid Disorders in Children and Adolescents

Andrew J. Bauer, Kuk-Wha Lee, and Norman Lavin

I. GOITER

A goiter is an enlargement of the thyroid gland that may result from several different pathogenic mechanisms. The incidence of goiter (4% to 5%) increases with advancing age, is more common in girls at all ages, and varies based on geographic location related to differences in iodine status as well as the incidence of autoimmune disease. The presence of goiter does not correlate with thyroid function; patients may be euthyroid, hypothyroid, or hyperthyroid. The etiology of a goiter may be classified in many ways; one such classification is given in Table 42-1.

A. Types of goiters (Fig. 42-1)

1. **Congenital goiter** may be present at birth or may develop over the first few years of life (see Chapter 40). Dyshormonogenesis should be considered in any patient with a goiter who tests negative for thyroid antibodies.
   - **a.** Iodine deficiency in the mother was once a major cause of congenital goiter (insufficient substrate for thyroid hormone synthesis).
   - **b.** Currently, the most common cause of congenital goiter is a defect in hormone formation. These disorders are inherited in an autosomal recessive pattern and most commonly involve an enzyme deficiency along the pathway of thyroid hormone synthesis. The deficiency leads to decreased levels of thyroid hormone, increased secretion of thyroid-stimulating hormone (TSH), and development of a goiter. The most well-known mutation is in the *pendrin* gene associated with both goiter and sensorineural hearing loss (Pendred syndrome). Inborn errors in thyroid hormone production account for 10% to 15% of congenital hypothyroidism.
   - **c.** Transplacental transfer of TSH-receptor stimulating or blocking antibodies may result in goiter associated with hyperthyroidism

(neonatal Graves disease) or hypothyroidism, respectively. The goiter may develop in utero. Maternal ingestion of antithyroid drugs (methimazole [MMI], propylthiouracil, or carbimazole), amiodarone (an iodine rich medication), or exposure to iodine containing skin disinfectants can also result in congenital goiter.

d. Congenital nonimmune hyperthyroidism is caused by an activating mutation in the TSH-receptor. It is inherited as an autosomal dominant condition.

2. Acquired goiter is an enlargement of the thyroid gland that occurs after the newborn period, most frequently noted in school age children with the highest incidence occurring in adolescent girls. Globally, iodine deficiency is the most common cause; however, in developed nations, including the United States, autoimmune thyroid disease is the common etiology.

a. Iodine deficiency

i. Iodine deficiency is the most common cause of goiter in the world. Extreme deficiency occurs when daily urine contains <25 μg of iodine, and moderate deficiency occurs when it is <50 μg; adequate iodine intake is reflected by an excretion of 100 to 200 μg/day. Iodine supplementation has led to eradication of endemic goiter in many countries. The diagnosis of iodine-deficient goiter can be confirmed if urinary iodide excretion is <50 to 100 μg/g of creatinine.

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TABLE 42-1 Classification of Goiter Etiology in Children and Adolescents

1. Congenital
- **a.** Dyshormonogenesis
- **b.** Transplacental transfer of maternal thyroid-stimulating or blocking antibodies or antithyroid medication
- **c.** Congenital nonimmune hyperthyroidism

2. Acquired
- **a.** Iodine induced (endemic goiter)
- **b.** Infectious
- **c.** Autoimmune
- **d.** Thyroid nodule disease
- **e.** Malignant

f. Environmental (goitrogens)

ii. Iodine deficiency may be associated with endemic goiter and normal thyroid function.

iii. The most serious consequence of iodine deficiency is endemic hypothyroidism. There are two types: **(1)** The **neurologic syndrome** includes mental retardation, deafness, abnormal gait, foot clonus, and Babinski sign. It is believed that the pathogenesis may be iodine deficiency and low T_4 in pregnancy, leading to fetal and postnatal hypothyroidism. **(2)** The **myxedematous syndrome** is characterized by mental retardation, deafness, neurologic symptoms, absence of goiter, myxedema, delayed growth, low T_4, and high TSH levels.

iv. Iodine-induced thyrotoxicosis is more common in iodine-deficient areas and affects patients with multinodular goiters with the introduction of iodine supplementation or with administration of iodinated contrast or medication with iodine content (**amiodarone**). Patients with autoimmune thyroiditis may also develop iodine-induced thyrotoxicosis potentially related to mild, subclinical iodine deficiency.

v. Laboratory findings

a) The T_4 level is slightly low, the tri-iodothyronine (T_3) level is normal or mildly high, and the TSH level is elevated. **T_3 is secreted preferentially** in greater amounts than normal in the iodine-deficient gland because **T_3 requires only 75% as much iodine** for synthesis. This adaptive mechanism for the more efficient use of iodine can occur only at the expense of goiter formation and TSH elevation.

vi. Treatment

a) Iodine

1) The World Health Organization recommended iodine intake is 90 μg/day between birth and 5 years of age, 120 μg/day between 6 and 12 years, 150 μg/day for adolescents and adults, and 250 μg/day for pregnant and lactating women.

2) Universal salt iodization is the safest and most cost-effective strategy to ensure sufficient iodine intake. When universal salt iodization is not available, a single oral dose of iodized oil administered every 6 to 12 months may be considered. Children <2 years of age should receive 200 mg/year, and the remainder of the population should receive 400 mg/year.

b) T_4 (for dosage, see Hypothyroidism, Section III). Because most of these goiters develop by mechanisms other than TSH stimulation, T_4 may not always be helpful when used alone.

b. Goitrogens. Goitrogens are substances that disrupt the production of thyroid hormone with subsequent increase in TSH. The goiter-inducing drugs, p. 560p. 561p. 561p. 562such as iodides (saturated solution of potassium iodide [SSKI]), amiodarone (inhibits conversion of T_4 to T_3 and interferes with thyroid hormone action and clearance), thiocyanate and perchlorate (decrease iodine uptake), and lithium (inhibits thyroid hormone release). Goitrogenic foods include cassava (soaking can reduce the goitrogenic effect), flax seed (contains cyanide which transforms to thiocyanate), and vegetables in the genus *Brassica* and other cruciferous vegetables if ingested in large quantities.

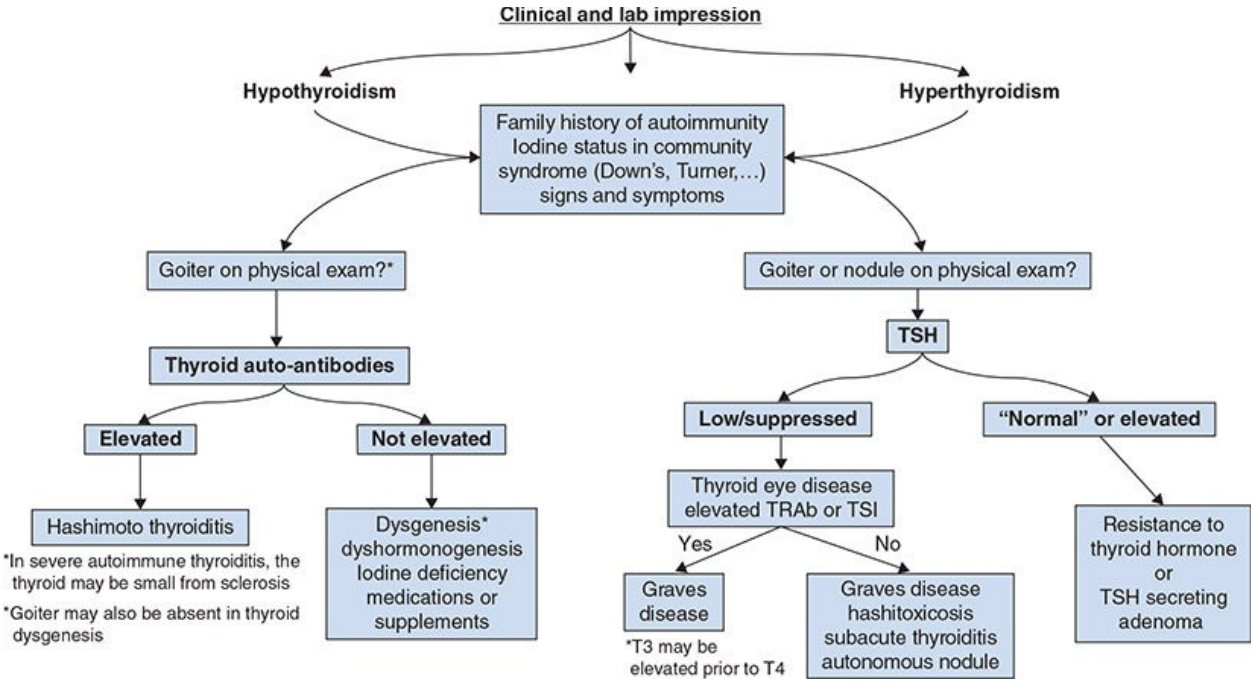

Figure 42-1. Flow diagram for the clinical evaluation of thyroid disease in children and adolescents. CT, computed tomography; T_4, free thyroxine; TSH, thyroid-stimulating hormone; CLT, chronic lymphocytic thyroiditis.

3. **Infectious thyroiditis.** See Thyroiditis, Section II.
4. **Hashimoto thyroiditis.** See Hypothyroidism, Section II.
5. **Graves disease.** See Hyperthyroidism, Section IV.
6. **Thyroid tumor.** See Thyroid nodules and Thyroid cancer, Section V.

II. INFECTIOUS THYROIDITIS

A. Acute bacterial thyroiditis (suppurative thyroiditis)

1. **Etiology.** This disorder is rarely seen today. It is usually caused by gram-positive bacteria, such as β-hemolytic streptococci, staphylococci, or pneumococci, and is amenable to appropriate antibiotic therapy. The gland is enlarged, tender, red, hot, and often fluctuant, with the left lobe affected predominantly in children. The presence of a pyriform sinus fistula increases the risk of recurrent infection. Thyroid surgery should be avoided if possible because it is associated with complications and high recurrence rates.
2. **Clinical findings.** The patient typically complains of chills, fever, and rapid onset of anterior neck pain, swelling, and redness; pain may radiate to the ears or mandible.
3. **Laboratory findings.** The white blood cell count (WBC) is

elevated, with a shift to the left and the erthyrocyte sedimentation rate (ESR) and C-reactive protein are also elevated. A search for anatomic defects that predispose to infection must be initiated in children to rule out a left pyriform sinus fistula. Once the acute edema has resolved, Neck magnetic resonance imaging (MRI), direct laryngoscopy, and/or barium swallow are the most useful diagnostic tools to identify the fistula tract. If present, excision of the tract and lobectomy should be considered to decrease recurrence.

4. **Differential diagnosis (Tables 42-2 and 42-3)**
   - **a.** Subacute thyroiditis (SAT)
   - **b.** Cellulitis
   - **c.** Thyroid cyst hemorrhage
   - **d.** Infected thyroglossal duct cyst
   - **e.** Infected branchial cleft cyst
5. **Treatment**
   - **a.** Antibiotics, preferably parenteral
   - **b.** Incision and drainage of the pyriform sinus tract, with or without lobectomy, if present

B. Subacute thyroiditis

SAT (also, termed de Quervain disease) is rare in childhood; it is most common in women between the ages of 20 and 50.

1. **Etiology.** SAT is thought to be caused by a viral infection because it often follows an upper respiratory illness. It is more common in colder climates, and there is a female predominance.

TABLE 42-2 Classification of Thyroiditis in Children

Type	Etiology	Frequency
Hashimoto	Autoimmune	Very common, 10%–20% of all thyroid disorders
Subacute	Viral	1.5% of all thyroid disorders
Acute (bacterial) suppurative	Bacterial	Rare

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TABLE 42-3 Differential Diagnosis of Thyroiditis

Type	Fever	Goiter	WBC	T_4, T_3	Thyroid antibodies	RAIU
Hashimoto thyroiditis	Absent	Firm, lobular, or pebbly	Normal	Normal or low	Elevated	Low, normal, or high
Subacute thyroiditis	Usually present	Firm, tender	Normal	Elevated initially, then may be low	Low titers early, absent later	Low
Acute bacterial thyroiditis	High	Tender	Elevated	Normal or elevated	Negative	Normal or low

RAIU, radioactive iodine uptake; T_3, tri-iodothyronine; T_4, thyroxine; WBC, white blood count.

2. **Clinical findings.** Patients usually complain of anterior neck pain with occasional radiation to the ear, mandible, skull, or chest. Dysphagia can occur in up to 50% of patients. Signs and symptoms of hyperthyroidism (tachycardia, weight loss, nervousness, and diaphoresis) can occur. On examination, the gland is tender, nodular, and often unilaterally enlarged.
3. **Laboratory findings.** There are several phases to the disease. In the initial, thyrotoxic phase the ESR is elevated (often >100 mm/hour) with a normal or moderate increase in the WBC. Thyroxine and thyroglobulin are elevated because of thyrocyte damage with a reflexive lowering of the TSH. This phase may last up to 30 days. During the second, hypothyroid phase, between days 30 and 60, the thyroxine decreases with a reflexive increase in TSH. Ultimately, the third phase occurs when thyroid function returns to normal, which may take 5 to 6 months from the initial phase. Antithyroid antibodies may be elevated, including antithyroid peroxidase and antithyroglobulin, but most patients do not develop autoimmune thyroid disease or permanent thyroid dysfunction. During the initial, hyperthyroid phase, the radioactive iodine uptake (RAIU) is low because of the destructive etiology of the disorder. Thus, the RAIU is very helpful in distinguishing these patients from those with other hyperthyroid syndromes, such as Graves disease (or toxic nodular goiter), in which the RAIU is increased.

4. **Clinical course summary**
   a. The acute phase of SAT usually lasts 4 weeks, but it may last longer and can be associated with hyperthyroidism. The RAIU is suppressed.
   b. Patients become euthyroid during the second phase, but occasionally hypothyroidism ensues that lasts 2 to 3 months. The RAIU gradually increases to normal. Low to normal T_4 and T_3 levels with elevated TSH can be seen at this time.
   c. During the recovery phase, thyroid function tests are normal, but the RAIU may be higher than normal as a result of greater trapping of iodine by the recovering thyroid gland.
5. **Prognosis.** Relapses may occasionally occur, but generally, the disease is self-limiting. Permanent hypothyroidism has rarely occurred.
6. **Treatment**
   a. **Acute phase**
      i. Analgesics—acetaminophen or ibuprofen.
      ii. Prednisone, 0.5 to 1.0 mg/kg/day in three or four divided doses (if no response to aspirin) for 1 week, then taper over next 2 to 3 weeks.
      iii. Propranolol, if hyperthyroidism is manifested.
      iv. **Not indicated**—thionamides, thyroidectomy, radioactive iodine (RAI), or antibiotics.

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   b. **Recovery phase.** If the patient is symptomatically hypothyroid, consider treatment with T_4 for 3 to 6 months, then taper and discontinue. Continue to follow for the rare case of permanent hypothyroidism. See Section III.C for L-T_4 dosing.

III. HYPOTHYROIDISM

A. General principles

Hypothyroidism is a thyroid disorder in which there is an inadequate amount of thyroid hormone to meet the body's metabolic requirements. In children, the earlier the age of onset of hypothyroidism, the greater is the chance of irreversible brain damage (see Chapter 38). If the onset is after age 2 or 3 years; however, most of the adverse effects are reversible. Table 42-4 reviews the clinical manifestations of hypothyroidism.

B. Causes of congenital hypothyroidism

1. Thyroid dysgenesis
2. Thyroid dyshormonogenesis
3. Transplacental transfer of maternal antithyroid antibodies or medication
   a. Positive **perchlorate discharge test**. This test is used to confirm the presence of a congenital or an acquired oxidation-organification defect such as found in Hashimoto thyroiditis (HT).
      i. Give potassium perchlorate, 10 mg/kg (or potassium thiocyanate) PO. After 2 to 4 hours, measure RAIU.
      ii. If a defect is present, >20% of the accumulated iodide leaves the thyroid gland. (Normally, iodide is not lost following perchlorate administration.)

C. Causes of acquired hypothyroidism in children

1. **Primary**
   a. **HT** is the most common cause of hypothyroidism in children. *See expanded discussion in section VIII.*
   b. **SAT** (de Quervain) is rare in children and seldom results in hypothyroidism.
   c. **Iodide ingestion** may result in a hypothyroid state.
      i. Underlying thyroid disease may predispose the patient to iodide-induced hypothyroidism.
      ii. Other goitrogens (e.g., sulfadiazine, lithium, and sulfonylureas) in combination with iodide may lead to hypothyroidism.
      iii. The fetus may become hypothyroid secondary to the transplacental passage of iodine.
   d. **Radioactive iodine ablation** of hyperthyroidism. The majority of patients achieve hypothyroidism within 6 months of treatment.
   e. **Thyroidectomy** for hyperthyroidism, thyroid nodules, and thyroid cancer. Select patients with thyroid nodules or thyroid cancer may be treated with lobectomy to avoid lifelong hypothyroidism.
   f. **Surgical removal of a thyroglossal duct cyst** may result in hypothyroidism. A thyroid ultrasound (US) and/or RAIU scan must be completed prior to surgery to determine if all of the thyroid tissue is found in the cyst wall or if there is a eutopic

thyroid gland. Thyroid function testing with a T_4 and TSH may also be considered prior and/or 6 to 8 weeks postoperatively to assess thyroid function.

g. Infiltrative disease of the thyroid gland with cystinosis or histiocytosis X may occasionally involve enough tissue to prevent normal hormonal production.

h. "Sick-euthyroid" syndrome or low T_3 syndrome. The thyroid gland in "sick-euthyroid" syndrome is functioning normally, but there is an abnormality in the peripheral metabolism of the thyroid hormones secondary to a severe nonthyroid illness that results in low T_3, elevated reverse T_3 (rT_3), low or normal T_4, low or normal free T_4, normal TSH, and low or normal thyroxine-binding globulin (TBG).

i. This condition is found in:

a) Infants with prematurity and respiratory distress syndrome;

b) Children with severe, acute illness, such as acute leukemia, trauma, renal failure and others (free T_4 and total T_4 correlate inversely with the degree of renal failure).

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TABLE 42-4 Clinical Manifestations of Childhood Hypothyroidism

Symptoms

Slow growth
Poor appetite
Constipation
Lethargy
Cold intolerance
Weakness, fatigue
Dry, coarse skin
Weight gain (may contribute, rarely the only cause)

Signs

General

- Decreased linear growth
- Mildly overweight

- Goiter
- Pale, cool skin
- Delayed dentition
- Slow, hoarse, low-pitched speech
- Constipation
- Dull, placid expression

Hematologic: anemia (three types)
- Normochromic normocytic
- Hypochromic-microcytic (iron deficiency secondary to menorrhagia or achlorhydria)
- Macrocytic (secondary to vitamin B_{12} or folic acid deficiency)

Cardiologic
- Bradycardia
- Pericardial effusions
- Flat T waves on ECG

Neuromuscular
- Delayed reflex return
- Acute encephalopathy (rare)
- Weakness and lethargy
- Occasionally hypertrophied muscles, e.g., Kocher–Debré–Sémélaigne syndrome (“herculean” appearance)
- Mental retardation (if untreated newborn)
- Memory loss
- Neurosensory hearing loss (Pendred syndrome)
- Myopathy (creatine phosphokinase elevation)

Hypothalamic–pituitary–gonadal axis
- Delayed puberty
- Overlap syndrome (pseudo-precocious puberty)
- Irregular and heavy menses (menorrhagia)

Skeletal
- Delayed bone age
- Epiphyseal dysgenesis (epiphyseal stippling)
- Slipped capital femoral epiphysis
- Enlarged sella turcica (in long-term primary hypothyroidism secondary to hypertrophy of thyrotropes)

ii. Treatment. Thyroid hormone replacement is not indicated for this condition.

i. Chronic medical conditions, especially those associated with decreased nutrition and repeated flares in illness, may be associated with subclinical hypothyroidism (cystic fibrosis and others).

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j. **Iodide deficiency** may lead to hypothyroidism with a compensatory TSH-stimulated goiter.

k. **Late-onset congenital thyroid disorders,** such as ectopia (cryptothyroid) and organification defects (dyshormonogenesis), may occur. Thyroid gland function may not fail until later childhood even though the disorder was present at birth.

i. **Lingual thyroid.** Most patients have inadequate functional thyroid tissue and ultimately require T_4 replacement. If the gland is enlarged or causes pressure symptoms and does not shrink with hormone treatment, then surgical removal may be considered. There is **no evidence that lingual thyroid glands have an increased incidence of malignancy in children**.

ii. **Dyshormonogenesis.** In the typical child with hypothyroidism, the gland is small or not palpable, but in disorders associated with deficiencies of enzymes, the thyroid gland may be enlarged. To assist in diagnosing the specific defect, the following tests may be ordered:

a) 24-hour RAIU.

1) Low value = iodine-trapping defect.

2) High value = other enzymatic defects.

b) Perchlorate discharge test is positive in peroxidase deficiency, such as **Pendred syndrome,** in which the child manifests a goiter and nerve deafness associated with euthyroidism or mild hypothyroidism.

2. **Central hypothyroidism (secondary [TSH] or tertiary [TRH]).** Deficiency of TSH or TRH occurs in <5% of hypothyroid pediatric patients and may be secondary to pituitary or hypothalamic disorders, such as tumors (adenoma or craniopharyngioma), trauma, infection, and congenital anomalies (e.g., septo-optic dysplasia), and irradiation or chemotherapy.

If adrenal insufficiency secondary to hypopituitarism is suspected, T_4 administration given alone before correcting the adrenal insufficiency may result in adrenal crisis. Therefore, it is important to evaluate adrenal function if the patient has a **low T_4 and low TSH** prior to initiating T_4 replacement.

D. Clinical findings

1. The clinical manifestations of childhood hypothyroidism vary and depend largely on the age of onset (Table 42-4; see Chapters 38 and 40). Typically, the child is short and mildly overweight rather than very obese. (The euthyroid child with marked exogenous obesity manifests accelerated growth with advanced bone age and advanced pubertal development.) If the hypothyroid state is prolonged before treatment, catch-up growth may be incomplete. Also, excess dosage may advance bone age disproportionately.
2. Commonly, the hypothyroid adolescent presents with delayed puberty; however, on occasion, a child may present with "altered" precocious puberty associated with a delayed bone age and ovarian cysts. This syndrome is known as **overlap syndrome or by the eponym Van Wyk and Grumbach syndrome**. In this situation, the low T_4 feeds back to stimulate TRH and TSH as well as prolactin secretion. High levels of TSH are believed to cross-react with the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) receptors in the ovary or testis as the glycoprotein hormones share the same α-subunit (or chain). The precocious puberty is incomplete, isosexual, associated with elevated TSH and low LH and FSH levels. Hyperstimulation of the ovary may result in large cyst formation and an increased risk for ovarian torsion. Thus, **hypothyroidism should be excluded in young girls with ovarian cysts with or without torsion.**

E. Diagnosis of hypothyroidism (Fig. 42-2 and Table 42-5)

1. The following **laboratory tests** may be useful in the diagnosis of hypothyroidism (not all of these tests need to be ordered. For primary hypothyroidism, a TSH may be adequate. For central hypothyroidism, a TSH and a T_4 are needed as well as assessment of other pituitary glycoprotein hormones):
   - **a.** TSH—high.
   - **b.** T_4—low.
   - **c.** T_3 resin uptake (T_3RU)—low.

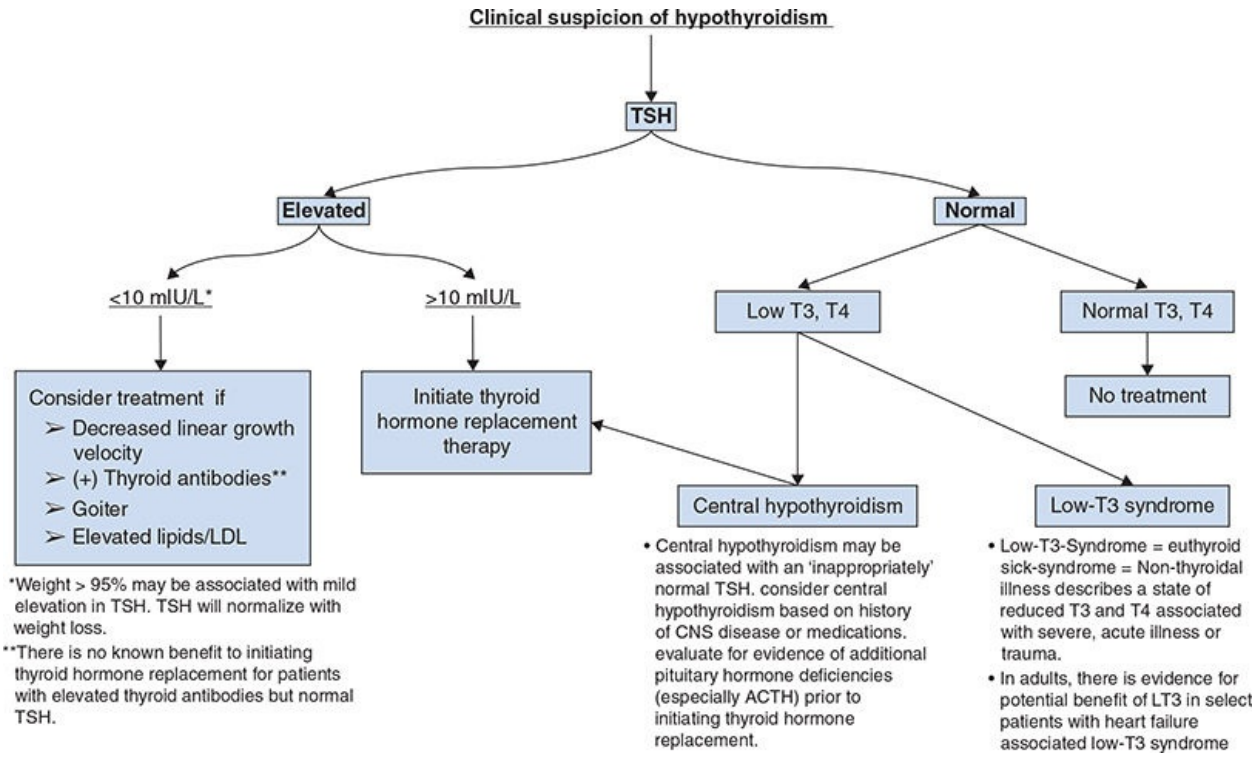

Figure 42-2. Clinical evaluation of hypothyroidism. FT_4I, free T_4 index; T_4, free thyroxine; TRH, thyrotropin-releasing hormones; TSH, thyroid-stimulating hormone.

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TABLE 42-5 Thyroid Function Tests in Various Thyroid Disorders

	T_4	Free T_4	T_3 (RIA)	FT_4I	TSH	RT_3	T_3
Primary hypothyroidism	↓	↓	↓	↓	↑	↓	↓ or N
Secondary hypothyroidism	↓	↓	↓	↓	↓ or N	↓	↓ or N
Tertiary hypothyroidism	↓	↓	↓	↓	↓ or N	↓	↓ or N
Low TBG	↓	N	↓	N	N	↑ or N	↓ or N
High TBG	↑	N	↓	N	N	N	↑ or N
Hyperthyroid	↑	↑	↑	↑	N or ↓	↑	↑
Sick-euthyroid syndrome (low T_3 syndrome)	↓ or N	↓ or N	↓ or N	↓ or N	↓or N	↑or N	↓

FT_4I, free thyroxine index; N, normal; RIA, radioimmunoassay; RT_3, reverse T_3; T_3, triiodothyronine; T_4, thyroxine; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone; ↑, high; ↓, low.

d. Free T_4 index (FT_4I)—low (useful in pregnancy and TBG deficiency).
e. T_3 (radioimmunoassay, RIA) (not usually needed)—low.
f. Free T_4 (useful in hypothalamic/pituitary hypothyroidism)—low.
g. Antithyroid antibodies (positive in thyroiditis).
h. TBG (see Table 36.1).
i. Thyroid scan (thyroiditis).
j. RAIU (enzyme deficiencies).

2. Other **laboratory tests** may be abnormal:
   a. Serum cholesterol may be elevated (secondary to decreased expression of the low-density lipoprotein (LDL)-receptor).
   b. Muscle enzymes (creatine kinase [MM fraction], aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase) may be elevated and be associated with myopathy.
3. **Primary hypothyroidism**
   a. High TSH with low T_4, low free T_4, low T_3RU (low FT_4I).
   b. Borderline elevated TSH (between 4.5 and 10 mIU/L) with low-normal T_4 or free T_4 may be seen in early primary hypothyroidism (called subclinical hypothyroidism).
4. **Secondary or tertiary hypothyroidism (pituitary or hypothalamus)**
   a. Normal (inappropriately) or low TSH with low T_4 or low free T_4.
   b. In some patients, serum TSH is in the normal range, but the TSH has reduced biologic activity.
   c. Computed tomography (CT) or MRI of the brain with pituitary cuts may be indicated to rule out a tumor.

F. Treatment

1. The **goals** of treatment are normal growth and development with normal TSH, T_4 and T_3 levels (“replacement” therapy). These are accomplished by:

a. Maintaining the serum T_4 in the upper half of the normal range

b. Reducing TSH into the lower-normal level (see Chapter 38)

2. Thyroid replacement

a. Levothyroxine (L-T_4) is the most commonly recommended drug for treatment of hypothyroidism.

i. Dose = 100 μg/m^2/day *or* age and weight based; 4 to 6 μg/kg/day in children 1 to 3 years of age, 3 to 5 μg/kg/day for children 3 to 10 years of age, 2 to 4 μg/kg/day for patients 10 to 16 years of age, and 1.6 μg/kg/day for patients 17 years of older (adult replacement dose).

ii. Brand name versus generic L-T_4—The majority of patients will have predictable response to generic L-T_4. For patients that would benefit from p. 567p. 568reduced variability (i.e., newborns with congenital hypothyroidism) or for patients with unpredictable and variable response to generic L-T_4, brand name is preferred over generic.

iii. The pill form of L-T_4 should never be made into a suspension, even for infants and small children. The pill form of L-T_4 is not stable in solution or suspension, and the patient will be at significant risk of being administered an unknown amount of L-T_4.

iv. Adjustment in dosage is based on the clinical and laboratory response:

a) Linear growth rate is followed every 3 to 6 months

b) TSH and T_4 measured every 1 to 6 months, depending on age (more frequent the younger the child)

1) Repeat TSH and T_4 should be assessed 6 weeks after each adjustment in L-T_4 dose.

c) A bone age should be evaluated every 1 to 2 years to determine if accelerated epiphyseal fusion has occurred from excessive L-T_4 administration.

b. Desiccated thyroid is extracted from pig (porcine) thyroid

glands and is regulated by the Food and Drug Administration. This form of thyroid hormone replacement contains both T_3 and T_4 (combined therapy) which may be an advantage for patients with low-T_3 and persistent symptoms of hypothyroidism on L-T_4 only treatment. The disadvantage is that the ratio of T_3:T_4 is porcine, not human and it may be difficult to obtain targeted TSH, T_4 and T_3 levels. There does not appear to be an advantage to this form of thyroid hormone replacement based on it being a "natural" compared to synthetic medication.

c. Liotrix is a 4:1 mixture of L-T_4 and L-T_3 that can cause elevated T_3 and normal or low T_4 values.

d. There is ongoing investigation to determine if a subgroup of patients with hypothyroidism may benefit from combined T_3 and T_4 therapy. Until further data are available, the majority of patients should be started on L-T_4 "only" replacement therapy.

3. Adverse effects with appropriate dosage. Pseudotumor cerebri may develop after initiation of L-T_4, most notably in patients with very elevated TSH prior to the initiation of thyroid hormone replacement therapy.

4. Adverse effects with excessive dosage

a. Nervousness
b. Tremors
c. Tachycardia
d. Hypertension
e. Delayed neurologic development
f. Premature craniosynostosis
g. Early closure of epiphysis

G. Prognosis

1. The signs and symptoms listed in Table 42-4 should be eliminated with adequate thyroid replacement therapy. If the age at onset of hypothyroidism is later than 2 to 3 years, there should be no permanent brain damage or impairment of central nervous system function.

2. The growth rate will accelerate and the bone age will advance to normal. Weight loss occurs because of increased metabolic rate and mobilization and excretion of myxedematous fluid.

3. The child's behavior may change from being quiet or placid to

more aggressive.

4. Hypothyroid patients with HT who recover thyroid function do not require lifelong T_4 therapy. They can be identified during T_4 treatment by a normal thyroid response to TSH in a TRH stimulation test, obviating the need to stop thyroid hormone for 6 to 8 weeks.

H. HT (autoimmune thyroiditis, chronic lymphocytic thyroiditis).

1. **Incidence.** HT is the most common thyroid disorder in children; it is the most common cause of euthyroid goiter as well as hypothyroidism. Females predominate in a ratio of 2:1, with a peak age in mid-puberty; HT is rare in children p. 568p. 569<4 years of age. The specific mode of inheritance is not yet known, but there is a high familial incidence (up to 25%).
2. **Etiology.** Altered cellular and humoral immunity occurs in HT from either **(1)** defective suppression of thyroid-directed T lymphocytes that act against the host thyroid or **(2)** liberation of an antigen after thyroid damage, such as by a viral infection (Epstein Barr, enterovirus, adenovirus, parvovirus, mumps, rubella, or other) that initiates an autoimmune reaction.
3. **Pathogenesis.** Goiter results from the marked lymphocytic infiltration of the thyroid as well as an elevated TSH as the autoimmune destruction of the gland eventually leads to decreasing thyroid hormone production. In addition to the apoptotic destruction, the damaged cells also exhibit a defect in organification associated with a positive perchlorate discharge test (discharge of more than 40% of radioiodine after administration of perchlorate). Some patients have an atrophic form of HT associated with the presence of TSH-receptor blocking antibodies.
   a. Hereditary susceptibility associated with persistence of B- and T-cells directed against thyroid antigens is associated with an increased risk for developing autoimmune thyroid disease. The haplotypes HLA-DR4 and HLA-DR5 are associated with an increased risk of goiter and thyroiditis, whereas the atrophic variant of thyroiditis is found with HLA-DR3. Autoimmune thyroid disease “clusters” in families, but does not follow a

predictable mode of inheritance with both autoimmune hypothyroidism and autoimmune hyperthyroidism often coexisting in the same family.

4. **Clinical findings.** The patient may present in one of three ways.
   a. The most common presentation initially is an **enlarged thyroid gland** with normal thyroid hormone levels (euthyroidism). This gland may be symmetrically or asymmetrically enlarged with a granular surface; it may be firm and lumpy, lobulated, irregular, or nodular in the later stages. Sometimes a **midline pea-sized lymph node (Delphian node)** may be present above the isthmus. As the disease progresses, the goiter may shrink in size, disappear, or remain unchanged.
   b. **Toxic thyroiditis** (Hashitoxicosis) is a transient, self-limited form of hyperthyroidism that occurs in <5% of patients, with manifestations of nervousness, irritability, sweating, hyperactivity, and tachycardia. This phase is caused by the immune mediated destructive **release of preformed thyroid hormone (in contrast to Graves disease that is caused by active production of thyroid hormone formation)**.
   c. **Hypothyroidism** can occur with or without thyromegaly (5% to 10%). Children who present with hypothyroidism may remain permanently hypothyroid. At least 10% to 20% of patients who are euthyroid will become hypothyroid within 5 years from the time of diagnosis. Most cases of atrophic (nongoitrous) hypothyroidism are caused by autoimmune thyroiditis. The lack of a goiter may be associated with a delay in diagnosis, even in patients that are manifesting decreased linear growth.
5. **Diagnostic evaluation**
   a. Thyroid function tests will reflect the metabolic state of the gland (low, normal, or elevated). Most children are euthyroid initially. The incidence of hypothyroidism is 3% to 13%, and subclinical hypothyroidism (high TSH, normal T_4) occurs in up to 35%. A small number of patients present with transient thyrotoxicosis at the time of diagnosis. Treatment is not initiated until the TSH increases.
   b. **Autoantibodies.** Antithyroglobulin (ant-Tg or Tg-Ab) and

antithyroid peroxidase (anti-TPO or TPO-Ab). TSH-receptor antibodies (TRAbs) may also be detected and the “blocking” antibodies may relate to the development of hypothyroidism and thyroid atrophy in patients with autoimmune thyroiditis. Other antibodies have also been described (against sodium/iodide symporter protein and pendrin) but are not used in the clinical setting to assess for disease.

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i. Tg-Ab and TPO-Ab are markers of disease. Tg-Ab does not appear to have biologic activity, but TPO-Ab may inhibit enzyme activity and stimulate killer-cell cytotoxicity.
ii. Tg-Ab and/or TPO-Ab are often elevated prior to the development of hypothyroidism (called euthyroid Hashimoto).
iii. Tg-Ab may be found in up to 15% of the general population; however, in most developed nations, an elevation in TPO-Ab appears to be more predictive for developing hypothyroidism. Tg-Ab may be more predictive of autoimmune thyroiditis in nations with dietary iodine excess.
iv. Tg-Ab and TPO-Ab may also be detected in up to 50% of patients with Graves disease. In patients presenting with hyperthyroidism, the differentiation between the toxic phase of HT and Graves disease may be difficult. However, the presence of thyroid-stimulating immunoglobulin (TSI) with or without TSI-mediated thyroid eye disease (TED) defines the diagnosis of Graves disease.

c. **Thyroid US** may be used to detect the autoimmune destruction associated with HT. US features include; hypoechogenicity (darker gray), heterogeneity (irregular pattern), and hyperemia (increased blood flow).
i. Patients with HT have an increased risk for developing thyroid nodules and differentiated thyroid cancer (DTC).
ii. The destructive process may be “patchy” making it challenging to determine if an area is a patch area of HT (a “pseudonodule”) or a true nodule. The pattern of blood flow on Doppler imaging may be helpful to distinguish if the area in question is a nodule (distinct increased blood flow

compared with surrounding tissue) compared with a pseudonodule (no distinct pattern to the blood flow when compared with surrounding tissue).

iii. Fine needle aspiration (FNA) of the area in question may be required to determine the etiology, to determine if an area is a "pseudonodule" or a true nodule.

d. RAI uptake and scan often reveals patchy distribution but there is no advantage to performing RAIU compared with thyroid US.

6. Treatment

a. The dose of L-T_4 is determined by age and weight; 4 to 6 μg/kg/day in children 1 to 3 years of age, 3 to 5 μg/kg/day for children 3 to 10 years of age, 2 to 4 μg/kg/day for patients 10 to 16 years of age, and 1.6 μg/kg/day for patients 17 years of older (adult replacement dose).

b. If a patient has "subclinical hypothyroidism" (normal T_4 but elevated TSH), L-T_4 administration is also recommended if the patient has a goiter, TPO-Ab are elevated, thyroid US is consistent with autoimmune thyroiditis, there is a history of concomitant autoimmune disease (celiac disease, type 1 diabetes mellitus, or other), and/or there is an elevation in total cholesterol. Patients with a TSH > 7.5 mIU/L may be more likely to progress to "overt" hypothyroidism (TSH > 10 mIU/L).

c. If a patient has positive antibodies but is euthyroid (normal TSH and T_4), L-T_4 administration is not necessary. However, the child should be followed at regular intervals (e.g., every 6 to 12 months) to monitor the T_4 and TSH levels. The initiation of L-T_4 does not appear to influence the thyroid antibody titer or the progression of the disease.

d. If the patient is symptomatically hyperthyroid secondary to Hashitoxicosis (transient phase of hyperthyroidism followed by subsequent hypothyroidism), a cardio-selective β-blocker such as atenolol may be prescribed (0.5 to 2 mg/kg/day). TSI or TRAb should be measured to screen for autoimmune hyperthyroidism (Graves disease). **In Hashitoxicosis, an RAI uptake and scan would show decreased uptake (<10% at 24 hours) in contrast to increased uptake**

that would be consistent with Graves disease (>30%).

7. **Associated disorders**
   a. **Thyroid cancer and HT**

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   i. Patients with HT have an **increased risk of developing thyroid nodules and DTC**. Some data support performing surveillance thyroid US on all patients with HT.
   b. **Chromosomal disorders or syndromes.** There is a higher association of HT in patients with Down, Turner, and Klinefelter syndromes.
   c. **Autoimmune syndromes**
      i. Type 1 diabetes mellitus and Celiac disease are the two most common comorbid autoimmune disease in pediatric patients.
      ii. Type I (autoimmune polyendocrinopathy candidiasis ectodermal dysplasia). The classic triad of (1) mucocutaneous candidiasis, (2) hypoparathyroidism, and (3) Addison disease. In addition, patients are at increased risk of developing type 1 diabetes mellitus, gonadal failure, alopecia, pernicious anemia, vitiligo, malabsorption, chronic active hepatitis, and HT.
      iii. Type II: Addison disease, type 1 diabetes mellitus, HT.
      iv. Type IIIa: type 1 diabetes mellitus, HT.
      v. Type IIIb: Graves disease or HT, pernicious anemia.
      vi. Type IIIc: Graves disease or HT, alopecia, vitiligo, myasthenia gravis, idiopathic thrombocytopenic purpura.

IV. HYPERTHYROIDISM

A. General principles

Hyperthyroidism is a disorder of an excessive secretion of thyroid hormone resulting in a hypermetabolic state of virtually all body organs. It is caused by a variety of conditions, including autoimmune-mediated hyperthyroidism (Hashitoxicosis and Graves disease), an autonomously functioning nodule, or genetic (congenital nonautoimmune hyperthyroidism [NAH], McCune–Albright disease, and others). Antithyroid medication, radioactive iodine ablation, and thyroidectomy are the three available treatment options. Iodine excess, either from dietary supplementation, from radiologic contrast media, or from

medication (amiodarone), may also induce hyperthyroidism (Jod–Basedow phenomenon). Patients at risk are those with endemic goiter from iodine deficiency, multinodular goiter, or Graves disease (see Chapter 38).

B. Causes of hyperthyroidism (Table 42-6)

1. Graves disease

a. Etiology. It is the autonomous production of excessive thyroid hormones by a usually enlarged thyroid gland that is not under pituitary control. It is the most common cause of hyperthyroidism in children. Pediatric patients may present with, or develop, TED; however, it is typically not associated with a risk of vision loss. Dermopathy (pretibial myxedema with hyperpigmented waxy plaques and digital clubbing/acropachy) in children is very uncommon.

i. There is a high familial incidence, and females predominate in a 3:1 to 5:1 ratio.

ii. Graves disease arises from autoimmune processes, which include production of immunoglobulins against antigens in thyroid, orbital tissues, and dermis.

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TABLE 42-6 Etiology of Hyperthyroidism in Childhood

Graves disease
Autonomously functioning nodule (toxic adenoma)
Excessive ingestion of thyroid hormones (factitious hyperthyroidism)
Inappropriate TSH hypersecretion (TSH secreting pituitary adenoma)
Subacute thyroiditis
Hashitoxicosis (transient hyperthyroidism due to Hashimoto thyroiditis)
Iodine-induced thyrotoxicosis (rare in United States)

TSH, thyroid-stimulating hormone.

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iii. TSIs (also known as TRSAb, thyrotropin receptor–stimulating antibody) have been demonstrated in virtually 100% of patients and are responsible for causing the

increased synthesis of thyroid hormone in Graves disease. TSI preferentially occupies the TSH-receptor on the thyroid gland and initiates the synthesis of the hormones in the same way it would if TSH was present. Measurement of TSI is important to confirm the diagnosis as well as to identify remission and relapse.

iv. **TPO-Ab and Tg-Ab** are found in **50% of patients** with Graves reflecting that both Graves and HT cover a spectrum of autoimmune thyroid disease. The presence of TSI defines the clinical diagnosis of Graves, and the balance between stimulatory, blocking, and neutral TRAb determines the degree of T_3 and T_4 production.

b. Clinical findings (Table 42-7)

i. **Graves ophthalmopathy or TED.** Up to 50% of children with Graves disease manifest ophthalmopathy; however, this problem is not as severe as in adults. Lid retraction and stare are the most common, whereas chemosis, lid eversion, paresis of extraocular muscles, and a risk of vision impairment/loss are found predominantly in adults.

ii. The severity of the TED correlates with the TSI level but is unrelated to the severity of thyroid dysfunction. Graves ophthalmopathy may present unilaterally or bilaterally and may be present prior to the onset of other clinical signs or symptoms.

iii. Similar to adults, exposure to tobacco smoke increases the risk and severity of TED

c. Laboratory findings (Table 42-5)

i. Elevated T_3 and T_4; in the early phases of Graves, T_3 may be preferentially elevated compared with T_4 (T_3-thyrotoxicosis).

ii. Elevated TSI or TRAb; TSI is a functional bioassay in contrast to TRAb which is a competitive binding assay. **TRAb may be substituted for TSI** as the newer assay has high sensitivity, faster turn-around time, and is less expensive than TSI.

d. Additional diagnostic evaluation. If the thyroid is not enlarged or is asymmetric, a thyroid US may be performed to

evaluate for a thyroid nodule as the cause of, or associated with, hyperthyroidism. A RAIU and scan may be used to diagnose patients with clinical hyperthyroidism but nonelevated TSI. If the TSI is elevated, there is no need to perform a diagnostic RAIU and scan.

i. **Marine–Lehnhart syndrome** describes a patient with an autonomously functioning nodule or toxic multinodular goiter in the setting of Graves disease.
ii. Patients with "**silent**" or **painless thyroiditis** are asymptomatic with mild or subclinical hyperthyroidism and low uptake at 24 hours. The expectant course for these patients is a period of subclinical hypothyroidism followed by euthyroidism.
iii. Rarely, a patient is so hyperthyroid that an early uptake at 2 to 4 hours is very high, but by 24 hours, the uptake is normal. These patients with high turnover of iodine may experience a rapid-response to antithyroid medication as well as a rapid rate of relapse. Radioiodine ablation may also be less effective but may be made more effective with coadministration of lithium.
iv. The ultrasensitive TSH will be normal or low unless the hyperthyroidism is caused by a rare TSH-producing tumor. A TSH-secreting adenoma is typically associated with an elevated T_3 and T_4 and nonsuppressed TSH. An elevated α-subunit and/or MRI showing a pituitary tumor is diagnostic.
v. Thyroglobulin (Tg) is elevated in all forms of thyroiditis but is not needed for diagnosis or management of autoimmune thyroid disease. A suppressed Tg in the setting of hyperthyroidism with nonelevated TSI or TRAb, no nodule on thyroid US, and no evidence of a genetic disorder associated with hyperthyroidism, should raise suspicion for the diagnosis of **"factitious" hyperthyroidism** secondary to ingestion of excess T_3 and/or T_4.

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TABLE 42-7 **Clinical Features of Graves Disease in Childhood**

Organ		Signs	Symptoms
Eyes	Less severe than in adults	Lid retraction	Blurring of vision
		Lid lag	Diplopia
		Proptosis	
		Chemosis	
		Ophthalmoplegia	
Thyroid		Enlarged	
		Bruit/thrill	
		Cervical/venous hum	
Skin		Soft, warm	Flushing
		Smooth, moist	Excessive sweating
	Very rare in children	Dermopathy	Swelling in legs
		Pretibial myxedema	
		Clubbing	
Heart		Increased heart rate	Palpitations
		Forceful apical beat	Rapid heart rate
		Flow murmurs	
		Arrhythmias	
		Increased pulse pressure (mitral regurgitation)	
Gastrointestinal		Hyperperistalsis	Increased BM/day
			Increased appetite
Central nervous system		Fine tremor	Nervousness
		Hyperreflexia	
Muscle		Muscle atrophy	Muscle weakness
		Myasthenia gravis	Easy fatigability
		Periodic paralysis	
Respiratory		Increased respiratory rate	Exertional dyspnea
Metabolic		Accelerated growth rate	Heat intolerance
		Hypercalciuria (hypercalcemia)	Weight loss
			Occasional weight gain from overeating
Mental			Nervousness
			Irritability
			Emotional lability
			School problems
			Poor attention span
Reproductive		Amenorrhea	

Delayed menarche

2. **Autonomously functioning thyroid nodule (AFTN).** Thyroid hormone from an AFTN is secreted independent of TSH stimulation. The excessive release of thyroid hormone suppresses the pituitary release of TSH, resulting in **diminished activity in the remainder of the gland**. On thyroid scan, the AFTN appears as a "warm" or "hot nodule" surrounded by little or no thyroid tissue. T_3 may be preferentially elevated. Somatic activating mutations of the TSH-receptor p. 574p. 575are the most common identifiable genetic etiology and may be helpful if FNA is performed with resultant indeterminate cytology.
3. **Factitious hyperthyroidism (ingestion of excess thyroid hormone).** The gland is not enlarged because of TSH suppression by exogenous hormone, and there is little or no uptake on radioiodine scan. Free T_4 and TSH are the same as in Graves, but the thyroglobulin is low, whereas in Graves it is elevated.
4. **Inappropriate TSH hypersecretion.**
   a. **TSH-secreting pituitary tumors.** These rare tumors secrete TSH alone or multiple pituitary hormones along with TSH. **Elevated serum levels of the free α-chain** (alpha-subunit) help distinguish this tumor from resistance to thyroid hormone (RTH). MRI will also reveal a pituitary tumor.
   b. **RTH.** Patients present with an inappropriately nonsuppressed or mildly elevated TSH in the setting of an elevated T_3 and T_4. In contrast to Graves where T_3 predominance is common, the **degree of T_3 and T_4 levels is typically similarly elevated in RTH**. The most common form of RTH is secondary to mutations in the β-isoform of the nuclear receptor with autosomal dominant transmission. Tachycardia, goiter, and attention deficit disorder-like symptoms are frequent. Short stature and delayed bone age with hearing loss are distinguishing criteria. RTH due to mutations in the alpha-isoform of the nuclear receptor is associated with dysmorphic

facies, skeletal dysplasia (macrocephaly, epiphyseal dysgenesis), poor linear growth, constipation, and intellectual deficits.

c. Congenital NAH. NAH is caused by activating mutations in the TSH-receptor. Mutations in the TSHR may be *de novo* (sporadic-NAH), transmitted as an autosomal dominant disorder (familial-NAH), or may be isolated to thyroid nodules with autonomous function (somatic). TSI is not elevated, but the other thyroid autoantibodies may be elevated. Interestingly, young patients may have eye prominence, from proptosis to exophthalmos. Newborns with severe FNAH may be born prematurely, have low birth weight, goiter, craniosynostosis, and be at increased risk for neurocognitive dysfunction. Antithyroid medication may be effective but definitive treatment is ultimately required, typically a combination of total thyroidectomy followed by RAI ablation to decrease the risk of recurrence.

5. Euthyroid hyperthyroxinemia. There are many conditions that cause hyperthyroxinemia but *not* hyperthyroidism (total T_4 is elevated, but free T_4 and TSH are normal):

a. Elevated TBG—most frequently secondary to estrogen (endogenous or oral contraceptives)

b. Dysproteinemia (e.g., familial dysalbuminemic hyperthyroxinemia). Total T_3 and T_4 are elevated with a normal (nonsuppressed) TSH in a clinically euthyroid patient. The condition is caused by mutations in the albumin gene associated with a 40% to 60% increased affinity of albumin for T_4. Depending on the assay used, the fT_4 may also be slightly elevated. The condition is inherited in an autosomal dominant pattern of the R218H mutation (R242H in the peptide).

C. Treatment of hyperthyroidism

1. Treatment plan for hyperthyroidism in children and adolescents. Not all therapeutic modalities are suitable for every child.

a. Begin antithyroid medication when diagnosis is confirmed. Only MMI is approved for use in pediatric patients (<19 years of age).

b. If symptoms are severe, add a β-blocker, continued until T_3 and

T_4 have normalized.

c. Follow serial T_3 and T_4 levels, initially at monthly intervals, then less frequently depending on the clinical course. Increase the MMI dose if thyrotoxicosis persists despite compliance. Decrease the MMI dose based on T_3 and T_4 levels.

d. Consider a trial off MMI once the TSI normalizes. Discontinuation of the MMI if the TSI is still elevated, even if the MMI dose is minimal, will result in quick return of the hyperthyroidism.

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e. The risk of relapse is highest in the first 3 to 12 months after stopping the MMI. Approximately 30% to 40% of patients may relapse.

2. Prognosis

a. Approximately 50% of pediatric patients will experience remission within 5 to 7 years of starting antithyroid medication with a 30% to 40% risk of relapse for an overall likelihood of remission of <30% to 35%.

b. TSI assay is important to identify remission, but a normal value does not correlate with a reduced risk for relapse. **TSI must be measured and be within the normal range prior to attempting to stop antithyroid medication.**

3. Antithyroid medication. MMI is the only antithyroid medication approved for use in pediatric patients in the United States. MMI inhibits the action of TPO and typically renders the patient euthyroid within 1 to 6 months of initiation of therapy. Approximately 50% of pediatric patients will achieve remission within 5 to 7 years of diagnosis; however, 30% to 40% of patients will relapse within 6 to 12 months of normalization of TSI and stopping MMI. Thus, less than 30% of patients will achieve long-term remission.

a. Dosage

i. MMI. 0.5 to 1.0 mg/kg/day may be given once a day. Serum half life is approximately 4 to 6 hours and tissue half life is approximately 17 to 20 hours. Maximum dose per 24 hours is 60 mg/day.

b. Complications. The majority of side effects and adverse

reactions occur within 6 months of initiation of therapy; however, they may occur at any time, even 15 to 18 months or longer after initiation of MMI. The risk appears to correlate with the dose of MMI. There does not appear to be any utility in serial surveillance of the CBC or LFTs.

i. **Mild.** Cutaneous reactions, most commonly pruritus and hives, occur in approximately 15% to 20% of patients. Decreasing the dose and adding an antihistamine may be attempted to see if continuation of MMI is possible. Arthralgia may occur in 2% to 5% of patients and decreasing the dose and adding ibuprofen may be attempted.

ii. **Severe**

a) **Agranulocytosis** and neutropenia occur in <1% of patients. A periodic WBC in an asymptomatic child is not useful, but if the patient develops a sore throat and fever, a WBC should be obtained immediately. The neutropenia is usually reversible by stopping the thionamides (propylthiouracil [PTU] or methimazole [MMI]) if the total WBC is <2,500/μL.

b) **Cholestatic jaundice.** MMI-induced hepatitis occurs in <1% of patients. It presents with jaundice, pruritis, dark-colored urine, and clay-colored stools. Patients may or may not have decreased appetite, nausea, or abdominal pain. Liver transaminases (AST, SLT, and GGT), and total and direct bilirubin levels are elevated. It is reversible if the MMI is discontinued.

c) Patients with Graves may also present with mild elevations in AST and ALT even prior to initiation of MMI. **If the AST and ALT are <4× elevated, MMI may still be started.** The Graves-induced elevation in liver transaminases resolves once T_3 and T_4 are normalized. Viral and autoimmune hepatitis should be considered in the differential for all forms of Graves or MMI-induced elevations in transaminases.

4. **Additional medications and mechanism of action of agents used to treat hyperthyroidism.** Drugs and other agents used in the management of hyperthyroidism act as

inhibitors at many different points in the chain of thyroid hormone synthesis, secretion, and metabolism.

a. Hormone synthesis inhibition

i. MMI. Blocks thyroperoxidase or thyroid peroxidase (TPO), organification of iodine.

b. Inhibition of hormone release

i. Iodide (Wolff–Chaikoff effect)

ii. Lithium carbonate

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c. Impaired peripheral conversion of T_4 to T_3 (drugs act extrathyroidal)

i. PTU

ii. Dexamethasone

iii. Propranolol

d. *β*-Adrenergic blockers. All of the *β*-adrenergic blockers effectively neutralize many symptoms of autonomic hyperactivity, but there is no inhibition of thyroid hormone synthesis or release. However, propranolol impairs conversion of T_4 to T_3 by approximately30%.

i. Propranolol

a) Dosage. 2.5 to 10.5 mg/kg/day given q6–8h.

b) Indications

1) Can be used alone in mild hyperthyroidism until results of evaluation are complete.

2) Can be used in combination with thionamides for moderate or severe hyperthyroidism until T_3 and T_4 normalize.

c) Action. Rapidly controls tremors, agitation, tachycardia, and cardiac arrhythmias.

d) Side effects. Bradycardia, hypoglycemia.

e) Contraindications

1) Asthma

2) Emphysema

3) Congestive heart failure

4) Complete heart block

5) Raynaud phenomenon

6) Should be used with caution in patients with diabetes

mellitus

ii. **Atenolol—**A β_1 blocker (cardio-selective).

a) **Dosage.** 0.5 to 2mg/kg/day

b) **Indication.** May be a better first line agent over propranolol with the exception of patients with severe thyrotoxicosis, where there is a benefit for using propranolol because of its ability to decrease the peripheral conversion of $T_4 \rightarrow T_3$.

e. Stable iodine (inorganic iodine). Physiologic amounts of iodine are essential in the synthesis of thyroid hormones, but pharmacologic amounts temporarily inhibit this synthesis **(Wolff–Chaikoff effect)** as well as retard hormone release from the gland. Improvement of hyperthyroidism may occur within 72 to 96 hours. Patients may "escape" from iodine-induced hypothyroidism after 2 or more weeks of use.

i. **Indications for use**

a) **It is used preoperatively** to decrease thyroid hormone levels and vascularity of the gland.

b) It should *not be used* preoperatively for patients with toxic adenomas or multinodular goiter because it can exacerbate the hyperthyroidism **(Jod–Basedow phenomenon)**.

ii. **Action**

a) Decreases expression of the Na–I symporter

b) Decreases thyroid hormone release

c) Decreases biosynthesis/organification

iii. **Dosage.** Three to five drops three times daily for 7 to 10 days; saturated potassium iodine oral solution (SSKI; 1 drop = 50 mg) or potassium iodide–iodine (Lugol solution; 1 drop = 6 mg).

iv. **Side effects.** Nausea, stomach pain, diarrhea, metallic taste, fever, and headache.

f. Lithium

i. **Mechanism of action.** Lithium inhibits thyroid hormone release.

ii. **Indications for use.** Lithium may be used to increase the efficacy of RAI for patients with rapid-turnover associated with previous failure to achieve RAI-induced

hypothyroidism.

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iii. **Dose.** 200 to 300 mg three times daily—some advocate giving it 6 days prior and 3 days after RAI and others 6 days starting on the day of RAI administration.

g. Oral cholecystographic agents (such as iopanoic acid)

i. **Mechanism of action.** Blocks peripheral conversion of T_4 to T_3.

ii. **Indications.** Thyroid storm, because it has a rapid onset of action.

iii. **Adverse effects.** No toxic effects have yet been reported.

iv. **Dosage.** A dose of 1 g sodium ipodate every 1 to 3 days is effective within 48 hours. Similar to stable iodine, it is not usually used for more than 3 to 4 weeks.

5. Definitive treatment

a. Radioactive iodine ablation (RAIA) and thyroidectomy are both effective approaches for definitive treatment of Graves. The goal for both RAIA and thyroidectomy is permanent hypothyroidism (corrected to euthyroidism with lifelong levothyroxine replacement therapy).

b. Timing for definitive treatment. Definitive treatment should be pursued if the patient develops or experiences;

i. Serious adverse reaction to MMI such as bone marrow suppression (neutropenia or agranulocytosis) or cholestatic jaundice

ii. Moderate but persistent reaction to MMI that is not relived by reduction in dose with attempt at using symptomatic medications, such as, hives (antihistamine) or arthropathy (nonsteroidal anti-inflammatory drug)

iii. Persistence of GD (= elevated TSI or TRAb) 5 to 7 years after initiation of MMI

c. <u>Approach to selection of definitive treatment</u>

i. RAIA is a reasonable choice if

a) Age is >10 years (not an absolute indication)

b) Thyroid gland is less than three to four times enlarged

c) No active eye disease or severe proptosis

d) No nodules on thyroid US

No plans for pregnancy for >1 year (elevated TSI
e) persists longer after RAIA vs. surgery)
f) History of Keloid formation
g) Time to conversion to hypothyroidism (typically takes 2 to 6 months to achieve hypothyroidism after RAIA)

ii. Thyroidectomy is a reasonable choice if

a) Access to a surgeon with low recurrent laryngeal nerve and hypoparathyroidism complication rate (<5%)
b) Age <10 years or reliance on care giver for activities of daily life (bathroom and bathing)
c) Thyroid gland greater than three to four times in size
d) Active or severe TED
e) Presence of nodules
f) Interest in quick resolution of Graves, conversion to hypothyroidism

d. RAI. RAIA is an effective modality to achieve hypothyroidism in appropriately selected patients. Although limited, the risk of RAI-induced second malignancies and salivary dysfunction is low.

i. Advantages. Easy administration and effectiveness.
ii. Contraindications. Pregnancy and gross enlargement.
iii. Complications

a) Need for repeated RAI treatment
b) Hypoparathyroidism or hyperparathyroidism is a rare complication that can occur **3 to 45 years** after RAI therapy.

iv. Techniques for the administration of ^{131}I

a) Perform a pregnancy test in adolescent females.
b) Discontinue antithyroid medication for several days (at least 3 days) before the administration of the RAI.
c) A β-blocker may be given during this time, if necessary, which will not interfere with the RAIU.

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d) The dose of ^{131}I is based on the estimated weight of the gland and the uptake of a tracer dose of the iodine. ^{131}I is measured at 6 hours and 24 hours. A dose of ^{131}I is chosen that will deliver 110 to 300 μCi/g resulting in

hypothyroidism in 50%, 70%, and 95%, respectively. A dose of >270 Gy (300 μCi/g) should be considered for large thyroid glands, adjusted based on % uptake. Dose = thyroid weight × 300 μCi/g/RAI.

e) Fixed dose. An average dose between 14 to 16 mCi results in hypothyroidism for the majority of adolescent patients between 1 and 6 months (average 2 to 3 months) after RAIA.

f) After RAI treatment:

1) MMI is generally not administered, but may be given 5 to 7 days after RAI treatment if the patient continues to experience hyperthyroid symptoms. MMI should then be tapered within a few weeks to months to determine when the patient achieves hypothyroidism.

2) A β-blocker may be used instead of or in addition to MMI.

3) ^{131}I treatment may be repeated at 6 months if the patient remains hyperthyroid after initial RAI treatment.

e. Surgery for hyperthyroidism

i. Advantage. Rapid control of hyperthyroidism.

ii. Contraindications. No access to a surgeon with a low-complication rate.

iii. Complications. Hypoparathyroidism and recurrent laryngeal nerve damage. Keloid formation.

iv. Techniques for thyroidectomy

a) Ensure normal or near normal T_3 and T_4 prior to surgery

b) Continue antithyroid medication until euthyroid

c) Between 7 to 10 days before surgery, add iodides, either Lugol solution (5 drops three times daily) or saturated potassium iodide (SSKI; three drops three times daily) with continuation of MMI until the day of surgery. The iodine drops can induce hypothyroidism in patients with persistent elevated T_3 and T_4 and reduces vascularity. For patients with normal thyroid function, consider using a reduced number of drops/day, reducing the dose of MMI, and using the iodine for only 7 days prior to

surgery.

v. **Possible complications of surgery for hyperthyroidism**

a) **Transient hypocalcemia** (up to 30% of patients). This occurs as a result of mild injury to the parathyroid glands during surgery. Parathyroid function typically recovers within 2 to 8 weeks.

b) Permanent hypoparathyroidism.

c) Recurrent laryngeal nerve damage.

d) Hypertrophic scar, Keloid formation.

V. THYROID NODULES

A. Thyroid nodules in children and adolescents

1. **General approach.** The risk of thyroid malignancy is three to four times higher for a pediatric patient with a thyroid nodule compared with an adult; approximately 20% to 25% risk in children and adolescent compared with a 5% to 10% risk in adults. See the American Thyroid Association guidelines on the evaluation and management of thyroid nodules and DTC for further details; http://www.thyroid.org/professionals/ata-professional-guidelines/.
2. **Pediatric thyroid Centers.** Regular experience and expertise is positively correlated with improved accuracy of diagnosis, reduced risk of medical and surgical complications. The pediatric thyroid center should include one or two providers from the following disciplines:
   - **a.** Pediatric endocrinology
   - **b.** Surgery—ENT or general surgery
   - **c.** Radiology—US and axial imaging, interventional radiology (FNA), and nuclear medicine
   - **d.** Pathology—cytopathology and anatomic pathology, molecular diagnostics
   - **e.** Oncology—familial tumor predisposition center with a pediatric oncology and genetic counselor. Partnering with adult oncology for management of p. 579p. 580patients that may benefit from systemic therapy (tyrosine kinase, BRAF, and/or MEK inhibitors)
   - **f.** Social Work Services

g. Child Life Services
h. Partnership with an adult thyroid center

B. Clinical presentation

1. Risk factors

a. **Radiation exposure** directed to the head and neck in early childhood is correlated with an increased risk for developing thyroid nodules and DTC. The lower the dose of radiation exposure (<15 Gy), the younger the age at the time of exposure (<10 years of age) and female gender appear to be associated with an increased risk and shorter latency to develop radiation-induced nodules and DTC. The relative risk of developing DTC is linear with an upward trend of approximately 1.3/Gy of radiation exposure up 15 Gy. At exposures above 15 Gy, the sclerosing effect of the radiation is associated with a downward trend in risk leveling out to a background risk at exposures greater than 40 Gy. Thyroid nodules and DTC may be detected as early as 1 to 5 years after exposure.

b. **Autoimmune thyroid disease.** There is an increase in developing thyroid nodules and thyroid cancer in patients with autoimmune hypo- and hyperthyroidism.

c. **Familial thyroid tumor predisposition syndromes.** There are several syndromes associated with increased risk of DTC, both papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC).

i. **Familial nonmedullary thyroid cancer**—Two or more first-degree relatives increase the risk for other first-degree relatives developing DTC. US screening is associated with detection of disease with a lower rate of metastasis. There are no molecular mutations or markers that predict an increased risk for disease.

ii. **PTEN Hamartoma syndrome** (PTHS)—PTHS is associated with macrocephaly and an increased risk of breast cancer (females only), endometrial cancer, and thyroid cancer as well as renal cancer and gastrointestinal polyps. Patients may also have mucosal neuromas, trichilemmomas, and lipomas. Males may have freckling of the glans penis. The condition is inherited in an autosomal dominant pattern. See https://www.ncbi.nlm.nih.gov/books/NBK1488/.

iii. **Familial adenomatous polyposis** (FAP)—FAP is associated with an increased risk for developing adenomatous gastric, small bowel and colonic polyps with an increased risk for adenocarcinoma, osteomas, hepatoblastoma, and other tumors, congenital hypertrophy of the retinal pigment epithelium, and thyroid cancer (~5%). The cribriform-morular variant form of PTC is most common, a variant that is only found in 0.1% to 0.2% of sporadic cases. The disorder is transmitted in an autosomal dominant pattern. See https://www.ncbi.nlm.nih.gov/books/NBK1345/.

iv. **A gene and protein (DICER1) pleuropulmonary blastoma familial tumor predisposition syndrome:** DICER1 is associated with an increased risk of pleuropulmonary blastoma (PPB), multinodular goiter and DTC, Sertoli-Leydig cell tumors, cystic nephroma, and several other tumors. The treatment of PPB is associated with an increased risk and decreased latency for developing FTC. The syndrome is inherited in an autosomal dominant pattern. See https://www.ncbi.nlm.nih.gov/books/NBK196157/.

v. **Multiple endocrine neoplasia type 2**—Activating mutations in the RET proto-oncogene are associated with an increased risk for developing medullary thyroid carcinoma (MTC) as well as hyperparathyroidism and pheochromocytoma. The risk correlates with the specific codon mutation.

a) **MEN2B** is associated with a mutation in codon 918 and the most aggressive form of MTC. Sporadic, *de novo*, mutations are common, and early recognition of physical features, including alacrima (absence of tear production), constipation (due to intestinal ganglioneuromatosis), mucosal neuromas, p. 580p. 581facial dysmorphism, and marfanoid features is critical for identification prior to metastasis. There is an increased likelihood for surgical remission if surgery is performed prior to 5 years of age. Thyroidectomy is performed at the time of diagnosis.

b) **MEN2A** is associated with an increasing number of *RET* mutations with the risk of MTC designated as highest (634) or moderate (the remainder). The timing for prophylactic thyroidectomy is based on the mutation as well as surveillance calcitonin and thyroid US surveillance. The risk of pheochromocytoma and hyperparathyroidism, as well as chronic lichen amyloidosis (rash on the upper back) and Hirschsprung disease is based on the specific *RET* mutation.
    1) Screening for ***pheochromocytoma*** and ***hyperparathyroidism*** starts at 11 years for patients with *RET* 918 and 634 and at age 16 years for all other MEN 2A patients.
    2) Refer to the ***American Thyroid Association Guidelines*** for evaluation and management of medullary thyroid cancer for more information; http://www.thyroid.org/professionals/ata-professional-guidelines.
c) **Sporadic MTC** is exceedingly uncommon in the pediatric population. Thus, for the majority of patients, obtaining a random serum calcitonin is not informative during the evaluation of a thyroid nodule unless there is a family history of MEN2 or the history and physical examination increases the likelihood of MEN2B.

2. **Symptoms.** The majority of patients are asymptomatic at the time of diagnosis with the nodule discovered on physical examination or incidentally on nonthyroid head and neck imaging.
3. **Physical examination**
    a. **Thyroid examination** should include complete visual assessment of the anterior neck with three maneuvers; chin neutral, neck extension, and neck extension with swallowing. This is best accomplished by facing the patient rather than an examination from behind the patient. The visual examination is then followed by a complete examination by palpation. See the following video for more information; search “CHOP thyroid examination” or copy and paste https://www.youtube.com/watch?v=Z9norsLPKfU.
    b. **Lymphadenopathy** is a common finding in pediatric patients, most frequently found under the mandible (levels 2A and 2B).

Persistent lymphadenopathy in the mid- to lower neck (levels 3 and 4) should raise concern for an infection or malignancy. Prior to excisional biopsy, a thyroid US should be obtained to evaluate for the possibility of papillary thyroid cancer with metastasis to cervical lymph nodes. Lymphadenopathy is also common in autoimmune thyroid disease, although this is typically in the central neck (level 6) and only noted on US, not on physical examination.

i. Even though most malignant tumors are very **firm**, due to calcifications, the consistency of a nodule has limited diagnostic value. However, an infiltrative variant of thyroid cancer, diffuse sclerosing variant PTC, is often associated with a firm thyroid without a nodule in the presence of firm and fixed lateral neck lymphadenopathy. Thyroid US should be performed for any and all abnormal physical examinations.

ii. **Fixation** of lymph nodes to adjacent tissue increases the possibility of malignancy.

iii. **Tenderness** of a thyroid nodule or lymph node suggests an inflammatory or infectious process.

4. **Laboratory findings**

a. Almost all patients with thyroid nodules are euthyroid. If the **TSH** is suppressed, even with normal T_3 and T_4, there is an increased likelihood for an autonomously functioning nodule(s). These have a lower risk for malignancy. FNA may be considered if there is lymphadenopathy or the US features are concerning for malignancy. Thyroid scintigraphy (^{123}I uptake and scan or Tc-99m scan) can confirm autonomous function.

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b. **Calcitonin** elevation is a useful diagnostic marker for medullary carcinoma. However, due to the infrequent diagnosis of sporadic MTC in pediatric patients, calcitonin should not be a routine laboratory for evaluation of thyroid nodules. The normal range for calcitonin is age dependent with levels up to 40 pg/mL in the first 1 to 2 years of life, declining to adult values by age 3 to 4 years.

c. **Serum Tg** may be elevated in patients with papillary and

follicular carcinoma, but unfortunately, it can be high in benign conditions (e.g., thyroiditis); therefore, it is of **little diagnostic value** in the evaluation of a thyroid nodule. However, it is clinically informative postoperatively to detect persistent or recurrent disease (see Chapter 39 and 41) in patients with DTC.

5. **Thyroid imaging**
   a. **Thyroid scintigraphy** using radioiodine (^{123}I) or technetium (Tc99m) is very useful in the evaluation of a thyroid nodule with a suppressed TSH; evaluation for the likelihood of an autonomously functioning nodule. The comparison between a "cold" versus "warm" versus "hot" nodule is not an accurate means to assess for the risk of malignancy. Thyroid US and FNA should be used for this assessment.
   b. **Ultrasound of the thyroid**
      i. Thyroid US is the best modality to assess thyroid nodules. The following features should be assessed and documented in the report;
      ii. Composition—complex and spongiform nodules have a lower risk of malignancy compared with solid nodules
         a) Echogenicity—anechoic, hyperechoic, and isoechoic have a lower risk for malignancy compared with hypoechoic
         b) Shape—taller than wide dimensions on transverse imaging has a higher risk for malignancy
         c) Margin—smooth or ill-defined have a lower risk of malignancy compared with lobulated/irregular or evidence of extrathyroidal extension
         d) Echogenic foci—hyperechoic foci with comet-tail artifact or no tissue correlation (in the setting of an anechoic cyst) have no risk of malignancy compared with the presence of macro-, peripheral, or punctate hyperechogenic foci
         e) Abnormal lymph nodes—the presence of cervical lymph nodes with features concerning for thyroid malignancy supersedes all other features.
      iii. The pattern of blood flow on Doppler imaging may be helpful to discern a "true" nodule versus a "pseudonodule" (= an area of patchiness) in patients with autoimmune

thyroid disease.

iv. **US assessment of the lateral neck lymph nodes must be performed for any and all patients with a nodule of indeterminate or concerning features.** This is in keeping with the American Institute of Ultrasound in Medicine guidelines; AIUM, last version 2013, http://www.aium.org/resources/guidelines/thyroid.pdf.

c. Fine needle aspiration

i. **Rationale**—FNA is the most simple and direct method to determine malignancy of a thyroid nodule. FNA should be performed under the following guidance.

ii. **Conscious sedation or distraction**—decreases anxiety and may increase the likelihood of obtaining an adequate sample. Distraction methods may also be used effectively depending on the expertise of the center.

iii. **US guidance**—The use of US guidance increases the likelihood of adequate sampling of all areas of the nodule and if there are additional nodules or lymph nodes of concern.

iv. **Bedside confirmation of sample adequacy**—(= 5 to 6 groups of well-preserved follicular epithelial cells with 10 or more cells/group).

v. Thyroid cytopathology—**The Bethesda Classification for Reporting Thyroid Cytopathology** is the most commonly used system to stratify the risk for malignancy.

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vi. **Limitations**—The major limitation is the requirement for an experienced and knowledgeable cytologist to interpret the aspirate. Even with expertise, up to 20% to 30% of FNA samples will have indeterminate cytology. The addition of oncogene testing can help in establishing the risk for malignancy with the presence of *BRAF*, *RET/PTC*, *NTRK*-fusion, and *ALK*-fusion proteins associated with an increased likelihood of malignancy. Mutations in *RAS* are also associated with an increased risk of malignancy but the % of cells with a mutation may correlate with the risk. Further study within the pediatric population is needed.

Gene-expression classifiers have not been validated in patients <21 years of age and, thus, should not be used in the pediatric setting.

vii. **With rare exception, all children with a thyroid nodule should undergo FNA prior to surgery** to ensure appropriate and complete surgical resection.

viii. **Assessment of the lateral neck prior to surgery is critical to optimize the surgical approach for patients with PTC on FNA.** Failure to perform this step is associated with an increased likelihood of incomplete surgical resection. FNA of lateral lymph nodes, at least one per cervical level, must be performed to confirm if a therapeutic lateral lymph node dissection is warranted.

d. Additional Radiography beyond thyroid US

i. **Axial imaging of the neck (CT with contrast or MRI)** may be considered for preoperative planning in patients with metastasis to the lateral neck lymph nodes. US has reduced sensitivity to screen for lymph nodes in the retropharyngeal space, paratracheal space, subclavicular region, and upper mediastinum.

ii. **Chest radiographs** have low sensitivity for detecting pulmonary metastases. Chest CT may be considered but typically does not impact the surgical approach.

iii. **PET/CT** does not provide actionable information in the preoperative evaluation for thyroid malignancy in pediatrics. However, a thyroid nodule incidentally detected by unrelated PET/CT has an increased risk for malignancy (~30%) and the patient should undergo evaluation with thyroid US and FNA.

6. Treatment. There are several possible approaches:

a. Observation, if the nodule is believed benign based on thyroid US and/or FNA. See Table 42.8 for risk factors associated with thyroid cancer, and Table 42.9 for classification of thyroid nodules.

b. Thyroid hormone suppression

i. Differentiated thyroid tumor growth is influenced by TSH, and targeting a TSH below the lower limit of normal (<0.5 mIU/L) is recommended until remission from disease is established.

ii. In high-risk patients (postradiation exposure or patients with a history of a nodule in the setting of iodine deficiency), there is some data supporting p. 583p. 584the use of mild thyroid hormone suppression (targeting the TSH to less than 1.0 mIU/L) to decrease the risk of thyroid nodule formation, thyroid nodule growth, and malignant transformation; however, even in this situation, the US appearance of the thyroid nodule is more highly correlated with predicting malignancy than the response to TSH-suppressive therapy.

TABLE 42-8 Risk Factors Associated with an Increased Risk for Thyroid Cancer

Prior history of irradiation
Family history of thyroid cancer syndrome
Ultrasound features—solid, hypoechoic (dark gray), taller than wide, irregular margin or extrathyroidal extension, calcifications
Abnormal cervical lymph nodes on physical exam and ultrasound
FNA with indeterminate, suspicious or malignancy cytology
Presence of a thyroid oncogene on FNA sample

FNA, fine needle aspiration.

TABLE 42-9 Classification of Thyroid Nodules

A. Non-neoplasm
- **1.** Cyst
- **2.** Abscess
- **3.** Subacute thyroiditis (in one lobe)
- **4.** Hashimoto thyroiditis (pseudonodules)

B. Benign neoplasm
- **1.** Adenoma
  - **a.** Follicular
  - **b.** Hürthle cell adenoma

C. Malignant neoplasm
- **1.** Well differentiated
  - **a.** Papillary (PTC)—classic, follicular variant, solid, or diffuse sclerosing variant
  - **b.** Follicular (FTC)—minimally or widely invasive, Hürthle cell carcinoma
  - **c.** Poorly differentiated
- **2.** Medullary thyroid carcinoma (MTC)

FTC, follicular thyroid carcinoma; PTC, Papillary thyroid carcinoma.

c. Surgical excision

- **i.** Removal of the nodule surgically is recommended based on the results of the FNA and/or family preference. Based on the Bethesda classification;
  - **a)** Unsatisfactory—surveillance or resection
  - **b)** Benign—surveillance
  - **c)** Indeterminate—lobectomy
  - **d)** Follicular lesion of undetermined significance (FLUS)
  - **e)** Follicular neoplasm (FN)
  - **f)** Suspicious for malignancy or malignant (PTC) = total thyroidectomy ± prophylactic central lymph node dissection
- **ii.** Families and patients may opt for surgical removal of benign lesions because of anxiety and/or ease of follow-up.
- **iii.** The presence of a thyroid oncogene mutation or rearrangement in an FNA with indeterminate cytology (FLUS or FN) may be used to alter the approach to surgery; pursue total thyroidectomy rather than lobectomy.
- **iv.** In the setting of autoimmune thyroid disease, one should discuss the option for total thyroidectomy rather than lobectomy because of an increased risk of developing a nodule in the remaining lobe and the likely need for L-T_4 even if lobectomy is performed.

d. Postoperative management

- **i.** The **American Thyroid Association (ATA) pediatric guidelines** defines **three-pediatric risk levels** to help guide postoperative management. http://www.thyroid.org/professionals/ata-professional-guidelines/.
  - **a)** ATA pediatric low risk
  - **b)** ATA pediatric intermediate risk
  - **c)** ATA pediatric high risk
- **ii.** Complete preoperative evaluation and subsequent surgery is the most critical step to increase the likelihood of surgical remission of regional disease.
- **iii.** The presence of **antithyroglobulin antibody** (TgAb)

decreases the ability to use Tg as a marker for persistent or recurrent disease. It is critical to use the same laboratory to decrease interassay variation of Tg and TgAb p. 584p. 585levels. The Tg RIA is less interfered by TgAb than the immunochemiluminescent assay.

iv. **^{123}I-diagnostic whole body scan (DxWBS**) is a helpful step in assessing patients for surgical remission or persistent disease. The addition of SPECT/CT is useful to assess for anatomic correlation. The posttreatment whole body scan (RxWBS) has improved sensitivity to detect disease compared with the DxWBS secondary to the amount and isotope (^{123}I vs. ^{131}I) of RAI administered.

v. All patients are placed on **TSH-suppressive therapy** irrespective of whether they received RAI treatment or not. The goal is to target the TSH below the lower limit of detection (usually <0.5 mIU/L) without causing symptoms of hyperthyroidism.

vi. Patients with **persistent, macroscopic disease in the neck** should be considered for repeat surgery rather than RAI treatment after FNA confirmation.

vii. **Patients with pulmonary metastasis** often require more than one RAI treatment to achieve remission. Up to one third of pediatric patients with pulmonary metastasis may develop persistent, but stable, pulmonary metastasis that does not resolve despite repeated RAI treatments. These patients should be followed with repeat Tg and TgAb as well as serial chest CT imaging to determine if and/or when additional treatment is warranted.

   a) RAI is an extremely effective treatment for patients with persistent disease that is not amenable to surgery. The risk of RAI-induced short-term complications (sialadenitis and xerostomia), pulmonary fibrosis, and RAI-induced second nonthyroid primary malignancies increases with the amount and frequency of RAI administered. There is no absolute cutoff that correlates with increased risk. There is a very low risk of gonadal

toxicity; however, **irregular periods** may occur several months after RAI treatment and it is recommended that pregnancy be avoided for at least 6 to 12 months.

viii. **Following the trend in the TSH-suppressed Tg** with non-nuclear medicine imaging is the most effective way to assess for response to treatment. The Tg and TgAb may continue to decrease 18 to 24 months or longer after initial surgery with or without RAI treatment. TSH, Tg, and TgAb are followed by every 3 months with repeat neck US 6 months after initial treatment. There may be slight increases and decreases in the Tg and TgAb trend, so assessing the trend over 6 to 12 months (with data points every 3 months) is more informative.

ix. TSH-stimulated Tg and DxWBS should be repeated to confirm remission in patients with more aggressive pathology as well as to assess for persistent or recurrent disease that is not found by neck US or axial imaging.

x. **FDG-PET/CT imaging** should be considered for patients with persistent high and/or increasing Tg and/or TgAb levels and no evidence of disease by axial imaging or RAI imaging (either DxWBS and/or RxWBS for patients where an empiric RAI treatment was attempted).

xi. **Systemic therapy** with tyrosine kinase, MEK, or BRAF inhibitors may be considered for patients with **progressive DTC** that is not responsive to RAI.

a) For patients with **persistent MTC** as determined by serum calcitonin and/or carcinoembryonic antigen levels, the doubling time is a helpful calculation to determine the rate of progression and to identify patients that may benefit from systemic treatment.

e. **Summary: treatment of thyroid carcinoma**

i. Ensure complete presurgical radiologic evaluation of the thyroid and neck with FNA confirmation of disease to optimize the surgical plan targeted to ensure complete surgical resection.

ii. For patients with papillary thyroid cancer, perform total (or near-total) thyroidectomy.

iii. Remove affected lymph nodes in a compartmental approach

to lymph node dissection, the levels of the neck determined by US, confirmed by FNA.

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iv. Use the ATA pediatric risk levels with laboratory and radiologic imaging to select which patients may or may not benefit from RAI treatment.

v. Institute thyroid hormone suppression postoperatively.

vi. Follow TSH, Tg, and TgAb every 3 months to assess for biochemical remission.

vii. Use neck US and axial imaging to assess for anatomic remission.

viii. Pursue TSH-stimulated Tg and DxWBS with consideration for additional RAI treatment if the Tg and/or TgAb trend are/is not continuing to decrease or increase, and there is no identifiable disease by other imaging modalities.

ix. The timing for thyroidectomy of patients with MEN2 is based on the *RET* proto-oncogene mutation as defined by the ATA guidelines (insert link —http://www.thyroid.org/professionals/ata-professional-guidelines/ [general web page] or http://online.liebertpub.com/doi/pdf/10.1089/thy.2014.0335 [specific link to MTC guidelines]). For moderate risk mutations, delayed thyroidectomy may be considered if annual calcitonin levels remain reassuring.

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SECTION 7

Metabolic Disorders

43

Obesity

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I. GENERAL PRINCIPLES

Obesity and overweight are a worldwide problem and affect more than 100 million Americans (68.5% of the adult population). The presence of obesity or overweight should suggest the possibility of associated diseases such as diabetes mellitus, hypertension, heart disease, obstructive sleep apnea, and many other comorbidities. Whether the associated disorders are present or not, the patient with obesity should be encouraged to lose weight by appropriate methods. As first steps, self-directed approaches (diet, physical activity, support groups, and commercial programs with an evidence base to support efficacy) are appropriate and many patients may succeed. For patients who struggle, and who have medical issues that will improve with weight loss, intensification is appropriate, including hospital and community-based lifestyle intervention programs and medically supervised approaches that employ adjunctive medications, surgical devices, and surgical procedures.

II. DEFINITION AND MEASUREMENT OF OBESITY

A. Obesity and overweight. The body mass index (BMI), which is the weight in kilograms divided by the square of the height in meters, provides the most widely accepted measure of overweight and obesity. It is a valid estimate for assessing overweight and obesity in populations because it correlates with total fat mass but has limitations

for individual patients. When evaluating a patient with obesity, the health care provider should consider waist circumference along with BMI in some patients (those with BMI 25) to improve the assessment of an individual's health risk. **A BMI > 25 kg/m^2 is defined as overweight, and a BMI of 30 kg/m^2 or more is defined as obesity** (Table 43.1). Adding information on waist circumference, as indicated in Table 43.1, refines health-risk estimation.

B. Visceral fat. An increase in visceral fat reflects central adiposity and increases risk for heart disease and diabetes. The waist circumference is used as a surrogate to assess the amount of visceral obesity. A waist circumference greater than 102 cm (40 in) in men or greater than 88 cm (35 in) in women is the current threshold for increased metabolic risk for Americans, but for other populations, a waist circumference >80 cm for women and >94 cm for men may be more appropriate.

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TABLE 43-1 Classification of Overweight and Obesity by Body Mass Index, Waist Circumference, and Associated Disease Risk

			Disease risk relative to normal weight and waist circumference	
			Normal category	Above normal cut-point
Weight category	**BMI (kg/m^2)**	**Obesity class**	**Men <102 cm (<40 in) Women <88 cm (<35 in)**	**>102 cm (>40 in) >88 cm (>35 in)**
Underweight	<18.5		—	—
Normal	18.5–24.9		Increased	Increased
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	I	High	Very high
	35.0–39.9	II	Very high	Very high
Extreme obesity	≥40	III	Extremely high	Extremely high

BMI, body mass index.

Adapted from National Institutes of Health/National Heart, Lung, and Blood Institute. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.* Washington, DC: U.S. Government Printing Office; 1998. Publication No. 98-4083.

Sahakyan KR, Somers VK, Rodriguez-Escudero JP, Hodge DO, et al. Normal-weight central obesity: implications for total and cardiovascular mortality. *Ann Intern Med* 2015. doi:10.7326/M14-2525 e-pub 10 Nov 2015.

III. PREVALENCE OF OVERWEIGHT

The frequency of overweight increases with age, to a peak at 45 to 54 years in men and at 55 to 64 years in women. The National Health and Nutrition Examination Surveys in 2014 noted that a BMI of ≥25 was present in 71.3% of men 20 years or older and in 65.8% of women 20 years or older. The prevalence of obesity (BMI ≥ 30) was 33.5% for men and 36.1% for women. Females at any age are disproportionately at greater risk for obesity and especially extreme obesity (BMI ≥ 40 8.3% in females; 4.4% in males). The prevalence of obesity has risen dramatically since 1980.

At birth, the human infant has about 12% body fat, on average. During the first years of life, body fat increases rapidly to reach a peak of about 25% by age 6 months and then decreases over the next 10 years to about 18%. At puberty, there is a significant increase in the percentage of fat in females and a decrease in males. At the same BMI, females have on average about 12% more fat than males. Between ages 20 and 50, the fat content of males approximately doubles and that of females rises by about 50%. However, total body weight rises by only 10% to 15%. The increased fat is accounted for in part by the rise in body weight and in part by a reduction in lean body mass. With advancing age, this decrease in lean body mass, often called sarcopenia, continues.

IV. RISKS RELATED TO OBESITY

A. Obesity, excess mortality, and morbidity. Many population studies demonstrate that as the BMI increases, there is a curvilinear rise in excess mortality from a BMI nadir that is usually 20 to 22 kg/m^2. This excess mortality rises more rapidly when the BMI is above 30 kg/m^2. A BMI greater than 40 kg/m^2 is associated with a further increase in excess mortality. The effect of obesity on life expectancy is equivalent to the impact of smoking; compared to those of normal BMI, for nonsmoking 40-year-olds with obesity lose about 7 years of life; for smokers with obesity, about 13 years of life are lost. The principal causes of the excess mortality associated with obesity include hypertension, stroke and other cardiovascular diseases,

diabetes mellitus, p. 589p. 590some cancers (although obesity increases risk for almost all types of cancer), sleep apnea, and sudden death. Obesity is also associated with reproductive disorders, gallbladder disease, and increased risk of cognitive dysfunction with aging.

B. Insulin resistance is strongly associated with excess visceral adiposity and may include consequences such as prediabetes, type 2 diabetes mellitus, hypertension, polycystic ovarian syndrome, dyslipidemia, and other disorders. These manifestations usually improve with weight loss, especially when it is achieved early and the loss is maintained.

V. DEVELOPMENT OF OBESITY

There are multiple contributory etiologic pathways to obesity.

A. Neuroendocrine obesity

1. Hypothalamic obesity can follow damage to the ventromedial hypothalamus caused by tumors (i.e., craniopharyngioma), inflammatory lesions, trauma, or other hypothalamic conditions. Treatment is both symptomatic and specific when the underlying disease can be identified.
2. Cushing's disease may present with obesity, and treatment should be directed at the cause of the increased production of corticosteroids, usually from a pituitary adenoma.

B. Drug-induced weight gain. Treatment of diabetics with insulin, sulfonylureas, or thiazolidinediones may increase hunger and food intake, resulting in weight gain. Metformin, glucagon-like peptide 1 (GLP-1) agonists, and gliflozins do not cause weight gain and may produce a small weight loss. Treatment with some antidepressants, antiepileptics, neuroleptics, and glucocorticoids can increase body weight, as can cyproheptadine, probably through effects on the monoamines in the central nervous system.

C. Dietary obesity

1. **Food intake.** An energy-dense diet, larger portion sizes, tasty, inexpensive food and convenient foods, and reduced physical activity of most Americans are among the environmental causes of the increase of corpulence during the past century. Excessive consumption of sugar- or high-fructose corn syrup–sweetened beverages and the prevalence of abundant varieties of food in

cafeterias or supermarkets may also be dietary factors contributing to the development of obesity. Estimates show that calorie intake has risen approximately 200 to 300 kcal/day over the past 30 years.

D. Reduced energy expenditure relative to energy intake is an important contributor to obesity in modern society. Energy expenditure can be divided into four parts.

1. **Resting metabolism** ranges from 800 to 900 kcal/m^2 (1 350 to 1 750 kcal) per 24 hours. It is lower in females than in males and declines with age. This decline with age could account for much of the increase in fat stores if food intake does not decline similarly.
2. **Physical exercise** is variable but on average is responsible for about one third of the daily energy expenditure. From a therapeutic point of view, this component of energy expenditure is the one most easily manipulated.
3. **Dietary thermogenesis** is the energy expenditure, measured as oxygen uptake, which follows the ingestion of a meal. This thermic effect of food may dissipate up to 10% of the ingested calories. Protein appears to have the greatest effect. The thermic effect of food is one type of metabolic "inefficiency" in the body, that is, where dietary calories are not available for "useful" work. In those with obesity, the thermic effect of food is reduced, particularly in individuals with impaired glucose tolerance or diabetes.
4. **Adaptive thermogenesis.** Acute overfeeding or underfeeding produces corresponding shifts in overall metabolism, which can be as large as 15% to 20%.

E. Genetic factors in obesity

1. **Dysmorphic or syndromic obesity.** In some types of obesity, genetic factors are primary. Dysmorphic individuals usually have distinctive features, including **(a) Bardet–Biedl syndrome**, characterized by retinal degeneration, mental retardation, obesity, polydactyly, and hypogonadism; **(b) Alström syndrome**, characterized by pigmentary retinopathy, nerve deafness, obesity, and diabetes mellitus; **(c) Carpenter syndrome**, characterized by acrocephaly, mental retardation, hypogonadism, obesity, and preaxial syndactyly; **(d) Cohen syndrome**, characterized by mental retardation, obesity, hypotonia, and characteristic facies; p. 590p. 591and **(e) Prader–Willi syndrome**,

characterized by hypotonia, mental retardation, hypogonadism, and obesity.

2. **Genes with a major effect on obesity.** Genes with major effects on body weight were identified in rodent models of obesity and confirmed in human mutations including leptin and leptin receptor, pro-opiomelanocortin, and the melanocortin-4 receptor, the latter accounting for up to 5% of cases of severe early-onset childhood obesity.
3. **Genetic susceptibility:** There are at least 100 common gene variants that are associated with small effects, with the most potent fat mass and obesity-related protein (FTO) being associated with an additional 3 kg of body weight in those homozygous for the susceptibility variant. Estimates made from genome-wide surveys suggest that more than 20% of the variation in BMI may be attributed to genetic variation.
4. **Environmental factors.** Studies with identical twins suggest that hereditary accounts for up to 70% of the variance in weight gain. Family studies suggest a lower genetic contribution of approximately 30% to 50%. Many environmental factors modify individual genetic susceptibility for excess body weight, including sleeping time, levels of physical activity, sedentary time, smoking, maternal weight gain, and many others. Recent observations in human populations have supported the role of epigenetic events in programming the risk for obesity, with intrauterine and early-childhood nutritional factors seeming to play a key role. Thus, there is increased interest in weight gain and nutrition during pregnancy, with guidelines limiting weight gain in obese women. Microbes in the intestine and colon (microbiota) also appear to play a role in the risk of obesity.

VI. EVALUATION OF THE PATIENT WITH OBESITY

A. Thorough medical evaluation, including:

1. A comprehensive history incorporating the history of the illness (obesity and weight gain, family history, personal and social history, past medical history, system review, and medication history). The Review of Systems should include questions to elicit symptoms of sleep apnea and social issues related to obesity.
2. A psychological and mental health status assessment, including questions targeting night eating, binge eating, and bulimia.

3. A comprehensive physical examination, including assessment of the patient's height, weight, waist circumference for those with BMI 25 to 35, blood pressure, and level of health risk due to obesity.
4. Appropriate laboratory testing, including lipid panel, glucose level, hemoglobin A_{1c}, and, if indicated, an oral glucose tolerance test (OGTT), chemistry panel for hepatic function and uric acid, thyroid-function testing, and cortisol level, where indicated by the clinical findings.

B. The evaluation of the patient is directed to:

1. Establishing the degree of the patient's obesity and estimating visceral fat.
2. Determining the level of the patient's risk for obesity-related conditions, including hypertension, dyslipidemia, obstructive sleep apnea, glucose intolerance, diabetes mellitus or insulin-resistant state, hyperandrogenism, and polycystic ovary syndrome.
3. Discovering underlying psychological disorders, such as eating disorders, sexual abuse, substance abuse, depression, or use of drugs that cause weight gain.
4. Identifying the rare genetic syndromes that are associated with obesity or neurologic disorders contributing to weight gain.

VII. RISK–BENEFIT CLASSIFICATION OF OBESITY (Table 43.2)

A.

Most individuals with a normal BMI (20 to 24.9 kg/m^2) have little or no risk associated with their weight status (Table 43.3). Any individual in this weight range who wishes to lose weight for cosmetic reasons should do so only by conservative methods. An exception is individuals of South Asian descent, where susceptibility to obesity-related comorbidities is associated with lower BMI categories.

Most individuals who are overweight with a BMI of 25 to 29.9 kg/m^2 and who are otherwise healthy are in the low-risk group for developing diseases associated with obesity. They too should be encouraged to use low-risk treatments, such as caloric restriction and exercise. Individuals with a BMI of ≥25 to 30 kg/m^2 who p. 591p. 592have associated comorbid conditions or who have BMI > 30 kg/m^2 are at higher risk; therefore, use more intensive

approaches. For those with health reasons to lose weight and who meet medication label indications (BMI > 30 kg/m^2 or BMI > 27 kg/m^2 with a comorbidity), adjunctive pharmacotherapy for weight loss and control may be appropriate.

TABLE 43-2 A Risk–Benefit Classification of Obesity

Body mass index (BMI) (kg/m^2)	Obesity classification relating BMI category to choices of treatment		
	Lifestyle	Drugs	Surgery
<25	1 (Counseling on healthy lifestyle, targeting weight gain prevention is indicated.)	NA	NA
25–29.9	1 (If health risk is present, comprehensive lifestyle intervention targeting weight loss and maintenance is indicated.)	2 (For patients with comorbidity and BMI ≥ 27 kg/m^2, medications may be used as an adjunct to comprehensive lifestyle intervention.)	NA
30–39.9	1 (Comprehensive lifestyle intervention targeting weight loss and maintenance is indicated.)	2 (Medications may be used as an adjunct to comprehensive lifestyle intervention.)	2-3 (For patients with a serious comorbidity and BMI ≥ 35 kg/m^2, bariatric surgery is a consideration.)
40+	1 (Comprehensive lifestyle intervention targeting weight loss and maintenance is indicated.)	1-2 (Medications may be used as an adjunct to comprehensive lifestyle intervention.)	1-2-3 (Bariatric surgery is a consideration for individuals with BMI ≥ 40 kg/m^2 who struggle with weight loss and maintenance.)

NA, not applicable; 1, first choice; 2, second choice; 3, third choice. For patients who need to lose weight to achieve health benefits, comprehensive lifestyle intervention is foundational. If patients struggle, medications and bariatric surgery may be useful adjuncts, depending on the severity of the patient's health risk.

B. Individuals with a BMI of 30 to 39.9 kg/m^2 have moderate to high risk for developing diseases associated with obesity. Although some patients in this weight range appear initially to have "healthy obesity," their excess weight may presage increased disease developing years

later. For those in the moderate-risk category of obesity, caloric restriction, drugs, and exercise all appear to be appropriate forms of treatment. Individuals with significant excess weight often find exercise a difficult method for losing weight; however, exercise is very useful in helping to maintain weight loss. The use of medications indicated for chronic weight management as an adjunct to treatment may also be beneficial in this group.

C. Individuals who have a BMI of at least 40 kg/m^2 have a high to very high risk of developing diseases associated with their obesity. Moderate to severe restriction of calories is the first line of treatment, but for many of these patients, antiobesity medications or surgery may be advisable.

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TABLE 43-3 Commonly Used Diets and Their Characteristics

Type of diet	Example	General dietary characteristics	Comments	Evaluati AHA/AC and othe sources
Typical American diet		Carbohydrate: 50% Protein: 15% Fat: 35% Average of 2 200 kcal/d	Low in fruits and vegetables, dairy, and whole grains. High in saturated fat and unrefined carbohydrates	
Balanced nutrient, moderate-calorie approach	DASH diet or diet based on MyPyramid food guide; Commercial plans such as Diet Center, Jenny Craig, NutriSystem, Physician's Weight Loss, Shapedown Pediatric Program, Weight Watchers, Setpoint Diet, Sonoma Diet,	Carbohydrate: 55%–60% Protein: 15%–20% Fat: 20%–30% Usually 1 200–1 800 kcal/d	Based on set pattern of selections from food lists using regular grocery store foods or prepackaged foods supplemented by fresh food items. Low in saturated fat and ample in fruits, vegetables, and fiber. Recommended reasonable weight-loss goal of 0.5–2.0 lb/wk. Prepackaged plans	Meta-ana showin DASH approa better control healthy (weigh mean differe 0.87–1

	Volumetrics		may limit food choices. Most recommend exercise plan in addition to diet. Many encourage dietary record keeping. Some offer weight-maintenance plans/support	
Low and very low fat, high-carbohydrate approach	Ornish Diet (Eat More, Weigh Less), Pritikin Diet, T-factor Diet, Choose to Lose, Fit or Fat	Carbohydrate: 65% Protein: 10%–20% Fat: ≤10%–19% Limited intake of animal protein, nuts, seeds, other fats	Long-term compliance with some plans may be difficult because of low level of fat. Can be low in calcium. Some plans restrict healthful foods (seafood, low-fat dairy, poultry). Some encourage exercise and stress management techniques	Same we loss at compa <30% 40% fa Strength eviden moder
p. 593p. 594 Low-energy density	Volumetrics	Carbohydrate: 55% Protein: 10%–25% Fat: 20%–35% Focus on fruits, vegetables and soups	Four food categories: 1) Very low density—nonstarchy fruits and veggies, nonfat milk, broth-based soups 2) Low density—starchy fruits/veggies, grains, breakfast cereal, low-fat meats, and mixed dishes 3) Medium density—meat, cheese, pizza, fries, dressings, bread, etc. 4) High density—desserts, nuts, butter, oils. Focus on categories	More wei loss at with lo energy diet sh randon clinical

			1 and 2, some from 3, minimum from 4.	
Portion-controlled	Use of meal replacements both liquid and solid meals			Weight lo yr in L AHEA related freque consu portion meals
Mediterranean style diets		Carbohydrate: 35%–40% Protein: 12%–20% Fat: 40%–50% - ~25%–30% of energy from monounsaturated fat	Eat primarily plant-based foods (fruits, vegetables, whole grains, legumes, and nuts) Healthy oils (olive) instead of saturated fats Limit red meat to a few times a month Eat fish and poultry at least twice a week Red wine in moderation, if you choose to drink alcohol Be active and enjoy meals with family and friends	Meta-ana showe weight with Medite diet tha fat diet (Weigh mean differe 2.2 kg favorin Medite diet)
Low-carbohydrate, high-protein, high-fat approach	Atkins New Diet Revolution, Protein Power, Stillman Diet (The Doctor's Quick Weight Loss Diet), the Carbohydrate Addict's Diet, Scarsdale Diet	Carbohydrate: ≤20% Protein: 25%–40% Fat: ≥55%–65% Strictly limits carbohydarate to less than 100–125 g/d	Promote quick weight loss (much is water loss rather than fat loss). Ketosis causes loss of appetite. Can be too high in saturated fat. Low in carbohydrates, vitamins, minerals, and fiber. Not practical for long term because of rigid diet or restricted food choices	Same we loss at compa <30 g/ 55% carboh —15% or 40% carboh and 30 protein Strength eviden suppor efficac

p. 594p. 595 Higher protein, moderate-carbohydrate, moderate-fat approach	The Zone Diet, Sugar Busters, South Beach Diet	Carbohydrate: 40%–50% Protein: 25%–40% Fat: 30%–40%	Diet rigid and difficult to maintain. Enough carbohydrates to avoid ketosis. Low in carbohydrate; can be low in vitamins and minerals	Same we loss at compa 25%–3 15% p Strength eviden suppor efficac
Glycemic Load	The Glycemic-Load Diet—Rob Thompson	Carbohydrate: 40%–>55% Protein: 15%–30% Fat: 30% (note that I attached an abstract below)	Focus on low-GL foods	Same we loss at compa high vs glycem Strength eviden suppor efficac
Low or nonsugar-sweetened beverages	Not really a diet but just a call to reduce SSB intake as a preventive strategy	No recommendation other than to reduce/remove SSBs from your overall diet plan	Meta-analyses show that consumption of sugar-sweetened beverages is related to risk of obesity, diabetes, and heart disease.	In sustai interve studies energy bevera showe energy and we gain th sugar-contai bevera
Novelty diets	Immune Power Diet, Rotation Diet, Cabbage Soup Diet, Beverly Hills Diet.	Most promote certain foods, or combinations of foods, or nutrients as having allegedly magical qualities	No scientific basis for recommendations	
Very low-calorie diets	Health Management Resources, Medifast, Optifast	Less than 800 kcal/d	Requires medical supervision. For clients with BMI ≥ 30 or BMI ≥ 27 with other risk factors; may be difficult to transition to regular meals	
Weight-loss	Cyberdiet,	Meal plans and	Recommend	

online diets	DietWatch, eDiets, Nutrio.com	other tools available online	reasonable weight loss of 0.5–2.0 lb/wk. Most encourage exercise Some offer weight-maintenance plans/support

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D. Measurement of waist circumference to detect central adiposity can enhance identification of individuals at increased risk according to data from the National Center of Health Statistics. Persons with normal-weight central obesity had the worst long-term survival. Thus, a man with a normal BMI (22 kg/m^2) and central obesity had greater risk of mortality than one with similar BMI but no central obesity. This man had twice the mortality risk of people who were overweight or obese by BMI only. Women with normal-weight central obesity also had a higher risk of mortality than women with similar BMI but no central obesity and those who were obese according to BMI only. Expected survival estimates were consistently lower for those with central obesity when controlled for age and BMI.

VIII. MANAGEMENT OF OBESITY

A. Multicomponent program for managing body weight. This approach uses diet, behavioral strategies, and exercise tailored to a patient's needs. The components of such a program include **(1)** an energy-restricted diet, commonly a 1 000- to 1 500-calorie diet that uses portion-controlled food, such as formula drinks and frozen foods; **(2)** nutritional education, aimed primarily at long-term healthy-eating strategies; **(3)** an exercise prescription that builds long-term habits to increase physical activity; **(4)** and behavioral changes to enforce diet and physical activity strategies.

B. Changing behavioral patterns of eating. The techniques used in behavioral modification include self-monitoring, problem solving, stimulus control, stress management, social support, cognitive restructuring, and contingency management.

C. Exercise and physical activity. The only part of energy expenditure that is amenable to significant manipulation is physical

activity. During sleep, energy expenditure is approximately 0.8 kcal/min, the lowest of the day. Thus, if an individual sleeps for an entire 24 hours, approximately 1 150 calories will be expended. Reclining increases this level to approximately 1.0 kcal/min. Patients with obesity and diabetes should be encouraged to increase their physical activity for two reasons: First, exercise consumes calories, but second, and more important, exercise increases glucose utilization and may enhance insulin sensitivity.

D. Dietary modification

1. **Calorie restriction.** The goal of any diet is to reduce caloric intake below daily caloric expenditure. When restricting calories, it is worth remembering that biologically the calories provided by sugar or high-fructose corn syrup in beverages may be "invisible" calories and not detected by the body, thus adding to the calorie burden. Assessing caloric requirements can be done in two ways.
   - **a.** The first way is a simple, but practical, rule of thumb: 10 calories per pound of current weight will generally equate to daily caloric requirements.
   - **b.** The second method involves assessing caloric requirements by use of a more complex calculation. After the caloric requirement is determined, a reasonable calorie deficit can be prescribed. A caloric deficit of 500 kcal/day (3 500 kcal/week) will produce the loss of approximately 0.45 kg (1 lb) of fat tissue each week for the early phase of the diet.
2. **Counting calories to meet an energy-intake target.** A common strategy is to set a fixed calorie intake likely to produce weight loss (1 200 to 1 800 kcal/day), based on baseline weight and sex. The calories are tracked to stay under this goal. Two tips aid in this strategy.
   - **a.** The first is to "count calories." Patients can weigh or measure the foods they eat and obtain the caloric values from various tables or popular free websites such as calorieking.com or apps like Lose It or My Fitness Pal.
   - **b.** A second way is to use the information that is published on the nutrition labels of packaged foods. A typical nutrition label shows the serving size; the number of servings per container; the calories per serving; the protein, carbohydrate, and fat in each serving; and the percentage of eight selected nutrients in each serving. This is followed by the ingredients listed in order

of weight from highest to lowest.

3. **Reduced-calorie diets with specific food strategies**
   a. **Types of diets.** Diets with >1 000 kcal/day can be divided into several categories. These categories are based on the relative proportion of macronutrients p. 596p. 597 included in the diet and whether it involves special foods (Table 43.3). All diets must reduce the caloric intake to produce a negative energy balance.
      i. The **low-carbohydrate diet** that allows you to eat all of the protein and fat you want has been shown to end up reducing total calorie intake to approximately 1 400 kcal/day. These diets, which generally have carbohydrate levels <50 g/day, are thus **ketogenic** and can be monitored clinically by the appearance of ketones in the urine. The low-carbohydrate diets have been popular for nearly 150 years. They vary in the level of fiber that is included. The Atkins diet has low fiber levels; the Sugar Busters diet has higher fiber levels. Head-to-head comparisons with other macronutrient approaches suggest that very-low-carbohydrate diets may produce somewhat more weight loss initially.
      ii. **Low-fat or high-carbohydrate diets** can be associated with either low or very low levels of fat. The very-low-fat diets (in the range of 10% to 20% of total calories) have increased fiber intake. These diets were developed in a setting designed to reverse the atherosclerotic plaques associated with the risk for heart disease, but because of the high fiber content, they were often associated with weight loss. Hedonic issues limit their popularity. Attempts to count fat grams as a way to diet have been undercut by the ready availability of low-fat foods, which tend to be high carbohydrate.
      iii. **Moderate-fat levels with higher carbohydrate** are characteristic of the widely recommended “healthy diets.” For weight loss, the New York Department of Health diet that was adopted as the “Prudent Diet” and used by Weight

Watchers has stood the test of time.

iv. **Portion-controlled diets** make use of prepared foods that have a narrow range of calories. These include liquid or powdered drinks as well as frozen or canned entrees that contain about 100 to 300 kcal/unit. These can be combined conveniently, thus removing for the individual the problem of counting calories.

v. **Very-low-calorie diets (<800 kcal) and low-calorie (800 to 1 000 kcal) liquid diets.** Very-low-calorie diets (<800 kcal/day) will reduce the net loss of nitrogen to <1 g/day from levels of 4 to 6 g/day found during starvation and are used rarely and in limited clinical situations because loss of protein is not completely stopped. Protein from egg, casein, or soy comprises 33% to 70% of the energy in these diets. However, it is advisable that these diets should contain at least 25% of the calories as carbohydrate. Supplements of electrolytes, including potassium and other inorganic salts, as well as vitamins, including folate, pyridoxine, and thiamine, should be given. Very-low-calorie diets should be monitored with medical supervision. Low-calorie liquid diets (generally 800 to 1 000 kcal/day) can be used to achieve rapid weight loss safely, provided a high-quality protein source is used and similar supplementation is given. One of the advantages of this approach is the relatively good effect on appetite control; however, weight regain will occur unless there is a strong behavioral program when refeeding occurs.

vi. **Fasting.** Prolonged fasting is not recommended as a form of therapy because of protein loss and hypotension. However, recent studies support alternate day fasting, with 500 to 600 kcal intake alternated with *ad libitum* intake. This seems to be effective for some because the addition of a small amount of food reduces the hunger associated with a total fast and there is not compensatory increased food intake on the day following the modified fast.

vii. **Novelty or single food diets.** A number of popular diets focus on a single food. Although nutritionally unbalanced, these diets have two features. They are simple to follow, and the monotony of single items tends to limit food intake,

and new ones appear on an annual basis.

E. Pharmacologic therapy. Drugs for use in treating the patient with obesity are approved as adjuncts to diet and exercise and none have been approved for use in pregnancy, nursing, or pediatric populations. The use of these drugs should be reserved for patients with moderate- or high-risk obesity (BMI > 30 kg/m^2 or a BMI > 27 kg/m^2 if comorbidities are present). They are intended for patients who are struggling to lose and maintain weight loss. Thus, a history of lack of success in the p. 597p. 598past is a prerequisite. All these medications work through helping patients better adhere to their diets (all through reducing appetite, except orlistat which helps to enforce a low-fat diet). Thus, these medications should only be used with an effort at dieting. There is no ideal medication. In the right patient, any of these can be a successful. But no one medication works in every patient. Evaluation at 3 months on treatment should identify success. If patients have not lost 4% to 5%, then that drug should be stopped and another approach used.

The medications currently approved for chronic weight management are listed in Table 43.4. Abuse of amphetamines, methamphetamine, and phenmetrazine is well established, and these agents are not approved for long-term treatment of the patient with obesity.

1. **Orlistat** (marketed as Xenical or over the counter as Alli) blocks lipase in the intestine, thus reducing fat absorption. It produces modest weight loss and is approved worldwide. Its drawbacks are the gastrointestinal side effects from undigested fat in the intestine.
2. **Lorcaserin** (marketed as Belviq) is a serotonin-2C agonist which acts in the brain to reduce food intake. It is generally well tolerated. Caution is advised with concomitant use with Selective serotonin reuptake inhibitor (SSRI) and Serotonin norepinephrine reuptake inhibitor (SNRI).
3. **Liraglutide 3.0 mg** (marketed as Saxenda) is a GLP-1 agonist given by injection. It reduces food intake. Its major side effects are nausea and vomiting which can be minimized by a slow dose titration from 0.6 mg. Some patients cannot tolerate even with slow titration. Hypoglycemia during treatment with liraglutide can occur in patients with diabetes who are receiving antidiabetic drugs such

as sulfonylureas that can cause hypoglycemia.

It should not be prescribed to patients with a personal or family history of medullary thyroid cancer or MEN II, and caution should be used in prescribing to patients with a history of pancreatitis.

4. **Combination of phentermine and topiramate extended release** (marketed as Qsymia). This new medication is a combination of medications that produces larger weight loss, on average, than the other drugs. It should not be prescribed unless patients of childbearing potential are on good contraception and monitoring monthly pregnancy tests because topiramate can produce oral clefts.
5. **Combination of naltrexone sustained release and bupropion sustained release** (marketed as Contrave). Like liraglutide and topiramate/phentermine, the combination of naltrexone/bupropion requires titration to minimize the principle side effect, nausea. Patients with hypertension should be well controlled and monitored early in therapy. It is contraindicated in patients who have history of seizures or require chronic opioids.

F. Surgery

1. Gastric operations reduce the size of, or bypass, the stomach. Several different operations are currently done (Table 43-5). The gastric bypass consists of creating a small (50 mL) upper stomach pouch with a staple line. The pouch is drained into a loop of jejunum using a Roux-en-Y design. The second type of operation is a gastric sleeve in which the stomach along the greater curvature is removed producing an extension of the esophagus. The esophageal contents enter the intestine after passing through a narrowed stomach. The third type of operation consists of placement of a plastic inflatable ring around the upper stomach, along with a reservoir of saline under the skin that can be used to constrict the opening between the upper and lower stomach. The final operation is a biliary bypass in which two long sections of intestine allow separation of digestion and absorption except for a small length of bowel. In the Swedish Obese Subjects study, the weight loss with the gastric bypass was superior to banding and the obsolete gastroplasty. Mortality was significantly reduced after 11 years in this study because of reduced cardiovascular disease and stroke. Incidence of diabetes was also reduced. The safety of

bariatric surgical procedures has improved dramatically in recent years with the use of laparoscopic techniques and trained surgical teams. There is emerging evidence that gastric bypass p. 598p. 599p. 599p. 600p. 600p. 601p. 601p. 602and sleeve gastrectomy may reduce appetite through signals that originate in the gut. Bariatric operations are particularly beneficial in the amelioration of diabetes.

TABLE 43-4 Drugs That Have Been Approved by the Food and Drug Administration for Treatment of Obesity

Drug and mechanism of action	Trade names	Dosage	Comments
Pancreatic Lipase Inhibitor Approved for Long-Term Use Orally			
Orlistat (not scheduled)	Xenical	120 mg tid before meals	Gastrointestinal side effects from bloating and diarrhea are principal drawbacks; should be taken with a multivitamin.
Serotonin Receptor Agonist Approved for Long-Term Use Orally			
Lorcaserin DEA Schedule IV[a]	Belviq	110 mg twice daily	Headache, dizziness, nausea, dry-mouth and constipation are generally mild. Do not use with other serotonin active drugs
Glucagon-like Receptor-1 Agonist Approved for Long-Term Use by Injection			
Liraglutide (not scheduled)	Saxenda	3.0 mg/d by injection—dose-escalation over 5 wks from 0.6 to 3.0 mg/d	Nausea with some vomiting are principal side effects; acute pancreatitis or gall bladder disease can occur; hypoglycemia with some antidiabetic drugs; do not prescribe in patients with personal or family history of medullary thyroid cancer or MEN 2.
Combination of Two Drugs Approved for Long-Term Use Orally			
Phentermine-Topiramate extended release DEA Schedule IV	Qsymia	3.75 mg/23 mg, first week; 7.5 mg/46 mg thereafter;	Paresthesthesias and change in taste (dysgeusia) Metabolic acidosis and glaucoma are rare; Do not use within 14 d of an MAOI antidepressant; obtain

		can increase to 15 mg/92 mg for inadequate response	negative pregnancy test before prescribing and avoid pregnancy.
Naltrexone SR-BupropionSR (not scheduled)	Contrave	8 mg/90 mg tabs; take 2 twice daily after dose—escalation	Nausea, constipation, headache; avoid in patients receiving opioids, MAOI antidepressants, and with history of seizure disorder.
Noradrenergic Drugs Approved for Short-Term Use Orally			
Diethylpropion DEA Schedule IV	Tenuate Tepanil	25 mg tid	Dizziness, dry-mouth, insomnia, constipation, irritability, cardiostimulatory
	Tenuate Dospan	75 mg q AM	
Phentermine DEA Schedule IV	Adipex Fastin	15–37.5 mg/d	Dizziness, dry-mouth, insomnia, constipation, irritability, cardiostimulatory
	Oby-Cap Ionamin slow release	15–30 mg/d	
Benzphetamine DEA Schedule III[b]	Didrex	25–50 mg tid	Dizziness, dry-mouth, insomnia, constipation, irritability, cardiostimulatory
Phendimetrazine DEA Schedule IV	Bontril Plegine Prelu-2 X-Trozine	17.5–70 mg tid 105 mg qd	Dizziness, dry-mouth, insomnia, constipation, irritability, cardiostimulatory

[a]Scheduled by the U.S. Drug Enforcement Agency as Schedule IV.
[b]Scheduled by the U.S. Drug Enforcement Agency as Schedule III.
Data from AHFS Drug Information 2005. Bethesda, MD: American Society of Health-System Pharmacists DEA, Drug Enforcement Agency; MAOI, Monoamine Oxidase Inhibitor.

TABLE 43-5 Surgical Procedures for Treatment of Obesity

Procedure	Weight loss after 3 yr Δ BMI (kg/m^2) (95% CI)	Effects on type 2 diabetes remission (%) (95% CI) at years	Mortality % (95% CI) <30 d >30 d	Reoperation rate % (95% CI)	Complications % (95% CI)
Adjustable gastric banding (AGB)	−11.4 (−18.1 to −4.7)	67.6 (49.5–82.8)	0.07 (0.02–0.12) 0.21 (0.08–0.37)	7.01 (3.99–118)	7.80 (3.90–13.00)
Sleeve gastrectomy (SG)	−16.78 (−20.6 to −13.0)	85.5 (72.7–94.1)	0.29 (0.11–0.63) 0.34 (0.14–0.60)	2.96 (1.70–4.71)	8.90 (5.60–13.00)
Roux-en-Y gastric bypass (RGB)	−21.9 (−28.0 to −15.8)	92.8 (85.3–97.2)	0.38 (0.22–0.59) 0.39 (0.01–0.86)	5.34 (4.48–6.48)	12.00 (7.30–17.00)

Note that for this analysis, surgical procedures were grouped: AGB includes laparoscopic gastric banding and Swedish band; SG includes sleeve gastrectomy and vertical-banded gastroplasty; RGB includes laparoscopic and open procedures as well as biliopancreatic diversion with or without duodenal switch.
BMI, body mass index; CI, closed interval. Data in table are from Chang (2014).

2. Scopinaro or biliopancreatic diversion. In this operation,

the stomach is separated and the contents entering the upper stomach are bypassed into a loop of jejunum that is anastomosed to the upper stomach. The gastric juices from the lower stomach join the duodenal contents and flow downstream, where they are anastomosed to the ileum where these digestive enzymes and food from the stomach connected for a short part of the intestine. The operation is technically difficult, and protein malnutrition has been a reported side effect.

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44 Disorders of Lipid Metabolism

Stanley H. Hsia

I. PHYSIOLOGY

Cholesterol and triglycerides (TGs) are poorly soluble in aqueous plasma. **Lipoprotein** particles are aggregates of phospholipids and free cholesterol that create a lipophilic core to transport lipid-soluble TG and cholesterol esters through aqueous plasma. **Apolipoproteins** are peptide constituents of lipoproteins that serve critical functions. The major lipoprotein classes differ widely in their size and composition (Table 44-1). The pathways and metabolic fates of lipids, lipoproteins, and intrahepatic free cholesterol are shown in Figure 44-1. The risk of coronary heart disease (CHD) correlates not only strongly with high levels of low-density lipoprotein cholesterol (LDL-C), but also independently with a **combined dyslipidemia triad**, consisting of (a) elevated TG, (b) low levels of high-density lipoprotein cholesterol (HDL-C), and (c) a phenotype of smaller, denser, more proatherogenic LDL particles, all of which are closely interrelated through the actions of cholesteryl ester transfer protein and hepatic lipase, and are strongly **associated with insulin resistance**.

II. DIAGNOSIS AND LABORATORY TESTING

A. Primary lipid disorders. Lipid disorders not attributable to other concurrent factors are most likely genetically determined. Known Mendelian and complex primary lipid disorders are listed in Table 44-2.

TABLE 44-1 Characteristics of the Major Classes of Lipoproteins

	Chylo and Chylo remnants	VLDL	IDL	LDL	HDL
Particle diameter (nm)	70–600	30–70	10–30	20–25	7–10
Density (g/mL)	<0.94	<1.006	1.006–1.019	1.019–1.063	1.063–1.21
Composition					
Cholesterol	~5%	~20%	~40%	~50%	~20%
Triglyceride	~90%	~60%	~35%	~10%	~5%
Phospholipid	~4%	~15%	~20%	~20%	~30%
Protein	~1%	~5%	~5%	~20%	~45%
Major core component	TG	TG	TG, CE	CE	CE
Major apolipoproteins	B48, CII, CIII, E, AI, AII	B100, CII, CIII, E	B100, E	B100	AI, AII, CII, CIII, E

CE, cholesterol esters; Chylo, chylomicrons; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very-low-density lipoprotein.

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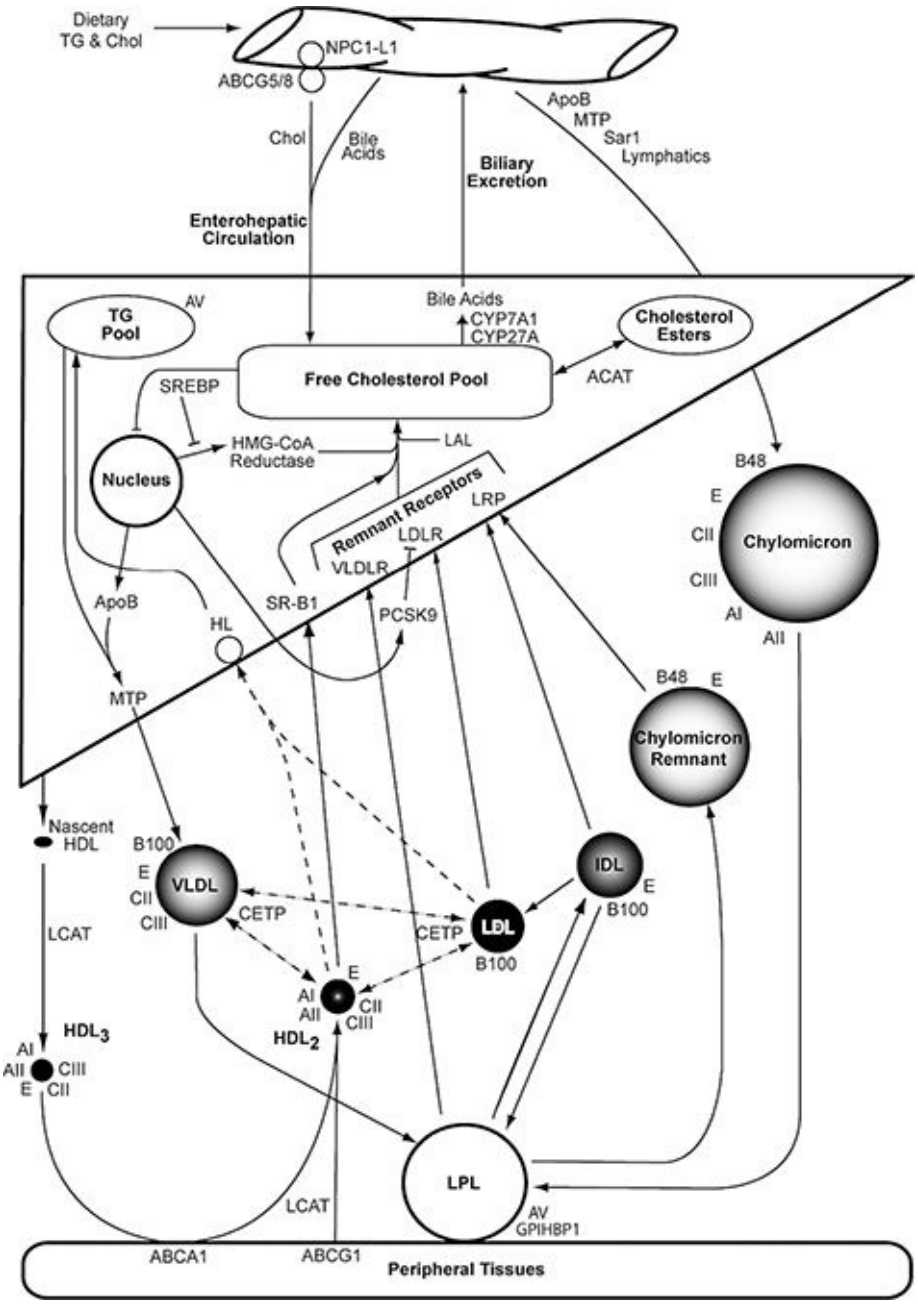

Figure 44-1. Metabolic fates of lipoproteins. *Solid arrows* indicate lipid and lipoprotein metabolic pathways; *dashed arrows* indicate pathways related to neutral lipid transfers among lipoprotein particles. AI, apolipoprotein AI; AII, apolipoprotein AII; ABCA1, ATP-binding cassette A1; ABCG1, ATP-binding cassette G1; ABCG5/8, ATP-binding cassettes G5 and G8; ACAT, acyl CoA-cholesterol acyltransferase; ApoB, apolipoprotein B; AV, apolipoprotein AV; B48, apolipoprotein B48; B100, apolipoprotein B100; CII, apolipoprotein CII; CIII, apolipoprotein CIII; CETP, cholesteryl ester transfer protein; Chol,

cholesterol; CYP7A1, cholesterol 7α-hydroxylase; CYP27A, cholesterol 27-hydroxylase; E, apolipoprotein E; GPIHBP1, glycosylphosphatidylinositol-anchored HDL binding protein-1; HDL, high-density lipoprotein; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LAL, lysosomal acid lipase; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; LDLR, LDL receptor; LRP, LDL receptor-like protein; LPL, lipoprotein lipase; MTP, microsomal triglyceride transfer protein; NPC1-L1, Niemann–Pick C1-like 1 protein; PCSK9, proprotein convertase subtilisin/kexin type 9; Sar1, Sar1-GTPase; SR-B1, scavenger receptor-B1; SREBP, sterol response element–binding protein; TG, triglyceride; VLDL, very-low-density lipoprotein; VLDLR, VLDL receptor.

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TABLE 44-2 Primary Lipid Disorders

Primary disorder	Molecular defect	Lipoprotein effects	Cholesterol	T
Hyperchylomicronemia Disorders				
Familial LPL deficiency	LPL	↑↑ Chylo	↔	↑
Familial ApoCII deficiency	ApoCII	↑↑ Chylo	↔	↑
Familial hypertriglyceridemia	Heterogeneous	↑ VLDL-C, Chylo	↔	↑
Familial ApoAV deficiency	ApoAV	↑↑ Chylo	↑	↑
Hypercholesterolemia Disorders				
Familial hypercholesterolemia	LDLR	↑↑ LDL-C, (↓ HDL-C)	↑↑↑	↓
Familial defective ApoB	ApoB100	↑↑ LDL-C, (↓ HDL-C)	↑↑	↓
PCSK9 (gain-of-function)	PCSK9	↑↑ LDL-C	↑↑	↓
Autosomal recessive hypercholesterolemia	LDLRAP1	↑↑ LDL-C	↑↑	↓
Polygenic hypercholesterolemia	Heterogeneous	↑ LDL-C	↑	↓
Cholesterol ester storage disease	LAL	↑↑ LDL-C, (↓ HDL-C)	↑↑	(
Sitosterolemia	ABCG5/ABCG8	↑↑ LDL-C (Phytosterols)	↑↑ (Phytosterols)	(
Mixed Hyperlipidemia Disorders				
Familial combined hyperlipidemia	Heterogeneous	↑ VLDL-C, ↑ LDL-C, ↓	(↑)	(

(hyperapobetalipoproteinemia)		HDL-C		
Familial dysbetalipoproteinemia	ApoE	↑ IDL-C, ↑ Remnants	↑	↑
Familial HL deficiency	HL	↑ VLDL-C, ↑ LDL-C, ↑ HDL-C	↑	↑
Low HDL-C Disorders				
Familial Apo-AI deficiency	Apo-AI	↓↓ HDL-C	↔	(
Familial hypoalphalipoproteinemia	Heterogeneous	↓ HDL-C	↔	
Tangier disease	ABCA1	↓↓ HDL-C	↓	↓
Familial LCAT deficiency	LCAT	↓↓ HDL-C	↑/↓	↑
Fish-eye disease	LCAT	↓ HDL-C	↑	↑
High HDL-C Disorders				
Familial hyperalphalipoproteinemia	Heterogeneous	↑ HDL-C	(↑)	
Familial CETP deficiency	CETP	↑↑ HDL-C	↑/↓	↑
Low LDL-C Disorders				
Familial LDL deficiency (abetalipoproteinemia)	MTP	↓↓ VLDL-C, ↓↓ LDL-C	↓↓	↓
Familial hypobetalipoproteinemia	ApoB	↓↓ LDL-C	↓↓	↓
Chylomicron retention disease	Sar-1	↓↓ LDL-C, ↓ HDL-C	↓↓	↓
PCSK9 (loss-of-function)	PCSK9	↓↓ LDL-C	↓↓	↓

(), possible increase/decrease; ABCA1, ATP-binding cassette A-1; ABCG5, ATP-binding cassett G-5; ABCG8, ATP-binding cassette G-8; Apo, apolipoprotein; CETP, cholesteryl ester transfer protein; Chylo, chylomicron; HDL-C, high-density lipoprotein cholesterol; HL, hepatic lipase; LAL lysosomal acid lipase; LCAT, lecithin-cholesterol acyltransferase; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LDLRAP1, low-density lipoprotein receptor adaptor protein 1; LPL, lipoprotein lipase; MTP, microsomal triglyceride transfer protein, PCSK9 proprotein convertase subtilisin/kexin type 9; Sar-1, Sar-1-GTPase; TG, triglyceride; VLDL, very low-density lipoproteins.

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B. Secondary lipid abnormalities. Concurrent conditions or medications may exacerbate lipid profiles (Table 44-3), and should be comanaged because they may reduce or obviate the need for lipid-lowering agents. Primary disorders sometimes cannot be definitively diagnosed unless these conditions have been controlled or ruled out.

C. Clinical signs. In extreme hypertriglyceridemia, **lipemia retinalis**

may be seen on fundoscopy as pallor of the retinal vessels due to turbidity from plasma chylomicron accumulation, and cutaneous **eruptive xanthomata** may be seen on extensor surfaces as multiple small, raised papules. Nonspecific signs of chronic severe hypercholesterolemia include **xanthelasmas** that appear as yellow, well-demarcated, irregular plaques of cholesterol in the periorbital skin, a **corneal arcus** on the iris, and **tuberous xanthomata** that appear as larger, globular cutaneous deposits on extensor surfaces. **Palmar xanthomata** are yellowish discolorations in the palmar creases, and are more specific for familial dysbetalipoproteinemia. **Tendon xanthomata** usually affect extensor tendons (e.g., Achilles), and are more specific for familial hypercholesterolemia (FH).

D. Measurements. TG levels increase postprandially, so *TG must be measured only after an adequate (10- to 12-hour) fast*. *Levels of the cholesterol fractions are not affected by meals prior to the time of blood draw*. Levels of LDL-C are usually not directly measured, but rather calculated using the Friedewald equation (in mg/dL):

LDL-C = (Total cholesterol) – ([HDL-C] + [TG ÷ 5])

This relationship applies *only if the TG level is <400 mg/dL and familial dysbetalipoproteinemia is absent*. Otherwise, LDL-C cannot be calculated with certainty. In such situations, "direct" LDL-C assays are available, but these are still not as reliable as LDL-C calculated after lowering TG to <400 mg/dL. **Non-HDL-cholesterol (NHDL-C)** encompasses the cholesterol content of all proatherogenic particles (including LDL-C), is strongly correlated with and less labile than TG levels, does not require fasting, and is a secondary treatment target recommended by the National Cholesterol Education Program's Third Adult Treatment Panel (ATP-III) guidelines:

NHDL-C = (TC) – (HDL-C)

Severe illnesses (e.g., myocardial infarction, sepsis) may *falsely lower serum lipids* by as much as 50% as an acute-phase response, beginning within 24 hours after onset and lasting for up to 4 to 6 weeks; lipid profiles obtained during such hospitalizations do not rule out hyperlipidemia, and should be repeated after the patient has recovered.

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TABLE 44-3 Secondary Lipid Abnormalities

Underlying disorder	Lipoprotein effects	Chol	TG
Obesity, insulin resistance, type 2 diabetes	↑ VLDL, ↓ HDL, (↑ LDL)	(↑)	↑
Uncontrolled type 1 diabetes	↑ VLDL, ↓ HDL	(↑)	↑↑
Alcohol	↑ VLDL, ↑ HDL	↔	↑↑
Hypothyroidism	↑ LDL, (↑ VLDL)	↑	(↑)
Pregnancy	↑ VLDL, ↑ HDL	↑/↓	↑
Nephrotic syndrome	↑ VLDL, ↑ LDL	↑	(↑)
Chronic renal failure	↑ VLDL, ↑ LDL	(↑)	↑
Obstructive liver disease	↑ Lp-X	↑	↔
Acromegaly	↑ VLDL, ↓ HDL, (↑ LDL)	(↑)	↑
Growth hormone deficiency	↑ VLDL, ↑ LDL	↑	↑
Cushing syndrome, glucocorticoids	↑ VLDL, ↓ HDL, (↑ LDL)	(↑)	↑
Dysglobulinemia	↑ VLDL, ↑ LDL	↑	↑
Glycogen storage disease	↑ VLDL	(↑)	↑
Sphingomyelinase deficiency	↑ LDL	↑	↔
Anorexia nervosa	↑ LDL	↑	↔
Lipodystrophies	↑ VLDL, (↓ HDL, ↑ LDL)	(↑)	↑
Acute intermittent porphyria	↑ LDL	↑	↔
Estrogens (nontransdermal)	↑ VLDL, ↑ HDL, ↓ LDL	↓	↑
Raloxifene	↓ LDL	↓	↔
Tamoxifen	↑ VLDL, ↓ LDL	↓	↑
Androgens, progestins, danazol	↓ VLDL, ↓ HDL, ↑ LDL	↑	↓
Aromatase inhibitors	↓ VLDL, ↑ HDL	↔	↓
Thiazides, *β*-blockers (nonselective, non-ISA)	↑ VLDL, (↑ LDL)	(↑)	↑
Isotretinoin, acitretin	↑ VLDL, (↓ HDL, ↑ LDL)	↔	↑
Cyclosporine, sirolimus	↑ LDL, (↑ VLDL)	↑	↔
Carbamazepine, phenytoin, phenobarbital	(↑ HDL), ↑ LDL	↑	↔
Valproic acid	↓ LDL	↓	↔
Interferon-*α*	↑ VLDL, ↓ HDL	↔	↑
Saquinavir, indinavir, nelfinavir, ritonavir, tipranavir, lamivudine	↑ VLDL, ↓ HDL, (↑ LDL)	↑	↑
Lopinavir, fosamprenavir	↑ VLDL, ↑ LDL	↑	(↑)

Atazanavir, zidovudine, stavudine	↑ VLDL, (↑ HDL, ↑ LDL)	↑	↑
Didanosine, efavirenz	(↑ VLDL, ↑ HDL), ↑ LDL	↑	(↑)
Abacavir, nevirapine	↑ VLDL, ↑ HDL, ↑ LDL	↑	↑
Tenofovir	(↓ VLDL), ↓ HDL, ↓ LDL	↓	↔
Clozapine, olanzapine, quetiapine	↑ VLDL, ↓ HDL, (↑ LDL)	(↑)	↑

(), possible increase/decrease; Chol, cholesterol; HDL, high-density lipoprotein; ISA, intrinsic sympathomimetic activity; LDL, low-density lipoprotein; Lp-X, lipoprotein-X; TG, triglyceride; VLDL, very-low-density lipoprotein.

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III. TREATMENT GUIDELINES

The ATP-III guidelines advocated the lowering of lipids below specific LDL-C and NHDL-C target levels based on CHD risk stratification. In contrast, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, developed solely based on the best-quality clinical trial evidence available, advocated the use of statin agents to achieve specific intensities of relative LDL-C lowering from baseline instead of targeting absolute lipid levels, because the latter strategy is actually not directly supported by clinical trial evidence. However, guidelines from other groups such as the National Lipid Association, the American Association of Clinical Endocrinologists, and the International Atherosclerosis Society still advocate a target-driven approach similar to ATP-III, based on the totality of evidence showing a direct and continuous correlation between absolute levels of atherogenic cholesterol and absolute event risk. Both guidelines are discussed, because there is currently substantial controversy regarding the relative merits of each approach. There is agreement that aggressive lipid lowering with statins in high-risk or secondary prevention patients is strongly evidence based, but for lower-risk or primary prevention patients, the ACC/AHA guidelines identify more higher-risk, statin-eligible individuals than do the ATP-III guidelines. It should be emphasized that *no guidelines are intended to substitute for individualized clinical judgment*.

A. ATP-III guidelines

1. **Population screening.** ATP-III recommends obtaining a full fasting lipid profile for all adults age ≥20 years, at least once every 5 years. Any results that are less than optimal for the patient's risk profile warrant more frequent assessments as treatment is instituted.
2. **Risk assessment.** Therapy is targeted more aggressively for higher-risk patients while minimizing unnecessary therapy and cost for lower-risk patients. Risk stratification is indexed to the Framingham 10-year CHD risk, and can be simplified to the broad risk categories shown in Table 44-4. High or very high risk usually applies to patients with a known history of **CHD or CHD equivalents**. Moderate or low risk is determined by the number of risk factors in the absence of CHD or CHD equivalents, but these patients can be heterogeneous, so the **Framingham risk assessment tables** (Table 44-5; *a downloadable software application is also available*) may more accurately determine their 10-year risk for classification purposes.
3. **Recommended treatment targets.** Risk assessment (from Section III.A.2) dictates the recommended treatment targets, shown in Table 44-4. *LDL-C should be the primary treatment target*, and statins should be the first-line agents used, aiming to *also achieve at least a 30% LDL-C reduction from baseline*. Once the LDL-C goal is achieved, patients (particularly those with TG > 200 mg/dL) should have their NHDL-C levels determined and optimized as well. *NHDL-C should be a secondary treatment target*, because it is a surrogate measure of the **combined dyslipidemia triad**, so *it can be elevated independent of the patient's LDL-C level*. The same therapeutic choices to lower LDL-C may be considered for lowering NHDL-C (because LDL-C is a component of NHDL-C). *NHDL-C goals are always 30 mg/dL above the corresponding LDL-C goal* (Table 44-4). After the primary and secondary targets have both been met, lipid profiles should be monitored every 4 to 6 months to ensure that they remain at goal. If necessary, nonstatin agents may be added to statins to achieve or maintain lipid goals.

B. ACC/AHA guidelines

1. **Population screening.** For primary prevention, the ACC/AHA guidelines recommend assessing every 4 to 6 years the 10-year risk

status of patients without diabetes who are not already taking a statin.

2. **Risk assessment.** Therapy is targeted at **specific, high-risk groups** for whom there is strong evidence supporting the benefit of risk reduction using statins (summarized in Fig. 44-2). Adults aged ≥21 years who are candidates for statin therapy include:
   - **a.** Those with clinical atherosclerotic cardiovascular disease (ASCVD)
   - **b.** Those with a primary cholesterol disorder with a baseline LDL-C ≥ 190 mg/dL

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TABLE 44-4 ATP-III Risk Classifications and Treatment Goals

Risk category (10-yr Framingham risk)	LDL-C goal (mg/dL)	LDL-C level for initiating or intensifying drug therapy (mg/dL)[a]	NHDL-C goal (mg/dL)
High Risk: (10-yr risk >20%) CHD or CHD equivalents[b]	<100 <70[c]	≥100 (Optional if 70–99)	<130 <100[c]
Moderate Risk: (10-yr risk 10%–20%) ≥2 risk factors[d]	<130 <100[e]	*If 10-y risk 10%–20%:* ≥130 *If 10-y risk <10%:* ≥160 *If LDL-C goal is <100:* ≥100	<160 <130[e]
Low Risk: (10-yr risk <10%) 0 or 1 risk factor[d]	<160	≥190 (optional if 160–189)	<190

[a]Initiation or intensification of Therapeutic Lifestyle Change should be instituted for all patients who are above their goals.

[b]CHD equivalents are defined as symptomatic carotid artery disease or carotid stenoses >50%, peripheral arterial disease, abdominal aortic aneurysm, diabetes mellitus, or a 10-year Framingham CHD risk >20% (as determined by Table 44-5 or the corresponding software applications).

[c]The lower LDL-C and NHDL-C goals (70 and 100 mg/dL, respectively) are justified for *high-risk patients* with acute coronary syndrome, CHD plus multiple major risk factors (especially diabetes mellitus), severe or uncontrolled risk factors, or multiple components of the metabolic syndrome (especially if TG ≥200 mg/dL with HDL-C <40 mg/dL and NHDL-C ≥130 mg/dL).

[d]Risk factors used to define the patient's risk category include the following criteria: (a) any current cigarette smoking; (b) diagnosed hypertension, blood pressure ≥140/90 mmHg or on antihypertensive medications; (c) HDL-C < 40 mg/dL; (d) family history of *premature* CHD, defined as onset in a first-degree male or female relative before the age of 55 or 65 years, respectively; and (e) age ≥ 45 or 55 years for a male or female patient, respectively; HDL-C ≥ 60 mg/dL reduces the total number of risk factors by 1.

[e]The lower LDL-C and NHDL-C goals (100 and 130 mg/dL, respectively) are justified for *moderate-risk patients* with advanced age, more than two risk factors, severe or uncontrolled risk factors, multiple components of the metabolic syndrome (especially if TG ≥ 200 mg/dL with HDL-C < 40 mg/dL and NHDL-C ≥ 160 mg/dL), or highly sensitive C-reactive protein level > 3 mg/L.

ATP-III, Third Adult Treatment Panel; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NHDL-C, non-high-density lipoprotein cholesterol.

TABLE 44-5 Framingham Risk Assessment Tables

Men

Age (yr)	Points
20–34	−9
35–39	−4
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	11
70–74	12
75–79	13

TC (mg/dL)	Points (based on age): 20–39	40–49	50–59	60–69	70–79
<160	0	0	0	0	0
160–199	4	3	2	1	0
200–239	7	5	3	1	0
240–279	9	6	4	2	1
≥280	11	8	5	3	1

Smoker	Points (based on age): 20–39	40–49	50–59	60–69	70–79
No	0	0	0	0	0
Yes	8	5	3	1	1

HDL-C (mg/dL)	Points	SBP (mmHg)	Points (based on treatment): Untreated	Treated
		<120	0	0
≥60	−1	120–129	0	1
50–59	0	130–139	1	2
40–49	1	140–159	1	2
<40	2	≥160	2	3

Add points from age, TC, smoking, HDL-C, and SBP:

Point total:	**<0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
10-y risk (%):	<1	1	1	1	1	1	2	2	3
Point total:	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
10-y risk (%):	4	5	6	8	10	12	16	20	25

Women

Age (yr)	Points	TC (mg/dL)	Points (based on age): 20–39	40–49	50–59	60–69	70–79
20–34	−7						
35–39	−3	<160	0	0	0	0	0
40–44	0	160–199	4	3	2	1	1
45–49	3	200–239	8	6	4	2	1
50–54	6	240–279	11	8	5	3	2
55–59	8	≥280	13	10	7	4	2
60–64	10						
65–69	12		Points (based on age):				
		Smoker	**20–39**	**40–49**	**50–59**	**60–69**	**70–79**
70–74	14	No	0	0	0	0	0
75–79	16	Yes	9	7	4	2	1

HDL-C (mg/dL)	Points	SBP (mmHg)	Points (based on treatment): Untreated	Treated
		<120	0	0
≥60	−1	120–129	1	3
50–59	0	130–139	2	4
40–49	1	140–159	3	5
<40	2	≥160	4	6

Add points from age, TC, smoking, HDL-C, and SBP:

Point total:	**<9**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
10-y risk (%):	<1	1	1	1	1	2	2	3	4
Point total:	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**≥25**
10-y risk (%):	5	6	8	11	14	17	22	27	≥30

HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol.

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c. Diabetic patients aged 40 to 75 years without ASCVD but with LDL-C of 70 to 189 mg/dL

d. Patients not meeting these three criteria but whose 10-year ASCVD risk as assessed using the new **Pooled Cohort Risk Equations** (available at www.cvriskcalculator.com; *a downloadable software application is also available*) is ≥7.5%.

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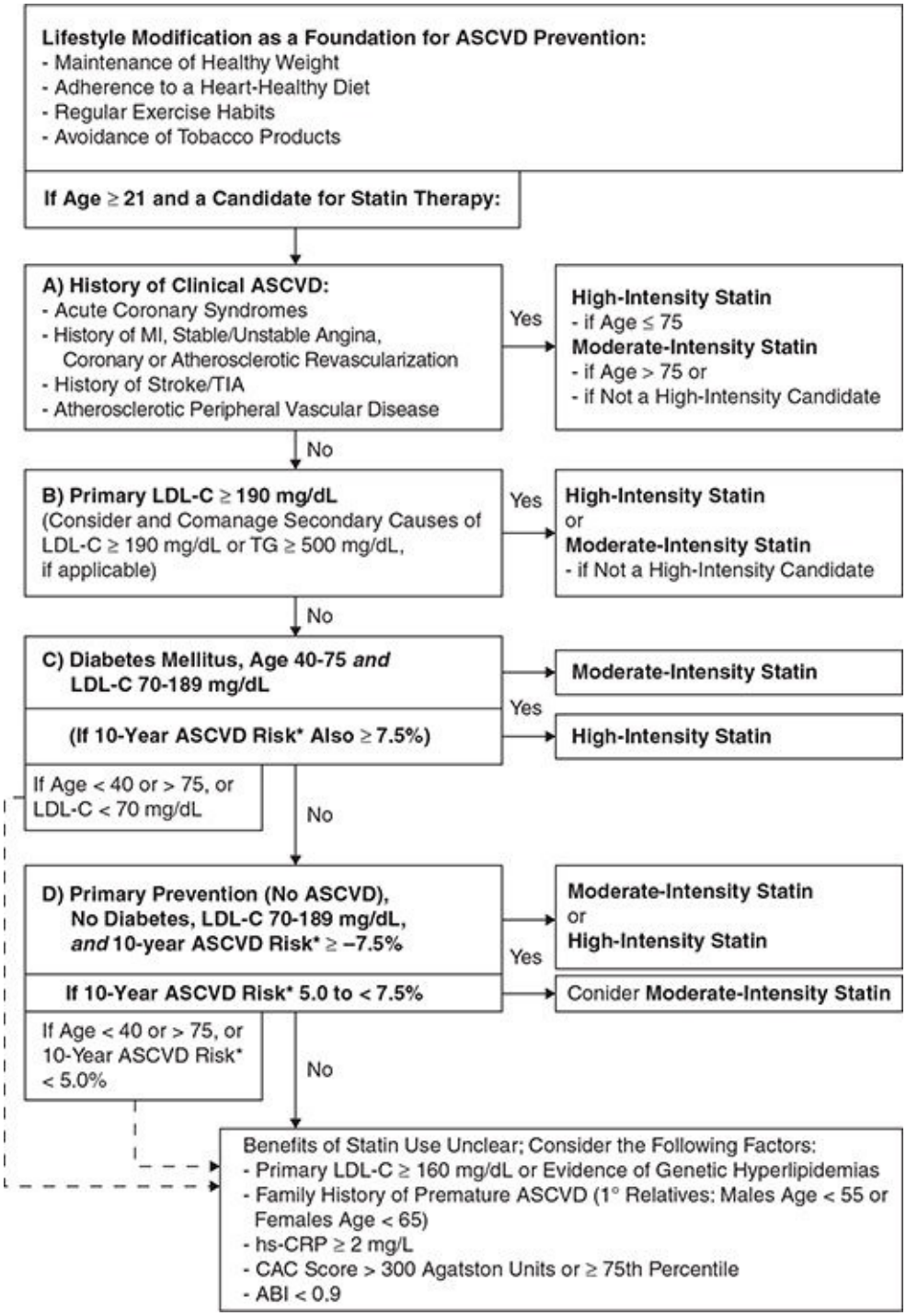

Figure 44-2. Major features of the 2013 American College of Cardiology/American Heart Association guidelines. *10-year atherosclerotic cardiovascular risk as estimated using the Pooled Cohort Risk Equations to inform decision making for patients not already taking a statin. ABI, ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery

calcium; hs-CRP, highly sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TG, triglycerides; TIA, transient ischemic attack. (Adapted from Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(Suppl 2):S1–S45.)

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Patients not meeting any of categories A to D should be managed on an individual basis, taking into account the risks versus benefits of statin treatment, potential drug–drug interactions, and patient preferences.

3. **Recommended treatment approach.** *Appropriate lifestyle modifications are emphasized as a foundation of ASCVD prevention prior to and throughout the course of statin therapy*. Patients meeting any of categories A to D above should additionally be prescribed statins of appropriate intensity, as indicated in Figure 44-2. Strong evidence supports statins reducing the risk of ASCVD irrespective of the pretreatment LDL-C level, and higher-risk patients benefit from more intense statin treatment that produces a larger percent reduction in LDL-C (listed in Table 44-6). In cases of statin intolerance, low-intensity choices can still reduce ASCVD, but to a lesser degree. Although the ACC/AHA does not advocate targeting specific LDL-C treatment goals, they still recommend obtaining a follow-up lipid panel 4 to 12 weeks after statin initiation to determine if the anticipated response has been achieved, and thereafter every 3 to 12 months. Reinforcement of lifestyle and medication adherence, dose escalation, and exclusion of secondary causes of hyperlipidemia should all be considered for any suboptimal therapeutic response. The ACC/AHA guidelines make no recommendations regarding nonstatin lipid-lowering agents added to statins, although they may still be considered for *high-risk* patients (e.g., those falling into categories A to C, above) who fail to achieve an adequate response, or for patients who are statin intolerant.

C. Hyperchylomicronemia and hypertriglyceridemia guidelines

1. **Acute management.** Severe and very severe TG elevations (defined as ≥1 000 and ≥2 000 mg/dL, respectively) reflect chylomicron retention and increase the risk of *acute pancreatitis*

rather than CHD. Such patients presenting with pancreatitis should be *admitted and kept NPO with intravenous fluid support* in order to stop chylomicron production and allow the TG load to clear over several days. Other invasive TG-lowering methods (e.g., intravenous heparin or insulin infusions in the absence of diabetes) are not routinely recommended. Alternative causes of pancreatitis, for example, alcohol, gallstones, poorly controlled diabetes, or systemic glucocorticoids, should be comanaged. TG levels should be monitored at least daily. Once TG levels fall to <1 000 mg/dL and the patient is clinically able to tolerate oral intake, *a diet very low in fat and simple carbohydrates should be started, with or without fibrates (not statins) as first-line pharmacologic agents*.

2. **Chronic management.** Ongoing treatment should emphasize strict adherence to nutritional restrictions and medications; *niacin or high-dose fish oils may* p. 612p. 613*be alternative medications* to help control TG levels. If there is an underlying primary cause, TG levels seldom normalize, but proper adherence can usually keep the TG level low enough to minimize the risk of pancreatitis recurrence. The TG threshold at which pancreatitis recurs is highly variable, and no specific TG target level has been recommended for pancreatitis prevention or treatment. Guidelines proposed by the Endocrine Society also acknowledge the association of mild or moderate hypertriglyceridemia (defined as TG levels 150 to 999 mg/dL) with increased CHD risk, and agree with the ATP-III strategy of optimizing NHDL-C goals as outlined in Section III.A.3, so *statins may still be useful for milder TG elevations* where CHD risk remains a concern.

TABLE 44-6 Daily Statin Dosages Corresponding to Various Intensities of LDL-C Lowering

High-intensity statin therapy (Average LDL-C lowering ≥50%)	Moderate-intensity statin therapy (Average LDL-C lowering ~30%–50%)	Low-intensity statin therapy (Average LDL-C lowering <30%)
Atorvastatin 40–80 mg Rosuvastatin 20–40 mg	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg Pravastatin 40–80 mg Lovastatin 40 mg	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

	Fluvastatin XL 80 mg Fluvastatin 40 mg b.i.d. Pitavastatin 2–4 mg

Adapted from Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(suppl 2):S1–S45.

IV. MANAGEMENT

A. Nutritional and lifestyle therapy.

Therapy for lipid disorders should always begin with modifications of nutrition and lifestyle. ATP-III recommends Therapeutic Lifestyle Change (TLC, Table 44-7) as first-line therapy, for no longer than 12 weeks if pharmacologic therapy is initially postponed so as to determine the effect of TLC alone; if targets have not been reached after 6 weeks, the TLC should be reinforced, intensified, and/or fiber or plant sterols should be added. However, TLC alone is often insufficient to achieve treatment goals, even with good adherence. *After starting pharmacologic therapy, regular counseling and reinforcement of adherence to nutritional and lifestyle therapy are always important.*

1. **Medical nutrition therapy.** This refers to nutritional treatment that is *intended to reduce the patient's risks*, ideally administered by appropriately trained registered dietitians.
   a. **Total calories.** Regardless of food choices, meal portion sizes should be controlled to *facilitate weight loss in overweight or obese individuals, and to maintain weight in normal-weight individuals*. Even modest weight reductions in obese individuals (~5% to 10% of baseline weight within 6 months) can significantly improve metabolic profiles. All weight control strategies should emphasize *practical, achievable, sustainable, and longitudinal* dietary changes.
   b. **Nutritional composition.** *To achieve LDL-C targets,* **saturated fat** *is the single most important nutritional component to be avoided*. Dietary ***trans*** **fats** and **dietary cholesterol,** which usually comprise a smaller percentage of daily calories, should also be avoided. Polyunsaturated fatty acids (PUFAs) may reduce LDL-C, and monounsaturated fatty acids (MUFAs) are relatively neutral to lipids, so combinations of PUFA and MUFA are preferable to saturated fats.

Carbohydrates should emphasize vegetables, fruits, whole-grain breads and cereals, and other **complex carbohydrate** sources; and soluble **dietary fiber** independently reduces LDL-C (~7% with 5 to 10 g of dietary fiber daily). **Modest alcohol intake** (averaging ≤1 standard drink/day for women or ≤2/day for men) is associated with lower mortality compared to nonuse, but in some individuals, it **can precipitate an excessive rise in TG levels**; thus, modest alcohol use p. 613p. 614does not need to be discouraged so long as there is no hypertriglyceridemia or other contraindications (e.g., liver disease, addiction history).

TABLE 44-7 ATP-III Therapeutic Lifestyle Change

Saturated fat (including *trans* fats)	<7% of total daily calories
Polyunsaturated fats	≤10% of total daily calories
Monounsaturated fats	≤20% of total daily calories
Total fat	25%–35% of total daily calories
Complex carbohydrates	50%–60% of total daily calories
Fiber	20–30 g daily
Protein	~15% of total daily calories
Dietary cholesterol	<200 mg daily
Total calories	Balance intake/expenditure to maintain desirable weight or prevent weight gain; physical activity to expend ≥200 kcal/day

c. **Plant sterols/stanols.** Available as margarine-like spreads, dietary plant sterols/stanols are not systemically absorbed and thus compete against animal-source cholesterol for intestinal absorption. They lower LDL-C by an additional 10% to 15% when taken in typical quantities (2 to 3 g daily) and are *useful as a dietary adjunct* to intensify the TLC therapy, if needed.

2. **Physical activity.** ATP-III recommends moderate physical activity to expend an average of 200 kcal/day. Like nutritional

therapy, physical activity must be sustained long term to be most effective.

B. Pharmacotherapy. Features of the available lipid-lowering agents in the United States are listed in Table 44-8.

TABLE 44-8 Lipid-Lowering Drugs Available in the United States

Medication	Dose	Efficacy	Potential side effects
HMG-CoA Reductase Inhibitors (Statins)			
Lovastatin (Altoprev, Mevacor)	10–80 mg q.d.	LDL-C ↓ 20%–60% HDL-C ↑ 5%–15% TG ↓ 5%–30%	Transaminase elevations Myopathy Possible drug interactions
Pravastatin (Pravachol)	10–80 mg q.d.		
Simvastatin (Zocor)	5–40 mg q.d.		
Fluvastatin (Lescol)	20–80 mg q.d.		
Atorvastatin (Lipitor)	10–80 mg q.d.		
Rosuvastatin (Crestor)	5–40 mg q.d.		
Pitavastatin (Livalo)	1–4 mg q.d.		
Fibric Acid Derivatives (Fibrates)			
Gemfibrozil (Lopid)	600 mg b.i.d.	TG ↓ 20%–50% HDL-C ↑ 10%–20% LDL-C ↓ 5%–20% (or ↑)	Dyspepsia, cholelithiasis Transaminase elevations Myopathy
Fenofibrate (Antara, Fenoglide, Fibricor, Lipofen, Lofibra, Tricor, Triglide, Trilipix)	30–200 mg q.d.		
Nicotinic Acid (Niacin)			
Niacin (Niacor)	1.5–3.0 g daily (b.i.d./t.i.d.)	TG ↓ 20%–50% HDL-C ↑ 15%–35% LDL-C ↓ 15%–25%	Flushing, pruritus Transaminase elevations Hyperglycemia, hyperuricemia Peptic ulcer disease, headache
Extended-release niacin (Niaspan, Slo-Niacin)	1.0–2.0 g q.d.		
Bile Acid Sequestrants			
Colestipol (Colestid)	Tablets: 2–16 g daily Granules: 5–30 g daily (q.d./b.i.d./t.i.d./q.i.d.)	LDL-C ↓ 15%–30% HDL-C ↑ 3%–5% TG ↑ 15%	Gastrointestinal distress Constipation Hypertriglyceridemia Medication absorption (less with colesevelam)
Cholestyramine (Questran, Prevalite)	4–24 g daily (q.d./b.i.d./t.i.d.)		
Colesevelam (Welchol)	1.875–3.75 g daily (q.d./b.i.d.)		
Cholesterol Absorption Inhibitors			

Ezetimibe (Zetia)	10 mg q.d.	LDL-C ↓ 10%–20% HDL-C unchanged TG ↓ 5%–10%	No significant side effects
Microsomal Triglyceride Transfer Protein Inhibitors			
Lomitapide (Juxtapid)	5–60 mg q.d.	TG ↓ 25%–65% HDL-C ↓ 6%–12% (transient) LDL-C ↓ 15%–50%	Diarrhea Transaminase elevations Hepatic steatosis
Anti-apoB Oligonucleotides			
Mipomersen (Kynamro)	200 mg sc q wk	LDL-C ↓ 25%–35% HDL-C ↑ 0%–15% TG ↓ 10%–25%	Injection site pain/erythema Flu-like symptoms Transaminase elevations Hepatic steatosis
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors			
Alirocumab (Praluent) Evolocumab (Repatha)	75–150 mg sc q 2 wk 140 mg sc q 2 wk, or 420 mg sc q mo	LDL-C ↓ 45%–60% HDL-C ↑ 4%–8% TG ↓ 5%–20%	Injection site reactions
Pharmacologic-dose Marine Fish Oils			
Omega-3 acid ethyl esters (EPA+DHA) (Lovaza)	4 g daily (1 g capsule = ~465 mg EPA + ~375 mg DHA) (q.d./b.i.d.)	TG ↓ 20%–40% HDL-C ↑ 5%–15% LDL-C ↑ 15%–40%	No significant side effects
Icosapent ethyl (EPA ethyl ester) (Vascepa)	2 g b.i.d.	TG ↓ 15%–20% HDL-C unchanged LDL-C unchanged	
Combination Agents			
Ezetimibe/simvastatin (Vytorin)	10 mg/10 mg–10 mg/80 mg q.d.	See individual agents	See individual agents

ApoB, apolipoprotein B; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C,

high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; sc, subcutaneously; TG, triglyceride.

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1. **HMG-CoA reductase inhibitors (statins).** Statins inhibit de novo cholesterol synthesis, leading to upregulation of LDL receptors and increased uptake of circulating LDL particles. All guidelines recommend statins as first-line agents for cardiovascular risk reduction, because they are the *most proven and effective LDL-C-lowering agents available* (up to 55% to 60% reduction with the highest-intensity choices), and are extensively supported by clinical trial evidence for reducing CHD morbidity, mortality, and also total mortality. Hepatic transaminase elevations and myositis are uncommon side effects. If liver transaminases increase to *>3 times the upper limit of normal range (ULN)*, the drug should be discontinued; transaminases will normalize over several weeks with no lasting sequelae; elevations of <3 times the ULN warrant monitoring, but discontinuation is not immediately necessary. **Myalgias**, defined as muscle symptoms *without* creatine kinase (CK) elevations, occur commonly (incidence p. 615p. 616as high as 2% to 5%), but their clinical significance is unclear. **Myositis**, defined as myalgias along with CK elevations *>10 times the ULN*, occurs with a frequency of approximately 0.1%, and requires immediate discontinuation of the statin followed by close monitoring; in most cases, it resolves with no lasting sequelae, but progresses to **rhabdomyolysis** and renal failure if it is left untreated. Asymptomatic and nonspecific CK elevations are highly prevalent in the population, so routine CK screening is not recommended; CK levels should only be measured to confirm or rule out myositis if patients report appropriate symptoms—typically generalized myalgias or weakness with no other identifiable cause (e.g., injury, vigorous exercise, or flu-like illness) occurring days to weeks after starting or intensifying therapy. Other causes of myopathy (e.g., alcohol, thyroid, inflammatory, neurologic, or congenital disorders) should also be

considered. In cases of classic myalgias presenting with *normal* CK levels, clinical judgment should be used to decide if the statin should be discontinued. If symptoms resolve after discontinuation, switching to a different statin or use of alternate-day dosing may not precipitate a recurrence. Caution is also warranted if there is concurrent use of macrolide antibiotics (erythromycin, clarithromycin), imidazole antifungals, cyclosporine, HIV protease inhibitors, or other drugs that share the cytochrome P450 3A4 clearance pathway along with many statins, which **increase the risk of statin toxicity**. Pravastatin, fluvastatin, rosuvastatin, and pitavastatin are least dependent on the 3A4 pathway, but caution should still be exercised. Statins are *pregnancy category X*, *and must not be used without appropriate contraception by women who are still of childbearing potential, or during lactation*. There is also a dose-dependent **association between statin use and incident diabetes mellitus**. Although the basis of this association remains unclear, it is still outweighed by the CHD benefit (per 1 000 patient years of use, one to three new cases of diabetes occur as compared to 5.4 CHD events prevented for every 40 mg/dL reduction of LDL-C), so statins generally should not be withheld from those who would benefit from CHD risk reduction simply due to concerns of precipitating new-onset diabetes.

2. **Fibric acid derivatives (fibrates).** Fibrates increase hepatic TG catabolism and reduce very-low-density lipoprotein (VLDL) production, increase lipolysis, and induce expression of apo-AI. They favorably affect all lipoproteins, although **LDL-C may paradoxically increase in a subset of patients with very high TG levels**. They reduce CHD events, particularly for patients with high TG and low HDL-C levels at baseline. They are *indicated for patients with combined dyslipidemias or severe hypertriglyceridemia*. Side effects of gastrointestinal (GI) intolerance, hepatic transaminase elevations, and myositis are uncommon; like statins, periodic monitoring of transaminases and muscle symptoms is warranted; individual clinical judgment should be used. Caution should be used in patients at risk of cholelithiasis because of increased lithogenicity of bile, and in patients with renal insufficiency in whom fibrate clearance may be impaired (use lower doses if estimated glomerular filtration rate is <60 mL/min/1.73 m^2, and discontinue if <30 mL/min/1.73 m^2).

Adding a fibrate to a statin significantly increases the risk of elevated transaminases and myositis compared to either agent alone, so more frequent monitoring of liver transaminases and myalgias is needed; gemfibrozil interacts with statins more than fenofibrate, so *fenofibrate is the preferred agent if used in combination with a statin*. Despite the additive lipid benefits with combined treatment, the Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid trial failed to show additive CHD protection compared to statins alone.

3. **Nicotinic acid (niacin).** Niacin mainly inhibits hepatic TG synthesis and VLDL production, and also inhibits hepatic catabolism of apo-AI, which increases HDL particle half-life. It favorably affects all lipoproteins, and reduces CHD events in secondary prevention. It is *indicated for patients with combined dyslipidemias or severe hypertriglyceridemia*. Its major side effect is the common, dose-related **flushing** reaction (see Chapter 87); treatment should start at a p. 616p. 617low dose (250 to 500 mg) and gradually titrate up to the therapeutic range. Patients should be advised to take it with food (but avoiding hot liquids or spicy foods), and/or try aspirin (325 mg) prior to the dose to reduce the flush. If the flushing becomes unbearable, rather than discontinuing (as is often done), the dose should be reduced and then retitrated up more slowly; discontinuation would require restarting the titration from the beginning. Uric acid and glucose levels can increase, so **niacin should be used cautiously in gout patients**, **and diabetic patients** may require adjustment of antihyperglycemic agents at the higher niacin doses. Despite the additive lipid benefits of niacin added to statins, both the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides (AIM-HIGH) and Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trials failed to show additive CHD protection compared to statins alone; the latter study also found a *significant increase in bleeding and infections with combined treatment*. Thus, while niacin may still be used as monotherapy, *it should not be added to statins*.
4. **Bile acid sequestrants.** These agents interrupt enterohepatic recirculation of bile acids, leading to reduced intrahepatic free

cholesterol and upregulation of LDL receptors. Older bile acid sequestrants (colestipol, cholestyramine) are powdered resins that must be mixed in water (or juice, to improve palatability), whereas colesevelam is a hydrogel tablet (that should still be taken with a large glass of water). They effectively *lower LDL-C, but an increase in TG may occur* with monotherapy (more so with resins than with colesevelam); *they can also be safely added to statins* to achieve LDL-C goals, although there are no outcome studies showing additive CHD protection with this combination. Dosing is usually started low and titrated upward to minimize GI side effects (constipation, bloating, nausea, flatulence, epigastric pain), but because they are not systemically absorbed, there is no liver transaminase or myositis risk. The resins may also bind and limit the absorption of medications such as L-thyroxine, warfarin, thiazides, propranolol, estrogens, progestins, digitalis, penicillin G, phenobarbital, or potentially any oral medication; pills should be taken at least 1 hour before or up to 4 hours after taking the resin. Colesevelam, however, does not interfere in the same manner.

5. **Cholesterol absorption inhibitors. Ezetimibe** inhibits the Niemann–Pick C1-like 1 protein at the intestinal lumen and interrupts enteric absorption of dietary cholesterol. As monotherapy, it lowers LDL-C less effectively than statins, but its side-effect profile is excellent. It has very limited effects on other lipid fractions. *Ezetimibe may be safely combined with any statin* to provide additive LDL-C lowering. Although several trials of ezetimibe added to statins found minimal or no additive reduction of CHD events, the IMProved Reduction of Outcomes: Vytorin Efficacy International Trail (IMPROVE-IT) found a modest (6%) but significant additive CHD event reduction.
6. **Microsomal triglyceride transfer protein (MTP) inhibitors and anti-apoB oligonucleotides. Lomitapide** interrupts the MTP-mediated lipidation of apoB during VLDL and chylomicron synthesis, thus lowering TG and LDL-C levels. As a result, diarrhea and increased liver transaminases and liver fat may be significant side effects. **Mipomersen** is a subcutaneously injected antisense oligonucleotide that interrupts apoB synthesis. Mild and transient injection site pain and erythema are minor side effects, but flu-like symptoms, and increased liver transaminases and liver fat may also occur. Currently, lomitapide and mipomersen can only

be prescribed for homozygous FH patients under Food and Drug Administration (FDA)'s Risk Evaluation and Mitigation Strategy.

7. **Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Alirocumab** and **evolocumab** are subcutaneously injected monoclonal antibodies directed against PCSK9, a mediator of intracellular LDL receptor degradation; their action thus increases LDL receptor availability. These agents lower LDL-C by 45% to 60% as monotherapy, and may be added to statins to produce dramatic cumulative LDL-C reductions. They are expensive, and are *currently* p. 617p. 618*indicated only for patients with cardiovascular disease who cannot achieve goals with maximally tolerated statin doses, or for heterozygous FH patients needing very-high-intensity LDL-C lowerin*g. They are well tolerated, even when used with statins; only minor, transient injection site reactions occur in some patients. There is also now good evidence that evolocumab significantly reduces ASCVD events in high-risk patients.
8. **Marine omega-3 fatty acids (Fish oils).** Past studies suggested that marine omega-3 fatty acids (eicosapentaenoic acid, EPA, and docosahexaenoic acid, DHA), taken in modest doses (1 to 2 g daily, roughly equivalent to eating 2 to 3 servings of fatty fish per week), reduce CHD events in high-risk patients, through mechanisms other than lipid lowering. However, the more recent Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial in which half of patients were taking statins at baseline failed to show any CHD risk reduction. Thus, in the current statin era, their value for CHD protection is unclear. When taken in *much higher doses (3 to 4 g/day of combined EPA+DHA), they significantly lower TG levels*, mostly by interfering with intrahepatic VLDL production. However, the *CHD benefits of such dosages remain unproven, because LDL-C may paradoxically increase* (attributed to the DHA component; the CHD benefits of an EPA-only preparation are still undefined). However, such doses may be useful in patients with *severe hypertriglyceridemia that is refractory to other TG-lowering therapies*. Over-the-counter (OTC) fish oil preparations are sold as dietary supplements and are not FDA regulated, so their contents, purity, and safety cannot be guaranteed. In contrast, *FDA-approved, prescription-grade omega-*

3 fatty acids are available (Table 44-8), and contain higher concentrations of EPA+DHA per capsule; although they are more costly than OTC preparations, they may be a safer and more preferred option.

C. LDL Apheresis. For very-high-risk patients like those with homozygous FH who have only dysfunctional alleles of the LDL receptor gene, the effect of statins and PCSK9 inhibitors is usually insufficient. In such patients, apheresis performed every 1 to 2 weeks can lower LDL-C by 50% to 60% and reduce CHD events, and should be considered in patients with severe cholesterol elevations who are refractory to all other therapies. The FDA has approved LDL apheresis for FH patients who are functional homozygotes with LDL-C > 500 mg/dL, functional heterozygotes without CHD and LDL-C > 300 mg/dL, or those with CHD and LDL-C > 200 mg/dL.

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45 Hypoglycemia in Adults

Mayer B. Davidson

Hypoglycemia is an abnormality, not a disease. An abnormally low glucose concentration can be caused by a number of factors, such as drugs, tumors, altered gastrointestinal anatomy, or failure of both endocrine and nonendocrine tissues. Hypoglycemia even occurs in association with impaired glucose tolerance, mild type 2 diabetes, and infection, situations that have classically been associated with elevated glucose levels. This chapter describes a practical approach in adults to the often-confusing subject of hypoglycemia.

I. DEFINITION

One major problem is how to define hypoglycemia, that is, what concentration of glucose is abnormally low? An important consideration is whether whole-blood or plasma glucose concentrations are being measured. The glucose concentration in plasma or serum is approximately 12% higher than in whole blood (*not* 12 mg/dL, sometimes written as 12 mg %). Although glucose meters measure concentrations in whole blood, recent models are now all calibrated to report out plasma values. The conditions under which the blood sample is drawn are also important. For instance, a plasma glucose concentration of 54 mg/dL is abnormal after an overnight fast but not 4 hours after an oral challenge with dextrose or a meal rich in simple carbohydrates. I define hypoglycemia by the criteria listed in Table 45-1 because, in my view, these values require clinical considerations whereas higher ones may not.

II. GENERAL APPROACH

The clinical approach to a patient with possible hypoglycemia involves the documentation of a low glucose concentration and systematic efforts to determine what condition is responsible for the low concentration. In making this determination, it is important to ascertain whether hypoglycemia occurs in the fasting or the fed state. Do the symptoms develop when the patient misses breakfast (or other meals), or do they routinely occur after the patient has eaten (especially after ingestion of large amounts of simple carbohydrate)? This distinction is important

because, with a few exceptions, fasting and fed (also termed reactive) hypoglycemia are caused by different conditions. Furthermore, the causes of fasting hypoglycemia are often more serious; consequently, a more diligent workup is usually required than with fed hypoglycemia. Therefore, p. 620p. 621the **distinguishing of fed from fasting hypoglycemia** considerably simplifies the differential diagnosis and alerts the physician to the potential gravity of the situation. So that the pathophysiology of the various types of hypoglycemia can be understood, normal fasting and fed glucose homeostasis are described.

TABLE 45-1 Criteria for Definition of Hypoglycemia

Glucose concentration (mg/dL)	Condition of patient	
	Fasted	Fed[a]
Plasma	<60	<50
Whole blood	<50	<40

[a]After ingestion of dextrose or a meal rich in simple carbohydrates.

III. NORMAL GLUCOSE HOMEOSTASIS

A. Fasting state

1. **Glucose utilization.** During a short fast, only a few tissues require glucose. The most important obligate glucose consumer is the brain, which in a 70-kg person uses approximately 100 g/day. The red blood cells and muscles are the next most avid consumers, utilizing approximately 35 g and 30 g/day, respectively. Most other tissues use predominantly free fatty acids (produced by the hydrolysis of adipose tissue triglycerides) or a small amount of ketone bodies (produced by hepatic catabolism of free fatty acids).
2. **Glucose production.** The liver is responsible for approximately 80% and the kidneys approximately 20% of glucose production during short fasts. Glucose is produced through two separate pathways: glycogenolysis and gluconeogenesis. Only gluconeogenesis operates in the kidneys.
   a. **Glycogenolysis.** It is the breakdown of glycogen, the storage form of glucose. Hepatic glycogen is slowly hydrolyzed and released as glucose to maintain stable levels of plasma glucose

during periods when an individual is not eating. During an overnight fast, approximately 75% of hepatic glucose is produced by glycogenolysis.

b. **Gluconeogenesis.** It is the synthesis of new glucose from noncarbohydrate precursors. There are three major gluconeogenic substrates: **lactate**, derived from glucose metabolism by the peripheral tissues; **amino acids** (especially alanine), released by muscle; and **glycerol**, derived from the breakdown of triglycerides in adipose tissue. Although only 25% of hepatic glucose production derives from gluconeogenesis after an overnight fast, the contribution from glycogen decreases considerably soon thereafter, and gluconeogenesis becomes dominant as the period of fasting lengthens.

3. **Response to fasting.** Because powerful mechanisms defend the plasma glucose concentration (even during a prolonged fast), the obligate glucose consumers can continue to function normally. The glucose level decreases initially by 15 to 20 mg/dL during the first several days and then usually stabilizes. However, in some normal-weight individuals (especially females), glucose concentrations may fall to values as low as 35 to 40 mg/dL without the development of symptoms of hypoglycemia. **Insulin concentrations uniformly fall to low levels and remain there.** Therefore, with regard to the workup of a patient with fasting hypoglycemia, the important point is that glucose concentrations decrease modestly in association with a profound drop in insulin levels during total starvation.

B. Fed state. A normal diet includes both simple (monosaccharide and disaccharide) and complex (polysaccharide) carbohydrates. There is little difference in the rate of appearance of glucose in the circulation derived from simple and complex carbohydrates as long as they are ingested with a meal rather than singly. The rising concentration of glucose in the bloodstream stimulates the β cells of the pancreas to release insulin into the portal vein. The newly secreted insulin first traverses the liver, where approximately 50% is degraded on each passage. The remainder escapes into the general circulation, where the hormone binds to specific receptors in the three insulin-sensitive tissues—liver, muscle, and adipose tissue. Approximately 10% of dietary carbohydrate is stored directly as hepatic glycogen. Another

10% to 15% is eventually stored in the liver but only after being converted to gluconeogenic precursors in the peripheral tissues, returning to the liver, and being converted to glucose via gluconeogenesis.

Postprandial changes in concentrations of glucose and insulin are shown in Figure 45-1. The normal pattern is one of peak values of both glucose and insulin at 1 hour with a return to baseline by 3 to 4 hours. Note the markedly higher insulin response and modestly elevated glucose concentrations in obese as opposed to lean subjects. However, a **peak value of insulin at 1 hour characterizes both groups**.

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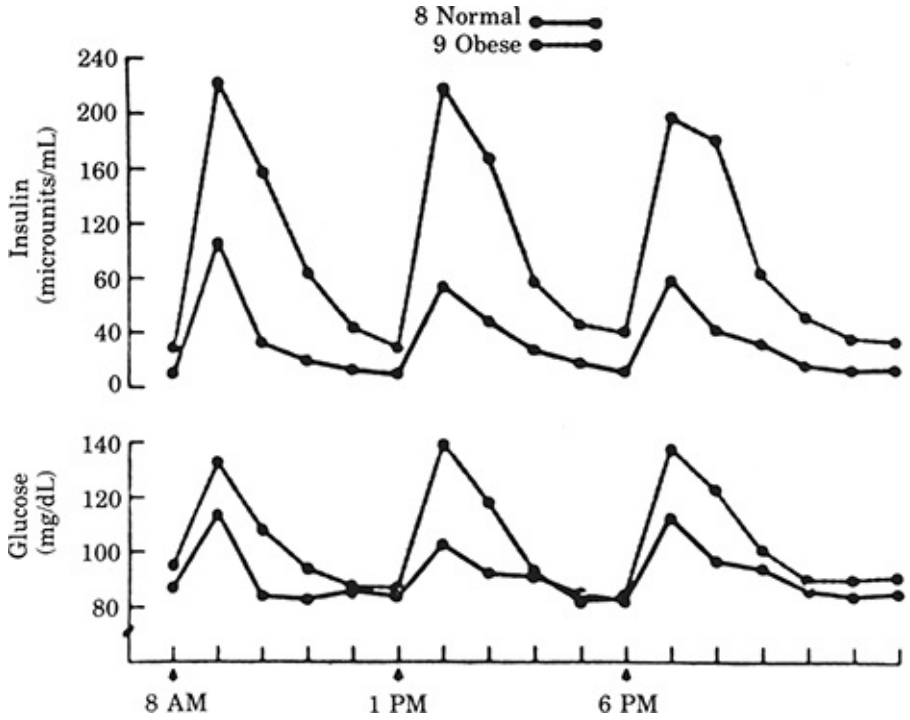

Figure 45-1. Concentrations of glucose and insulin throughout a 16-hour period in subjects who had normal carbohydrate tolerance and ate three identical meals. (Reproduced with permission from Genuth SM. Plasma insulin and glucose profiles in normal, obese, and diabetic persons. *Ann Intern Med* 1973;79:812.)

IV. HORMONAL RESPONSES TO HYPOGLYCEMIA

A. Normal. Glucoreceptors in the hypothalamus initiate certain hormonal responses to low levels of glucose. The released hormones (Table 45-2) stimulate potent metabolic mechanisms that prevent glucose concentrations from dropping to dangerously low levels.

Concentrations of epinephrine, norepinephrine, and glucagon quickly p. 622p. 623increase, whereas those of cortisol and growth hormone increase more slowly. Thus, the response to hypoglycemia is finely orchestrated (Table 45-2). Antihypoglycemic factors start to exert their effects almost immediately after hypothalamic recognition of low glucose concentrations and continue to operate until 8 to 12 hours later.

TABLE 45-2 Hormonal Responses to Hypoglycemia

Hormone	Onset of Secretion	Onset of Action	Effects
Epinephrine, norepinephrine	Rapid	Rapid	Inhibits glucose utilization by muscle; increases hepatic gluconeogenesis; stimulates glucagon secretion; inhibits insulin secretion; stimulates hepatic glycogenolysis[a]
Glucagon	Rapid	Rapid	Increases hepatic glycogenolysis; increases hepatic gluconeogenesis
Cortisol	Delayed	Delayed	Increases hepatic gluconeogenesis; inhibits glucose utilization by muscle
Growth hormone	Delayed	Delayed	Inhibits glucose utilization by muscle; increases hepatic gluconeogenesis

[a]Norepinephrine only.

B. Type 1 diabetes. Shortly after the onset of type 1 diabetes (1 to 5 years), the glucagon response to hypoglycemia decreases and eventually may be lost. Later (>10 years), the epinephrine response also becomes attenuated, even in patients without clinical evidence of autonomic neuropathy. Although the other hormonal responses remain nearly normal, these patients sometimes lose the ability to recognize the autonomic symptoms of hypoglycemia (see hypoglycemia unawareness in Section V) and are at increased risk for severe hypoglycemia (defined as assistance needed by another person for treatment) during intensive insulin therapy (see Chapter 53).

C. Type 2 diabetes. Hormonal responses to hypoglycemia remain mostly normal in type 2 diabetes, although after many years, when insulin secretion is markedly attenuated, glucagon concentrations are lower than normal. However, hypoglycemia unawareness is unusual in

patients with type 2 diabetes, probably because the catecholamine response is maintained.

V. SIGNS AND SYMPTOMS

The signs and symptoms of hypoglycemia (Table 45-3) fall into two categories: **neurogenic** (those caused by increased activity of the autonomic nervous system) and **neuroglucopenic** (those caused by depressed activity of the central nervous system). In normal individuals, the counterregulatory hormones begin to be released and the autonomic nervous system discharged when the plasma glucose level declines to approximately 70 mg/dL (Fig. 45-2). If the initial response does not restore euglycemia, the magnitude of the catecholamines and acetylcholine (the latter not shown in Fig. 45-2) released usually produces the autonomic symptoms at a glucose level of approximately 55 mg/dL. Neuroglucopenic symptoms usually start at approximately 50 mg/dL. These relationships between the counterregulatory hormones and autonomic nervous system responses, glucose concentrations, and signs and symptoms of hypoglycemia may not hold in diabetic patients.

As discussed earlier, patients with type 1 diabetes may have **hypoglycemia unawareness**, one cause of which is impaired glucagon, epinephrine, and autonomic nervous system responses. They experience the neuroglucopenic symptoms but not the autonomic ones. In addition, the brain seems to accommodate to the prevailing glucose concentrations. Therefore, diabetic patients (type 1 or type 2) with marked chronic p. 623p. 624p. 624p. 625hyperglycemia may experience the autonomic (but not the neuroglucopenic) signs and symptoms at glucose levels that are not hypoglycemic but are much lower than the patient is usually at (e.g., 120 to 150 mg/dL). Readjustment to the brain's perception that these levels are not low may take several weeks. On the other hand, hypoglycemic unawareness can occur in tightly controlled diabetic patients (type 1 or type 2) whose prevailing glucose concentrations are usually normal and necessarily associated with many low values. These individuals might not experience any signs and symptoms of hypoglycemia until much lower glucose concentrations are reached (e.g., 40 to 50 mg/dL). This decreased sensitivity to hypoglycemia is associated with a lowered threshold for counterregulatory hormone release and autonomic nervous system activation (i.e., these do not start to occur until glucose levels reach

approximately 50 mg/dL). Because chronic hypoglycemia from any cause is associated with this decreased sensitivity, patients with β-cell tumors (insulinoma) (see Section VI.G) often experience no symptoms until their glucose levels reach a very low point.

TABLE 45-3 Signs and Symptoms of Hypoglycemia

Neurogenic[a]	Neuroglucopenic[b]
Weakness	Headache
Sweating	Hypothermia
Tachycardia	Visual disturbances
Palpitations	Mental dullness
Tremor	Confusion
Nervousness	Amnesia
Irritability	Seizures
Tingling of mouth and fingers	Coma
Hunger	
Nausea[c]	
Vomiting[c]	

[a]Caused by increased activity of the autonomic nervous system.
[b]Caused by decreased activity of the central nervous system.
[c]Unusual.

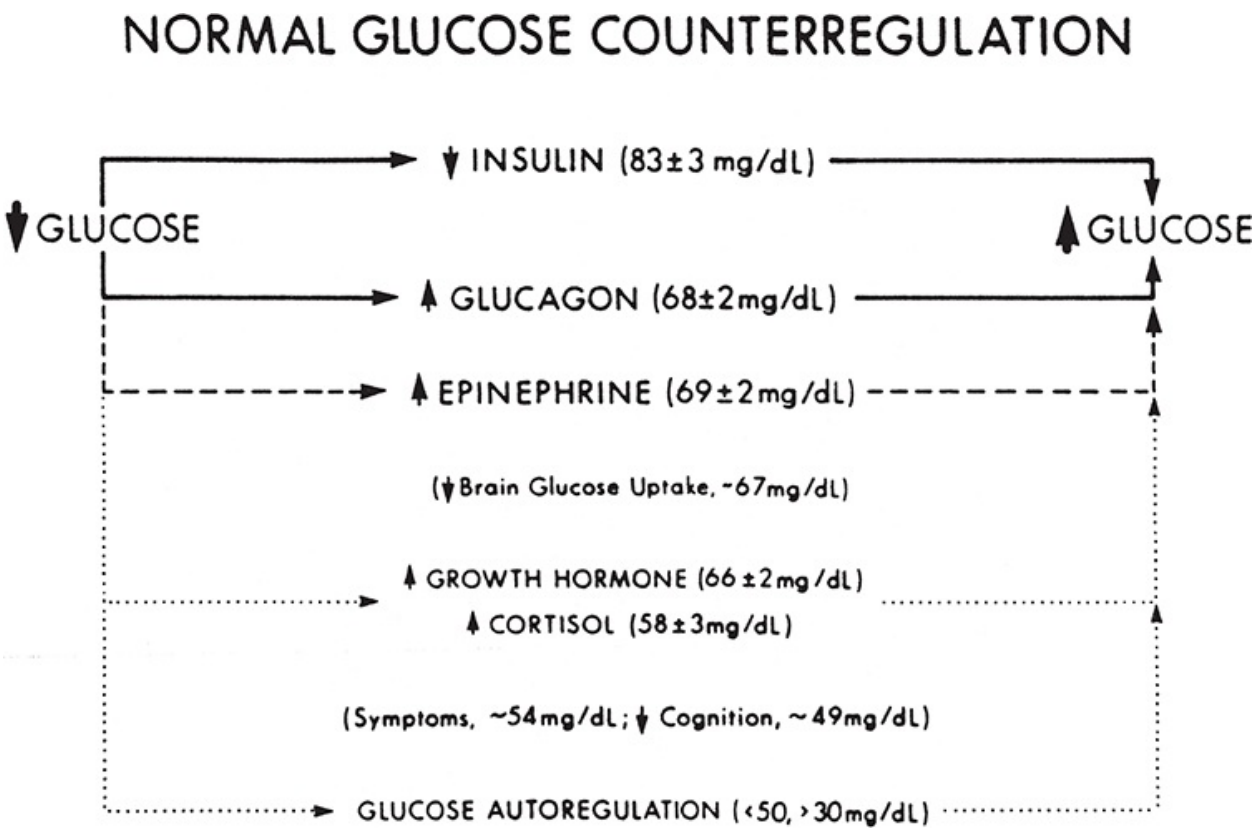

Figure 45-2. Normal glucose counterregulation. (Adapted from Cryer PE. Glucose counterregulation: the prevention and correction of hypoglycemia in humans. *Am J Physiol* 1993;264:E149.)

The other two causes of hypoglycemia unawareness (in addition to loss of glucagon and epinephrine responses in type 1 diabetes and maintaining below-normal glucose concentrations) are **antecedent hypoglycemia** and **autonomic neuropathy**. An episode of hypoglycemia the day before impairs the counterregulatory response to current hypoglycemia in both normal subjects and diabetic patients. Clinically, hypoglycemia unawareness occurs in type 1 diabetes patients who have frequent episodes of hypoglycemia and/or maintain below-normal glucose concentrations. Avoidance of hypoglycemia and/or maintenance of glucose concentrations in the normal or slightly elevated range often reverses hypoglycemia unawareness (see Chapter 53).

Autonomic neuropathy is an uncommon cause of hypoglycemia unawareness. As stated earlier, hypoglycemia unawareness is rarely a problem for type 2 diabetic patients. Finally, although the signs and symptoms of hypoglycemia vary widely among subjects, the pattern in an individual patient tends to be similar during each episode.

VI. FASTING HYPOGLYCEMIA

A. General principles.

Because the onset of fasting hypoglycemia is often gradual, the autonomic component of the signs and symptoms is minimal or absent in many cases. Fasting hypoglycemia is usually persistent and requires glucose administration for reversal. The **differential diagnosis** of hypoglycemia in adults is described in Table 45-4. Although hypoglycemia can occur both in the fasting state *and* after meals in three situations (adrenal insufficiency, with insulinomas, and in the presence of p. 625p. 626autoantibodies to insulin), the fasting component predominates. All of the other factors and conditions listed in Table 45-4 cause *either* fasting *or* postprandial hypoglycemia. This fact underscores the importance of determining whether the signs and symptoms occur in the fasted state or after a meal in a patient with suspected hypoglycemia.

TABLE 45-4 Differential Diagnosis of Hypoglycemia in Adults

Fasting	Fed (reactive)
Drugs[a]	Hyperalimentation
Ethanol	Impaired glucose tolerance/mild type 2 diabetes mellitus
Non–β-cell tumors	Idiopathic reactive
Hepatic failure	NIPHS[b]
Adrenal insufficiency	Adrenal insufficiency[c]
β-Cell tumors (insulinomas)	β-Cell tumors (insulinomas)[c]
Renal failure	Insulin autoantibodies[d]
Insulin autoantibodies	
Insulin-receptor autoantibodies	
Sepsis	

[a]Includes factitious hypoglycemia.
[b]Noninsulinoma pancreatogenous hypoglycemia syndrome—occurs mostly following gastric bypass surgery but can occur spontaneously.
[c]Although fed hypoglycemia occasionally occurs, fasting hypoglycemia predominates.
[d]Experience is too limited to determine which form of hypoglycemia predominates.

B. Drugs

1. **Specific drugs.** Insulin is obviously the most common drug causing hypoglycemia, and sulfonylurea agents are the next most common followed by the glinides (Prandin and Starlix). Although seldom used today, the first-generation sulfonylureas (tolbutamide, chlorpropamide, acetohexamide, tolazamide) are bound to serum albumin. This allows several other medications to potentiate the hypoglycemic effect of the first-generation sulfonylurea agents by competing for their binding sites on albumin, thus increasing the free component. These include the sulfonamide antibiotics, chloramphenicol, bishydroxycoumarin, phenylbutazone, oxyphenbutazone, clofibrate, and clarithromycin. The second-generation sulfonylureas (glyburide, glipizide, glimepiride) do not bind to albumin and are not subject to this potential interaction. Of the second-generation sulfonylureas, hypoglycemia is most common with glyburide. Other antihyperglycemic diabetic medications may increase hypoglycemia if taken along with insulin, sulfonylureas or glinides, but if used alone or with each other should not cause hypoglycemia.
2. **Salicylates and intravenous (IV) (but not inhaled) pentamidine** are the next most common drugs causing hypoglycemia when taken alone. Other drugs that occasionally cause hypoglycemia are angiotensin-converting enzyme inhibitors (ACE-I), β-blockers, monoamine oxidase inhibitors (only the hydrazine derivatives), oxytetracycline, disopyramide, quinine, chloroquine, and fluoroquinolones (especially gatifloxin). There are a number of isolated case reports of hypoglycemia secondary to various drugs acting either alone or in the presence of sulfonylurea agents or insulin, but often the circumstances do not support a bona fide cause-and-effect relationship, and usually there are no confirming reports.
3. **Treatment.** With the exception of insulin-induced hypoglycemia, the treatment (by IV glucose) of hypoglycemia caused by other drugs should not be discontinued too soon. Hypoglycemia relapse can be difficult to prevent with oral carbohydrate ingestion, especially if the inciting drug was a sulfonylurea agent. Patients with sulfonylurea-induced hypoglycemia and altered mental status should be admitted to the hospital because **hypoglycemia can recur for days**. Because IV glucose continues to stimulate insulin secretion in this situation, treatment with **octreotide** (the

long-acting form of somatostatin) or oral **diazoxide** can be helpful. **Factitious hypoglycemia** is an unusual form of drug-induced hypoglycemia in which emotionally disturbed patients surreptitiously take insulin or, occasionally, sulfonylurea agents. They are usually women in health-related occupations or female relatives of diabetic patients with access to these drugs. Because commercial insulin preparations do not contain connecting peptide (C-peptide), the diagnosis of hypoglycemia induced by **exogenously** administered insulin is made by finding low **concentrations of C-peptide** in association with low levels of glucose and high concentrations of insulin (Table 45-5). In patients harboring insulinomas with hypoglycemia induced by **endogenous** insulin, C-peptide levels are high p. 626p. 627because equimolar amounts of insulin and C-peptide are secreted by functioning pancreatic β cells. Because surreptitious ingestion of sulfonylurea agents also results in hypoglycemia associated with high levels of both insulin and C-peptide, measurement of these compounds or their degradation products in serum or urine is necessary to help diagnose this cause of factitious hypoglycemia. A high index of suspicion is necessary in these cases.

TABLE 45-5 Distinguishing among Patients with Insulinomas and Factitious Administration of Insulin or Sulfonylurea Agents

Condition	Glucose	Insulin	C-Peptide	Proinsulin
Insulinoma	Low	High	High	High
Insulin[a]	Low	High	Low	Normal
Sulfonylurea[a]	Low	High	High	Normal

[a]Factitious administration.

C. Ethanol. Ethanol ingestion is a common cause of hypoglycemia. In addition, many drug-induced cases of hypoglycemia occur in association with ethanol intake.

1. **Pathogenesis.** The metabolism of ethanol in the liver inhibits gluconeogenesis. Thus, ethanol-induced hypoglycemia is seen

when glycogen stores are no longer capable of sustaining glucose concentrations and gluconeogenesis is necessary. This obviously occurs in a setting of restricted food intake. This condition often takes place in malnourished chronic alcoholics but may also develop in heavy weekend drinkers or even in social drinkers who miss meals. It should be stressed that ethanol decreases glucose concentrations in patients with normal liver function. Children are particularly sensitive to this effect of alcohol.

2. **Clinical setting.** Clinically, the neuroglucopenic signs and symptoms predominate in alcohol-induced hypoglycemia. The autonomic response is inhibited by ethanol and is often diminished or absent. Because glucose utilization is not increased, glucose concentrations decrease gradually, which may contribute to a diminished autonomic response.
3. **Treatment.** Prompt diagnosis and treatment are important. Failure to recognize this syndrome may be responsible for the **high-associated mortality** (approximately 25% in children and approximately 10% in adults). **Glucagon therapy is usually not effective because glycogen stores are already depleted**. In contrast to drug-induced hypoglycemia, alcohol-induced hypoglycemia may not require long-term continuous IV administration of glucose after the initial response to such therapy. Relapses can usually be prevented by the ingestion of modest amounts of carbohydrate.

D. Non–*β*-cell tumors. Many non–*β*-cell tumors can cause hypoglycemia. The types and relative frequency are listed in Table 45-6.

1. **Pathogenesis.** Only in very rare instances can production of insulin be proven. Excess glucose consumption by the large mesenchymal tumors is not responsible. Non–*β*-cell tumors secrete incompletely processed **insulin-like growth factor type II** (IGF-II). Normally, IGF-II is synthesized in the liver and released into the circulation. In the serum, normal IGF-II is complexed to a heterotrimeric 150-kDa IGF-binding protein (IGFBP), which consists of IGF-I, IGF-II, an acid-labile protein, and the IGFBP. This renders IGF-II not very biologically active. Incompletely processed IGF-II is larger than normal IGF-II (specialized assays can measure “big” IGF-II) and is sequestered into a smaller binary complex with IGFBP-3, which increases its bioavailability. Thus,

although IGF-II levels are normal or only slightly elevated, there is more free IGF-II to bind to insulin receptors, which is the mechanism by which hypoglycemia is thought to occur. These levels of active IGF-II inhibit growth-hormone secretion, which not only p. 627p. 628limits the response to hypoglycemia but also causes low IGF-I levels, another growth factor synthesized in the liver. However, a patient has been described with metastatic large-cell carcinoma of the lung that secreted IGF-I, not IGF-II.

TABLE 45-6 Non–β-Cell Tumors Associated with Hypoglycemia

1. Large mesenchymal tumors (~50%)—mesotheliomas, fibrosarcomas, neurofibromas, neurofibrosarcomas, spindle-cell sarcomas, leiomyosarcomas, rhabdomyosarcomas
2. Hepatocellular carcinomas (hepatomas) (approximately 25%)
3. Adrenal carcinomas (5%–10%)
4. Gastrointestinal tumors (5%–10%)
5. Lymphomas (5%–10%)
6. Miscellaneous tumors (occasional)—most common: kidney, lung, anaplastic carcinomas, carcinoid

2. **Differential diagnosis.** The diagnosis of tumor hypoglycemia can be difficult if hypoglycemia is the initial manifestation of the neoplasm. The differential diagnosis usually includes only β-cell tumors, adrenal insufficiency, and factitious hypoglycemia because the other causes of fasting hypoglycemia (Table 45-4) are easily ruled out. Differentiation from β-cell tumors and factitious hypoglycemia requires a fast (usually only a short fast can be tolerated) with concomitant monitoring of glucose and insulin concentrations. Evaluation of the pituitary–adrenal axis is also simple and is described later. However, in many instances, the tumor is already known to be present. This is usually the case with large mesenchymal tumors and often with many other types because hypoglycemia is a relatively late manifestation. High or high-normal IGF-II levels and low or low-normal IGF-I levels are often seen in these patients. Since a **low IGF-I** level usually characterizes these patients, an elevated IGF-II to IGF-I ratio is very helpful in making the diagnosis of a non–β-cell tumor

producing big IGF-II.

Adrenal carcinomas deserve special mention from a diagnostic standpoint. Although they are rare, they are commonly represented among neoplasms associated with hypoglycemia. In endocrine testing, many of these patients have increased serum dehydroepiandrosterone sulfate (DHEAS) concentrations. Therefore, adrenal carcinoma should be suspected in a patient with fasting **hypoglycemia** and elevated serum **DHEAS** concentrations.

3. **Treatment.** The treatment of patients with tumor hypoglycemia is often difficult. If large amounts of the tumor (especially large mesenchymal tumors) can be surgically removed, long-term remissions from hypoglycemia are likely. Effective radiotherapy or chemotherapy may also increase glucose concentrations. However, in many cases, therapy directed at the tumor is not successful and specific treatment for hypoglycemia is necessary. Frequent feedings are the obvious first choice but are often not effective. Continuous IV administration of glucose is not practical for any length of time. Administration of glucocorticoids is sometimes helpful because they stimulate hepatic gluconeogenesis and to some extent inhibit peripheral glucose utilization. The initial dose should be the equivalent of 15 to 20 mg of prednisone, with fairly rapid increases if no effect is detectable. Although there are few published accounts of experience with this form of treatment for tumor hypoglycemia, if a dose equivalent to 60 to 80 mg of prednisone is reached and no effect is noted, the dose should probably be tapered off rapidly to avoid adrenal suppression and dependence on exogenous glucocorticoid. If the patient is given glucocorticoid therapy for less than a month, the hypothalamic–pituitary–adrenal axis usually returns to normal.

E. Hepatic failure. If someone has hepatic failure, death is common, but associated hypoglycemia is distinctly unusual. This is because the liver has a tremendous capacity to produce glucose, and hypoglycemia ensues only when the liver is severely compromised. The diagnosis is obvious because the patient has all the clinical and laboratory stigmata of hepatic failure. Although treatment is simple (i.e., support of the glucose concentration with IV dextrose until the liver regenerates the capacity to maintain appropriate levels itself), hypoglycemia in this situation is a serious prognostic sign indicating that there is little

functioning hepatic tissue left. Indeed, the capacity of the liver to produce glucose may be restored, but the patient still succumbs to the other complications of hepatic failure.

F. Adrenal insufficiency

1. **Pathogenesis.** The mechanism whereby either primary or secondary adrenal insufficiency leads to fasting hypoglycemia is straightforward. **Cortisol** is necessary to support gluconeogenesis; in its absence, hepatic glucose production is significantly impaired. Although a deficiency of growth hormone sometimes causes hypoglycemia in children, the absence of this hormone in adults is not associated with hypoglycemia. Patients with pituitary destruction who are receiving adequate replacement doses of glucocorticoids do not experience difficulties maintaining normal glucose concentrations.

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2. The **diagnosis** of adrenal insufficiency usually is also straightforward once it is considered. There are at least three stimulation tests with blood sampling. None of these tests differentiates between primary and secondary adrenal insufficiency, which must be distinguished by other means (see Chapter 24).
   a. **Cortrosyn stimulation test.** This test can be done routinely. Alternatively, if treatment with glucocorticoids is deemed imperative, the **Cortrosyn** (the 1 to 24 amino acid sequence of adrenocorticotropic hormone [ACTH]; cosyntropin) **stimulation test** should be performed before administration of the steroid. This is important because a reliable assessment of the pituitary–adrenal axis is extremely difficult after treatment is begun. The test, which can be completed within 1 hour, involves intravenous or intramuscular injection of 0.25 mg of Cortrosyn; blood samples for measurement of plasma cortisol levels are obtained before injection as well as 30 and/or 60 minutes afterward. A normal response is classically defined as a baseline value of at least 5 μg/dL *and* an increase of greater than 7 μg/dL *and* a maximal level of greater than 18 μg/dL. Some endocrinologists feel that any increase of greater than 10 μg/dL constitutes a normal response regardless of baseline and maximal levels. However, in some patients, plasma cortisol

levels may increase by less than 7 μg/dL over a relatively high baseline value. Therefore, if any value is greater than 20 μg/dL, adrenal insufficiency is essentially ruled out.

An abnormal Cortrosyn stimulation test in secondary adrenal insufficiency depends on atrophy of the adrenal cortex because of a normal lack of stimulation by ACTH. The test can be normal in 10% to 15% of patients with secondary adrenal insufficiency, especially if it is carried out soon after pituitary insufficiency occurs. The Cortrosyn stimulation test is the test of choice if primary adrenal insufficiency is suspected.

A low-dose (1-μg) Cortrosyn stimulation test is sometimes used to identify mild adrenal insufficiency, but because hypoglycemia is very unlikely to be part of this picture, the low-dose test is not helpful in this situation.

b. The **insulin tolerance test** is considered the "gold standard" for the diagnosis of adrenal insufficiency. However, it is very labor-intensive (in many institutions, physician presence is required throughout the test), unpleasant for patients, occasionally dangerous, and sometimes must be repeated. Contraindications to the test are a fasting serum cortisol of less than 5 μg/dL (already suggestive of adrenal insufficiency), a seizure disorder, altered mental status, and ischemic heart disease. Symptoms of hypoglycemia should be explained to the patient before the test, and a "crash cart" should be available. After an overnight fast, a baseline sample is drawn and 0.15 U/kg of insulin is given as an intravenous bolus. Blood samples are taken 30 and 60 minutes later. Blood glucose monitoring at the bedside should be performed on each of these samples to determine if adequate hypoglycemia (<40 mg/dL) has been achieved. If adequate hypoglycemia has not been achieved, the dose of insulin is repeated with timings of the subsequent samples 30 and 60 minutes later. A peak cortisol concentration of more than 18 μg/dL indicates adequate hypothalamic–pituitary–adrenal function. A meal should be given at the conclusion of the test. If adrenal insufficiency is strongly suspected, the initial dose of insulin should be 0.1 U/kg. Because most patients have moderate-to-marked symptoms of hypoglycemia during the test and because of the potential dangers of the test, I rarely use it.

c. **Metyrapone stimulation test.** Metyrapone (Metopirone) blocks 11-hydroxylation in the adrenal cortex, which is the final step in the synthesis of cortisol (compound F). The release of ACTH is not inhibited by its immediate precursor, 11-deoxycortisol (compound S). Therefore, the brain senses a low cortisol level and secretes more ACTH, which stimulates the adrenal cortex to synthesize more compound S. Compound S can be measured separately in the plasma, and its accumulation signals a normal pituitary–adrenal response to metyrapone.

Metyrapone (0.25-mg tablets) is given by mouth at about 11 P.M., and a plasma sample is collected at 8 A.M. the next day. For patients who weigh p. 629p. 630more than 50 kg, the dose is 3.0 g; for those who weigh less than 50 kg, the dose is 2.0 g. A normal response consists of a concentration of compound S of greater than 7 to 8 μg/dL (regardless of the concomitant compound F value). A valid abnormal response of less than 7 to 8 μg/dL **requires** that the cortisol level be less than 5 μg/dL. This latter value proves that the 11-hydroxylation step was adequately blocked and therefore the patient was unable to mount a satisfactory compound-S response. A concentration of compound S that is below normal in the presence of a compound F level of greater than 5 μg/dL signifies that the blockade was not complete. In this instance, either the test must be repeated (with a higher dose of metyrapone if a 2-g dose was used) or an alternative diagnostic approach used.

Some patients may experience nausea and occasionally vomiting secondary to metyrapone administration. These symptoms are recognized adverse reactions to the drug and do not represent acute adrenal insufficiency, which, although theoretically possible, has not, to my knowledge, been reported under these circumstances.

3. The **management** of the hypoglycemia associated with adrenal insufficiency is straightforward. In addition to the bolus of IV glucose, the patient should be given 100 mg of cortisol over an 8-hour period and started on maintenance doses thereafter.

G. β-Cell tumors

1. **Clinical findings.** Although **insulinomas** are rare tumors, the

correct diagnosis is extremely important. Not only are they usually curable, patients who remain undiagnosed for long periods may develop permanent neuropsychiatric sequelae. Because the glucose level usually drifts down slowly in affected patients, autonomic signs and symptoms (Table 45-3) are often lacking, and the presence of hypoglycemia may not be evident. Patients with insulinomas tend to present with the more confusing neuroglucopenic signs and symptoms, which can include visual difficulties, transient neurologic syndromes, mental confusion, convulsions, and personality changes. Weight gain is common in these patients because chronic hyperinsulinemia and hypoglycemia lead to excessive caloric intake and fat deposition.

2. **Diagnosis** of a β-cell tumor is usually not difficult once it is considered. The cardinal rule in the evaluation of glandular function is to stimulate the gland if hypofunction is suspected and to suppress it if hyperfunction is suspected.
   - **a.** The most physiologic way to suppress insulin secretion is by **fasting.** Characteristic changes in the relationship between glucose and insulin concentrations during total caloric deprivation are the most reliable diagnostic criteria for insulinomas and are found in almost every patient who is tested appropriately. In normal subjects, levels of both glucose and insulin fall during starvation. In some women, as mentioned previously, plasma glucose concentrations can decrease asymptomatically to values as low as 30 to 35 mg/dL after 24 to 72 hours without food. However, insulin levels usually fall proportionally more, so that the insulin/glucose (I/G) ratio decreases (Fig. 45-3). In patients with insulinomas, insulin concentrations are either not suppressed or increased somewhat during fasting, so that I/G increases.

     Therefore, the most reliable way to diagnose a β-cell tumor is simply to extend the overnight fast until the patient becomes symptomatic. Blood samples for glucose and insulin determinations are drawn after the overnight fast and then glucose concentrations every 2 to 4 hours after that. If the history reveals that the patient must get up and eat overnight to avoid hypoglycemia, the fast must necessarily start in the morning when the patient is under medical supervision. Glucose levels can be measured from a fingerstick sample. A separate

sample of blood should also be collected for insulin and plasma glucose if fingerstick values decrease to ≤50 mg/dL (or when symptoms of hypoglycemia occur). The test should be extended until symptoms of hypoglycemia preclude continuing. Approximately two thirds of patients will experience hypoglycemic symptoms within the first 24 hours of food deprivation. Another one fourth or so will become symptomatic during the second 24 hours of starvation. A third p. 630p. 631day of fasting is required in only approximately 5% of patients who harbor insulinomas. I/G ratios (μU/mL/:mg/dL) above 0.3 are abnormal and make the diagnosis, assuming that factitious hypoglycemia is excluded (see Table 45-5).

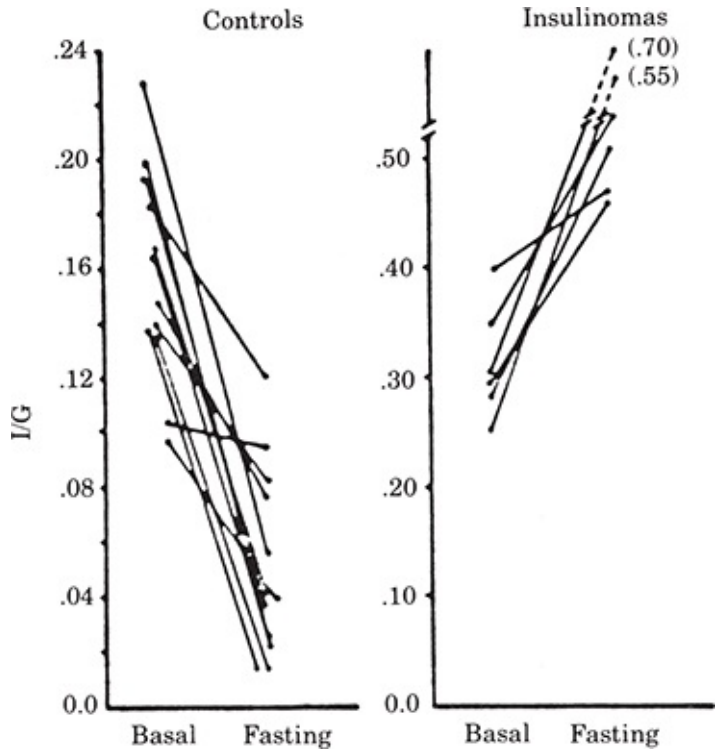

Figure 45-3. Plasma insulin (μU/mL)-to-glucose (mg/dL) ratios (I/G) at the beginning of a fast (basal) and at the nadir of the glucose concentration. (From Merimee TJ, Tyson JE. Hypoglycemia in man: pathologic and physiologic variants. *Diabetes* 1977;26:161. Reproduced with permission from the American Diabetes Association, Inc.)

b. Stimulatory tests with tolbutamide, glucagon, calcium (IV),

or leucine produce too many false negatives and false positives to be relied on. An oral glucose tolerance test is worthless in making the diagnosis of an insulinoma because it may be normal, flat (which occurs in 20% of the normal population), or show impaired glucose tolerance.

c. Measurement of the **proinsulin content** of the fasting plasma is very helpful. Normally, proinsulin (which is measured along with insulin in the older radioimmunoassays) is less than 20% of the total immunoassayable insulin. In the large majority of patients with insulinomas, proinsulin constitutes more than 20% of total immunoassayable insulin. Current assays can measure proinsulin directly. When these assays are used, almost all patients with insulinomas have elevated levels of proinsulin. An end of fast value of ≥27 pmol/L had a 100% sensitivity and specificity in an National Institutes of Health (NIH) series. Two patients have been described whose tumors produced proinsulin, not insulin. The diagnosis was made using an older assay for insulin that cross-reacted with proinsulin; insulin levels measured by a newer assay specific for insulin did not support the diagnosis of a β-cell tumor during the fast. Very high levels of proinsulin alerted the physicians to the diagnosis, emphasizing the importance of measuring this prohormone in the workup for a β-cell tumor.

d. Finally, in the extremely rare situation in which an insulinoma develops in an insulin-requiring type 2 diabetes patient, the secretion of endogenous insulin can be monitored by measurement of the levels of **C-peptide** because, as mentioned above, this polypeptide is not contained in commercial insulin preparations.

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e. The Endocrine Society's criteria for the diagnosis of an insulinoma are that in a patient with **Whipple's triad** (signs and/or symptoms of hypoglycemia associated with a low glucose with relief by raising the glucose concentration), end of fast values for glucose should be <55 mg/dL, insulin ≥3 μU/mL, proinsulin ≥5 pmol/L, and C-peptide >0.6 ng/mL. Indeed, these are very sensitive criteria which will be seen in 98% to 100% of patients harboring an insulinoma. However, there will be a

number of false positives simply using these values, for example, 40%, 59%, and 90% with the insulin, proinsulin, and C-peptide criteria, respectively, underscoring the importance of documenting Whipple's triad in patients being evaluated.

3. **Preoperative localization** of a diagnosed insulinoma is extremely helpful to the surgeon because of the small size of this type of lesion. **Localization should only be undertaken after the biochemical diagnosis of an insulinoma has been established.** Otherwise, false-positive results will lead to unnecessary surgery (up to 10% of people have nonfunctioning pancreatic adenomas at autopsy). On the other hand, patients with a biochemical diagnosis should undergo surgery even if the tumor has not been found by localization procedures. Pancreatic arteriography correctly identifies a β-cell tumor in only approximately half of the cases. Other methods of localizing the tumor (abdominal ultrasonography, radionuclide scanning, computed tomography, magnetic resonance imaging) may not be helpful because the tumors are often smaller than 2.0 cm in size. However, computed tomography with contrast has been used with success in the localization of small insulinomas in some patients. The most sensitive methods may be endoscopic ultrasonography or ultrasonography at surgery (i.e., with the pancreas exposed). Selective intra-arterial injections of calcium (0.025 mEq/kg body weight) as a secretagogue with subsequent measurements of insulin concentrations in the right hepatic vein are frequently successful and often used after an unsuccessful previous surgery. A positive response is a doubling or more of insulin concentrations 30 to 60 seconds after the arterial calcium injection. In general, a positive response after injection into the gastroduodenal or superior mesenteric artery helps localize the tumor to the head or uncinate process of the pancreas, respectively. A response after injection into the splenic artery helps localize the tumor to the body or tail of the pancreas. A positive response after injection into the hepatic arteries suggests liver metastases. If pancreatic arteriography is performed, this method of localization adds only a few minutes to the time needed.
4. **Treatment.** If surgery does not cure the patient because of the presence of multiple tumors, hyperplasia, or metastatic spread, drug therapy to block insulin secretion is often helpful. Oral

diazoxide (Proglycem), 100 mg three to four times a day, is used most often, conferring benefit in approximately half of the patients. A few patients will respond to phenytoin (Dilantin), chlorpromazine, propranolol, or verapamil. The drug of choice for metastatic islet cell carcinoma is streptozotocin. Patients whose carcinoma is refractory to streptozotocin, occasionally respond to L-asparaginase, doxorubicin (Adriamycin), or mithramycin.

H. Renal failure. Hypoglycemia accompanying renal failure is being increasingly recognized. Although poor dietary intake has been associated with many of the reported cases, some patients have clearly been well fed. Impairment of gluconeogenesis is probably involved, although a few patients remain hypoglycemic despite the IV administration of large amounts of glucose, suggesting enhanced glucose utilization in these circumstances. When it occurs, hypoglycemia may be a problem for several weeks to months and then spontaneously remit for no apparent reason. Because it tends to be intermittent in those patients in whom it occurs, frequent feedings should be used to prevent it. If that is ineffective, glucocorticoid therapy (15 to 20 mg of prednisone) may be needed, but such therapy should be tapered and eventually discontinued as soon as feasible. There is a clinical impression that hypoglycemia in patients with end-stage renal disease is a poor prognostic sign. Many of these patients die within a year or so, although usually not from hypoglycemia.

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I. Miscellaneous causes

1. **Insulin autoimmune syndrome.** Occasionally, a patient spontaneously develops antibodies to insulin despite never having received insulin injections. The mechanism involved in the hypoglycemia is probably related to the binding of large amounts of endogenous insulin with subsequent release of free insulin at inappropriate times. This unusual cause of hypoglycemia may be part of the autoimmune endocrine syndrome, as evidenced by its occurrence in patients with Graves disease, rheumatoid arthritis, and lupus erythematosus. The majority of cases have been reported in Japanese patients, many of whom had been taking sulfhydryl compounds (e.g., thionamides).
2. **Insulin-receptor autoantibodies.** A rare patient (usually female) has a syndrome of insulin resistance and acanthosis

nigricans associated with certain immunologic features, such as elevated erythrocyte sedimentation rates, high titers of antinuclear and anti-DNA antibodies, hypergammaglobulinemia, and decreased complement levels (see Chapters 2 and 84). Affected patients also have autoantibodies to the insulin receptor (not to the insulin molecule as described above). The presence of these antibodies accounts for insulin resistance in these patients because insulin is unable to exert its action at the critical initial step of binding. A few of these patients manifest recurrent hypoglycemia because the antibody bound to two adjacent receptors is able to exert an insulin-like effect under certain circumstances.

3. **Sepsis.** Hypoglycemia is not considered to be clinically associated with infection. Classically, in fact, insulin resistance and hyperglycemia have been described in conjunction with infection. However, hypoglycemia is occasionally seen in patients with septicemia with both gram-positive and gram-negative organisms.
4. **Falciparum malaria.** Hypoglycemia has been reported in severe falciparum malaria. The mechanism may involve increased glucose utilization by parasitized red blood cells. Although quinine (see Section VI.B.1) may have contributed to it, hypoglycemia was still seen in patients with low or absent quinine levels. Pregnant patients and those with cerebral involvement seem to be particularly prone. However, some feel that hypoglycemia is not a specific complication of cerebral malaria but occurs in severely ill, fasted patients, especially children.

VII. FED (REACTIVE) HYPOGLYCEMIAS

A. General principles.

In contrast to the signs and symptoms of fasting hypoglycemia, those of fed (reactive) hypoglycemia are predominantly **autonomic** (Table 45-3). Their onset is characteristically rapid. The neuroglucopenic component is unusual in reactive hypoglycemia. This type of hypoglycemia is transient and is usually reversed by the normal counterregulatory hormonal responses (Table 45-2). Administration of exogenous glucose will hasten but is usually not needed for abatement of the autonomic signs and symptoms.

The differential diagnosis of fed hypoglycemia is described in Table 45-4. As discussed earlier, two of the six causes listed (adrenal insufficiency and insulinomas) lead to predominantly fasting hypoglycemia. This may also be true for a third cause, the presence of

autoantibodies to insulin, although there are too few reported cases on which to base a firm conclusion. The remaining three diagnoses listed —**hyperalimentation, impaired glucose tolerance/mild type 2 diabetes mellitus,** and **idiopathic reactive hypoglycemia**— must be considered when a patient gives a history suggestive of postprandial hypoglycemia only.

B. Oral glucose tolerance test. The patterns of glucose and insulin concentrations in these three conditions after an oral challenge with dextrose are depicted in Figure 45-4. "Alimentary hyperglycemia" is an older name for what is now called hyperalimentation. "Diabetes" in this figure represents people with impaired glucose tolerance or mild type 2 diabetes; and "**functional hypoglycemia**" has been **renamed idiopathic reactive hypoglycemia**. Each curve in the figure represents data from a different patient. The characteristic pattern for hyperalimentation hypoglycemia consists of very high initial glucose concentrations and relatively early hypoglycemia (after 2 to 3 hours). Both impaired glucose tolerance/mild type 2 diabetes and p. 633p. 634idiopathic reactive hypoglycemia are associated with later hypoglycemia (after 3 to 5 hours). Abnormally high glucose levels in the early part of the oral glucose tolerance test obviously define impaired glucose tolerance and mild type 2 diabetes, whereas normal early concentrations characterize idiopathic reactive hypoglycemia.

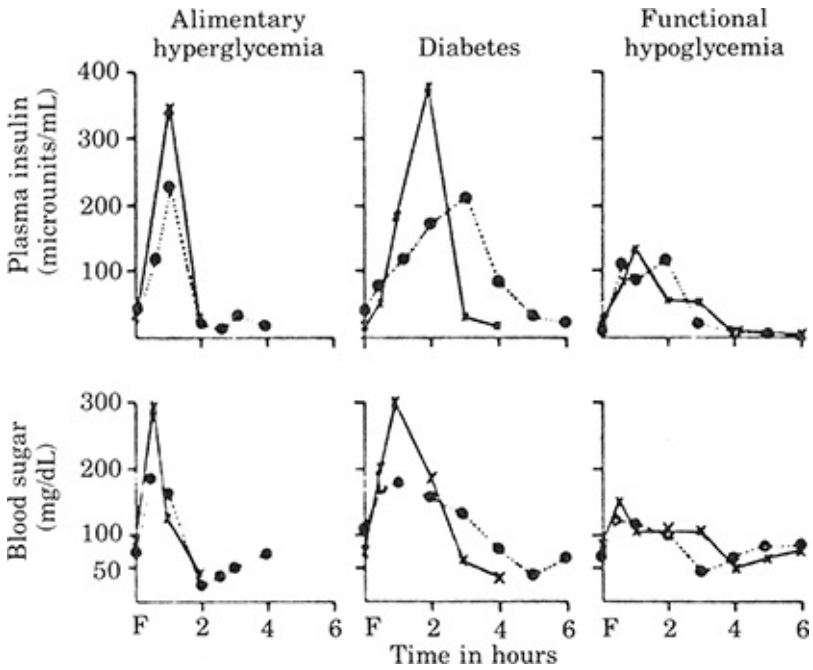

Figure 45-4. Hypoglycemia following an oral glucose load (100 g). Characteristic glucose and insulin concentrations in the three common types of fed (reactive) hypoglycemia. Data from two patients with each condition are shown. (From Yalow RS, Berson SA. Dynamics of insulin secretion in hypoglycemia. *Diabetes* 1965;14:341. Reproduced with permission from the American Diabetes Association, Inc.)

C. Hyperalimentation. The conventional setting for reactive hypoglycemia caused by hyperalimentation is in a patient who has undergone gastric surgery. The normal relationship between the stomach and the small intestine is altered, so that entry of the gastric contents into the duodenum is not delayed by the pyloric sphincter. This rapid entry into the duodenum increases the rate of absorption of glucose from the small intestine into the systemic circulation and accounts for the early hyperglycemia. These high glucose levels trigger an enhanced insulin response (Fig. 45-4), which subsequently causes hypoglycemia. However, rapid gastric emptying may not be the sole explanation. Patients who have undergone antrectomy (removal of the lower part of the stomach) are much less likely to become hypoglycemic despite the fact that food enters the duodenum quickly. This observation suggests a role for one or more of the gastrointestinal hormones that amplify glucose-stimulated insulin secretion. The situation is further complicated by the occasional patient who has all the characteristics of reactive hypoglycemia secondary to hyperalimentation but who has not had gastrointestinal surgery. Thus, reactive hypoglycemia secondary to hyperalimentation probably

represents more than one disorder.

D. Impaired glucose tolerance/mild type 2 diabetes mellitus. The normal response in an oral glucose tolerance test is peak values of both glucose and insulin at 1 hour, just as occurs after a meal (depicted in Fig. 45-1). This normal pattern contrasts with the insulin response in patients with reactive hypoglycemia caused by impaired glucose tolerance/mild type 2 diabetes, as shown in the middle panel of Figure 45-4. In the two patients depicted, insulin concentrations were maximal at 2 hours or later. The conventional explanation for the late hypoglycemia is that high levels of insulin p. 634p. 635several hours after a meal cause glucose concentrations to become abnormally low because the influx of enough glucose from the intestinal tract is not available at this time to buffer the effect of the hormone. Although insulin secretion in patients with impaired glucose tolerance or mild type 2 diabetes and reactive hypoglycemia is delayed in comparison with that in normal subjects, many individuals with abnormal glucose tolerance have delayed insulin responses without late hypoglycemia. Therefore, other unidentified factors may also have a role.

E. Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS). In contrast to the lack of neuroglucopenic symptoms in other causes of reactive hypoglycemia, patients with NIPHS may have these symptoms. Most of these patients will have undergone gastric bypass surgery although NIPHS does occur in a few spontaneously. Some feel that these are two distinct entities because females predominate in those following gastric bypass and males predominate in the spontaneous cases. However, the preponderance in females may reflect the gender imbalance of gastric bypass surgery. NIPHS occurs months to several years after gastric bypass surgery in <1% of patients undergoing this procedure. Postprandial hypoglycemia occurring 1.5 to 4 hours after eating is characterized by elevated levels of insulin, C-peptide and the incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Imaging studies for an insulinoma are negative, and the calcium arterial stimulation test is positive but also without localization. If a low carbohydrate diet is not effective, pharmacologic treatment with an alpha-glucosidase

inhibitor, octreotide, diazoxide, or a nondihydropyridine calcium-channel blocker may be effective. If these therapies are not effective, surgery (either a revision of the bypass or a partial pancreatectomy) has been successful. Pancreatic tissue obtained at the time of surgery has revealed beta cell hypertrophy and, in some cases, nesidioblastosis. A prevailing, but controversial, theory is that the increased incretins stimulate growth of the beta cells which causes NIPHS.

F. Idiopathic reactive hypoglycemia

1. **Definition.** Idiopathic reactive hypoglycemia is not a well-defined entity. The characteristic glucose pattern, as depicted in the right panel of Figure 45-4, consists of normal early concentrations and later low levels. The two subjects described in the figure had a normal insulin response, although other patients may have delayed or excessive responses.
2. **Controversial classification.** The classification of idiopathic reactive hypoglycemia as a discrete, bona fide clinical entity is beset by a number of problems. Because the results of an oral glucose tolerance test in a single individual are not reliably reproducible, is the diagnosis legitimate 1 week but not the next? The large amount of simple carbohydrate used in the oral glucose tolerance test is certainly not physiologic. Thus, the question arises as to whether a diagnosis based on the results of this test is a valid explanation for symptoms occurring under different conditions. In addition, a disparity often exists between the numbers generated in glucose tolerance tests and the symptoms or lack thereof experienced during the tests. Of more serious concern in the establishment of a clinically relevant entity is that many patients who show the pattern of idiopathic reactive hypoglycemia during the oral glucose tolerance test according to biochemical criteria do not experience symptoms compatible with this diagnosis in their daily lives.
3. **Diagnostic criteria.** In spite of these considerations, there seem to be a few patients who have idiopathic reactive hypoglycemia and who routinely have symptoms when they ingest large amounts of simple carbohydrates. These may represent mild cases of NIPHS described above.

   In my view, **four criteria** must be satisfied before the diagnosis of idiopathic reactive hypoglycemia can legitimately be made:

   a. Decreased glucose concentrations must be documented (Table

45-1).

b. Signs and symptoms must occur at the time of hypoglycemia.

c. Signs and symptoms must improve markedly **shortly** after the patient eats.

d. The pattern just described must occur regularly. The first point raises the additional question of what glucose level defines postprandial hypoglycemia. p. 635p. 636During oral glucose tolerance testing in asymptomatic normal people, a large proportion of those tested routinely have low glucose values. Therefore, the mere presence of a suitably low glucose concentration during a glucose tolerance test is not a sufficient basis on which to make the diagnosis of idiopathic reactive hypoglycemia. Only if all of these criteria are fulfilled in the patient's usual lifestyle setting is a diagnosis of idiopathic reactive hypoglycemia justified.

Few individuals meet these criteria. Typically, a patient gives a vague history that includes some of the following: tiredness, lethargy, anxiety, weakness, depression, mental dullness, headache, paresthesias, loss of vitality, irritability, and a tremulous feeling. It is usually difficult to obtain a clear description of these symptoms; rather, the history is characterized by its vagueness. There is no clear relationship between food intake and either the onset or the relief of symptoms. Patients often have these symptoms on awakening, which improve only slowly (several hours) after eating. Other patients complain of the onset of symptoms within 30 to 60 minutes of eating. Unfortunately, these individuals are usually convinced that they are "hypoglycemic" and that their condition will improve if only the correct diet, vitamin, mineral, or other nostrum is prescribed.

4. **Nonhypoglycemia.** The syndrome of nonhypoglycemia is the result of: (a) the superficial similarity between the symptoms of anxiety and those of hypoglycemia; (b) the high prevalence of low glucose values during an oral glucose tolerance test; (c) the high incidence of anxiety in our society; and (d) misattribution. The last term refers to the patient's (and sometimes the physician's) desire to attribute functional complaints to a biochemical abnormality rather than confront the social or personal situation that is usually

the basis for the symptoms. The fact that a high percentage of patients with the syndrome of nonhypoglycemia have abnormal profiles on the Minnesota Multiphasic Personality Inventory test or have had psychiatric disorders supports the link between **emotional disturbances and the syndrome of nonhypoglycemia**. However, a few individuals seem to have recurring symptoms following meals that are consistent with those of hypoglycemia in the absence of low glucose concentrations. This has been termed the **"postprandial syndrome."**

5. **Flat glucose tolerance test.** One other situation should be mentioned with regard to the diagnosis of idiopathic reactive hypoglycemia. Patients whose oral glucose tolerance tests give "flat" results are sometimes considered to have fed hypoglycemia. However, a flat glucose tolerance test result is seen in approximately 20% of the normal population and simply reflects the efficiency of the physiologic mechanisms in disposing of an oral glucose load.
6. **Diagnosis.** The usual task facing the physician is to persuade the patient that he or she does not have hypoglycemia and that the low glucose values during the oral glucose tolerance test have no clinical meaning. The most specific way to accomplish this is to teach patients about blood glucose self-monitoring and have them measure and record their blood glucose levels when symptoms are experienced. Only a very few will have bona fide hypoglycemia at these times. If that approach is not feasible, I perform a **meal tolerance test** consisting of 37.5 g of simple and 37.8 g of complex carbohydrate (Table 45-7), and sample every 30 minutes for 5 hours. Alternatively, the meal should include the components of meals that routinely precipitate the symptoms that the patient experiences. If a mixed meal test is not feasible, a nutritional supplement formula mixed meal can be used. When patients realize that they do not become hypoglycemic when they experience symptoms under these circumstances, some of them are more willing to consider the possibility of an emotional basis for their symptoms.

G. Management of reactive hypoglycemia

1. **Diet.** The mainstay of treatment for persons with fed hypoglycemia is diet. The most important element in the dietary prescription is the **avoidance of simple or refined**

carbohydrates. Patients who truly have reactive hypoglycemia usually make this discovery for themselves. Because approximately 50% or more of the calories in the typical American diet are derived from carbohydrate and half of the carbohydrate calories are in the simple form, there is much potential for decreasing simple p. 636p. 637carbohydrate intake. For obese individuals, a weight-reduction diet is important. If the reduction of simple carbohydrate intake is not entirely effective, the next step is to limit carbohydrate intake to 35% to 40% of the total number of calories ingested. Should this dietary change not alleviate the symptoms, food intake should be divided into multiple smaller feedings (e.g., three meals a day interspersed with three snacks). Placing limits on the intake of simple carbohydrates is effective in the majority of patients. A reduction in total carbohydrate intake takes care of the problem in most of the remaining cases. Multiple small feedings are usually not needed except in patients with hyperalimentation, in whom this dietary approach is often used.

TABLE 45-7 Menu for ~75-g Carbohydrate Meal (Half Simple and Half Complex)

Breakfast

1. 2.5- to 3-oz bagel (1 medium) (or 3 slices toast): 35-g complex CHO
   10-oz fruit juice (apple, orange): 37-g simple CHO
   or
2. 1½ cup unprocessed, unrefined cold cereal (bran type; no raisins, etc.): 30–40 g complex CHO
   4-oz low-fat milk: 6-g simple CHO
   10-oz fruit juice (apple, orange): 37-g simple CHO
   or
3. 1 cup unsweetened hot cereal (oatmeal, cream of wheat, etc.): 30-g complex CHO
   4-oz low-fat milk: 6-g simple CHO
   10-oz fruit juice (apple, orange): 37-g simple CHO

Lunch

1. Sandwich with 2 slices bread: 30-g complex CHO
   3 saltine crackers: 8-g complex CHO
   10-oz juice or regular cola: 37-g simple CHO
   or
2. 1 cup cooked pasta: 30-g complex CHO
   ½ cup tomato sauce: 5-g complex/simple CHO

10-oz juice or regular cola: 37-g simple CHO
or

3. 6-oz baked potato: 30-g complex CHO
   1 cup raw vegetables (broccoli, carrots, etc.): 5 g complex CHO
   10 oz juice or regular cola: 37 g simple CHO

CHO, carbohydrate.

2. **Drugs.** If dietary changes are not effective, several drugs may be tried. Propantheline bromide (Pro-Banthine), 7.5 mg taken 30 minutes before meals, has been helpful, although anticholinergic symptoms (dry mouth, blurred vision, and urinary retention) may limit its usefulness. Phenytoin, 100 to 200 mg three times a day, may be effective and probably works by inhibiting insulin secretion. Propranolol (10 mg given 30 minutes before meals) was effective in abolishing symptoms in patients with hyperalimentation, although the low glucose levels were not changed much. Finally, nondihydropyridine calcium-channel blockers and α-glucosidase inhibitors (acarbose and miglitol) may be helpful. The latter seem particularly appropriate because they inhibit the breakdown of complex carbohydrates to glucose in the small intestine.
3. **Surgery.** Finally, in patients with hyperalimentation with severe symptoms that are refractory to other therapy, placement of a reversed jejunal segment near the gastric outlet resulted in antiperistaltic inhibition of rapid entry of glucose into the circulation and uniformly corrected the hypoglycemia as well as alleviating the disabling symptoms in a small group of patients.

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46 Hypoglycemia in Infants and Children

Molly O. Regelmann, Cem S. Demirci, and Mark A. Sperling

I. GENERAL PRINCIPLES

A. Perspective. The hypoglycemia entities of infancy and childhood are a group of disorders that collectively reflect failure to maintain normal glucose homeostasis because of defects in available substrate, enzymes, or hormones. Pediatric hypoglycemia can be classified as occurring twice:

1. In the **immediate newborn period**, when hypoglycemia is due to prematurity or dysmaturity, reflecting inadequate substrate stores, genetic defects in enzymes, hyperinsulinism, and hormone deficiencies. These defects are relatively common and are an important cause of neonatal morbidity. The most common of these entities is hypoglycemia due to excessive insulin action, which may be either transient (typically associated with stressful delivery, hypoxia, prematurity, intrauterine growth retardation, maternal type 1 or type 2 diabetes mellitus, and/or gestational diabetes mellitus) or permanent (as a result of defects in the adenosine triphosphate [ATP]–regulated potassium channel that governs insulin secretion) as well as several other less common genetic defects in the regulation of insulin secretion. Other entities that should be considered include growth hormone deficiency with or without concomitant adrenocorticotropic hormone (ACTH)-cortisol deficiency as a result of hypopituitarism or cortisol deficiency from primary adrenal problems.
2. In **infancy and childhood**, when hypoglycemia is less common and is usually the result of an acquired lesion of the endocrine system, environmental insults, and, occasionally, persistence of congenital or developmental abnormalities such as hypoglycemia due to hyperinsulinism, glycogen storage disease, or a fatty acid oxidation defect.

B. Significance of hypoglycemia. The major impetus for recognition and treatment of neonatal hypoglycemia is to permit normal brain development; the larger proportion of glucose turnover is utilized by brain metabolism. Controversy remains as to the degree and duration, as well as associated conditions, such as seizures or hypoxia that lead to neuro-intellectual impairment. Although a threshold of 60 mg/dL or less is suggested as important for newborns, there is evidence that the neonatal brain may be more resistant than the adult brain to hypoglycemia, especially in its ability to use lactate (and ketones) as alternate fuel. However, the most common form of hypoglycemia due to excessive insulin action limits lipolysis and ketogenesis, thus depriving the brain of all potential nutrients. Duration and severity of hypoglycemia determine the outcome. Glycemic values below 30 mg/dL for 20 to 30 minutes or more or multiple episodes over a period of days are more likely to be associated with poorer outcome. Worse neurodevelopmental outcomes are more likely if symptoms of hypoglycemia, especially seizures, accompany the low glucose measurement.

C. Definition. Clinically significant hypoglycemia in the **first 48 hours of life**, whether symptomatic or not, is considered to be present when plasma glucose **is <50 mg/dL** (2.8 mmol/L) in full-term neonates. **Beyond the first 48 hours of life**, a plasma glucose <**60 mg/dL** (3.3 mmol/L) is consistent with hypoglycemia. Controversy exists as to whether the cutoff values for low-birth-weight and premature infants should be lower.

D. Symptoms and signs

1. Symptoms and signs in **older children** are similar to those in adults and include features associated with activation of counterregulatory sympathetic response, p. 640p. 641including sweating, trembling, tachycardia, anxiety, weakness, hunger, food seeking, nausea, and vomiting; and those reflecting cerebral glucopenia, including headache, mental confusion, somnolence, personality changes, inability to concentrate, convulsions, and loss of consciousness.
2. In **infants,** these features may be subtler and predominantly reflect the impairment of neurologic function, including cyanotic

episodes, apnea, refusal to feed, wilting spells or myoclonic jerks, somnolence, subnormal temperatures, and convulsions. Because these symptoms are nonspecific and can occur in other conditions, such as sepsis, asphyxia, intraventricular bleeds, congenital heart disease, and maternal drug therapy, it is important to be alert to the possibility of hypoglycemia as the cause of the symptoms, to demonstrate that the blood glucose is low at the time of the occurrence of symptoms, and that symptoms disappear when parenteral glucose is given in amounts adequate to elevate blood glucose concentrations (**Whipple triad**: low glucose at the time of symptoms; disappearance of symptoms and signs when glucose is elevated; reappearance of signs and symptoms when glucose is lowered). Moreover, obtaining blood at the time of symptoms provides the unique opportunity of the "critical sample," in which, once hypoglycemia is confirmed (preferably a plasma glucose <50 mg/dL; but above 60 mg/dL will not yield a valid result), insulin, growth hormone, cortisol, free fatty acids (FFAs), and ketones can be measured in order to arrive at a likely diagnosis (Fig. 46-1).

II. CLASSIFICATION AND INCIDENCE OF HYPOGLYCEMIA IN INFANTS AND CHILDREN

A. Classification.

A classification based on a developmental approach is outlined in Table 46-1. In the neonatal transient form, it is important to emphasize that hypoglycemia can be asymptomatic and that there are certain high-risk groups, as outlined in the table.

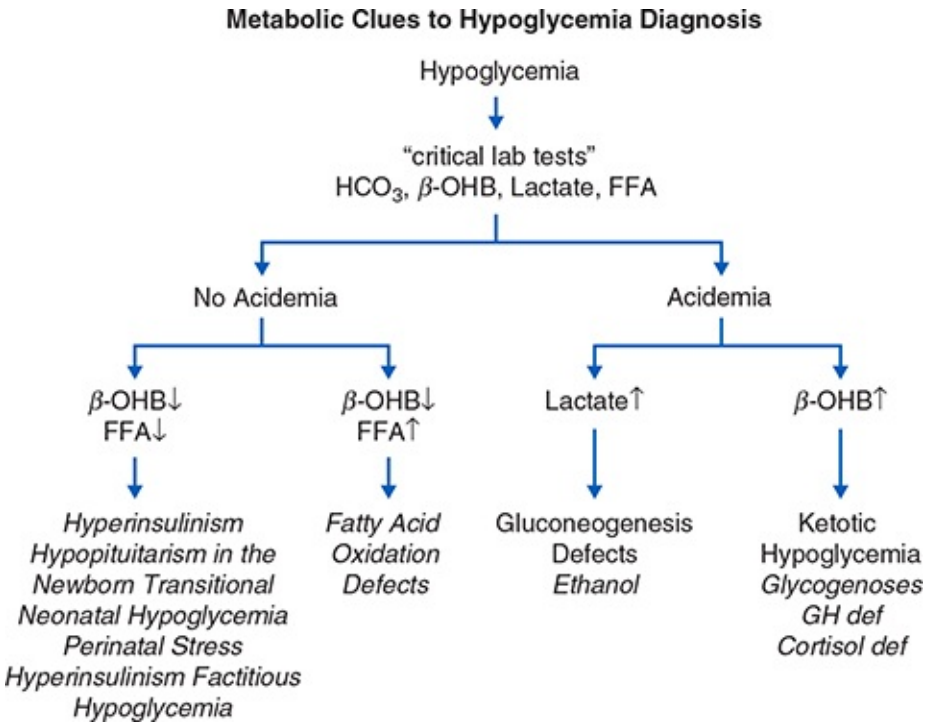

Figure 46-1. Metabolic clues to hypoglycemia diagnosis. Obtaining laboratory tests at the time of hypoglycemia (the "critical sample") can aid in determining the cause of the hypoglycemia. GH, growth hormone; HCO_3, bicarbonate; β-OHB, beta-hydroxybutyrate; FFA, free fatty acid.

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TABLE 46-1 Classification of Hypoglycemia in Infants and Children

Neonatal—Transient

Associated with inadequate substrate or enzyme function

- Prematurity
- Small for gestational age/*Intrauterine* growth restriction
- Smaller of twins
- Infants with severe respiratory distress
- Infants of toxemic mother

Associated with hyperinsulinism

- Infants of diabetic mothers
- Infants with erythroblastosis fetalis
- Infants with significant perinatal stress (hypoxia)

Neonatal, Infantile, or Childhood—Persistent

Hyperinsulinism states

- Hyperinsulinemic hypoglycemia of infancy (HHI)
- K_{ATP} channel defects
  - SUR1 mutations (*ABCC8*)
  - Kir6.2 mutations (*KCNJ11*)

- Glucokinase-activating mutations (*GCK*)
- Glutamate dehydrogenase–activating mutation (leucine sensitivity) (*GLUD1*)
- Short-chain L-3 hydroxyacyl-CoA dehydrogenase (*HADH*)
- Uncoupling protein 2 (*UCP2*)
- Monocarboxylate transporter—MCT1 (*SLC16A1*)
- Hepatocyte nuclear factor 4a (*HNF4A*)
- Hepatocyte nuclear factor 1 homeobox A (*HNF1A*)
- Hexokinase1 (*HK1*)
- *β*-Cell hyperplasia
- *β*-Cell adenoma: multiple endocrine neoplasia type I (*MEN1*)
- Beckwith–Wiedemann syndrome (deletion or mutations of imprinted genes within 11p15.5)
- Congenital disorders of glycosylation (CDGs)
  - CDG-Ia (phosphomannomutase 2 deficiency) (*PMM2*)
  - CDG-Ib (mannosephosphate isomerase deficiency) (*MPI*)
  - CDG-Id (carbohydrate-deficient glycoprotein syndrome) (*ALG3*)
- Insulin administration (Münchausen by proxy)

Hormone deficiency
- Multiple pituitary hormone deficiencies
- Isolated growth hormone deficiency
- ACTH deficiency (rare, typically found with other pituitary hormone deficiencies)
- Primary cortisol deficiency
- Epinephrine deficiency, adrenergic receptor blockers

Substrate limited
- Ketotic hypoglycemia
- Branched-chain ketonuria (maple syrup urine disease)

Glycogen storage disease
- Glucose 6-phosphatase deficiency (type I)
- Glycogen debranching enzyme (type III)
- Liver phosphorylase deficiency (type VI)
- Phosphorylase kinase deficiency (type IX)
- Phosphorylase kinase, GLUT2 (type XI)
- Glycogen synthetase deficiency (type 0)

Disorders of gluconeogenesis
- Carnitine deficiency
- Medium-chain and long-chain acyl-CoA dehydrogenase deficiency
- Acute alcohol intoxication
- Valproic acid ingestion
- Salicylate intoxication
- Fructose 1,6-diphosphatase deficiency
- Pyruvate carboxylase deficiency
- Phosphoenolpyruvate carboxykinase deficiency

Other enzyme defects
- Galactosemia: galactose 1-phosphate uridylyltransferase deficiency
- Fructose intolerance: fructose 1-phosphate aldolase deficiency

ACTH, adrenocorticotropic hormone; CoA, coenzyme A.

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B. Incidence. Data on the incidence of hypoglycemia vary considerably as the definition of hypoglycemia has been debated. The previously reported incidence of hypoglycemia in the full-term newborn of 1.5 to 3 in 1 000 live births may be higher with newer more conservative definitions of hypoglycemia of <50 mg/dL in the first 48 hours of life and <60 mg/dL after 48 hours of life. The same criteria have been applied to premature and low-birth-weight infants. The incidence of hypoglycemia can be several-fold higher in certain vulnerable groups. The premature or small-for-gestational-age (SGA) infant is especially vulnerable to hypoglycemia. Two thirds of infants who are both premature and SGA develop clinically significant hypoglycemia that usually is transient, lasting only several days. Hypoglycemia in these infants is a result of immaturity in the glucose regulatory mechanisms that involve hormones, receptors, their signaling cascades, enzymatic effectors, and substrate availability to sustain glucose production. The majority of infants (80% to 90%) born to insulin-dependent or gestational diabetic mothers are included in this group of neonatal transient hypoglycemia. Only a minority (<20%) have severe persistent hypoglycemia. When hypoglycemia persists, some form of hyperinsulinism is most likely, especially those presenting as newborns. The term “hyperinsulinism” is used to denote excessive insulin action because insulin is secreted into the portal vein so that variable liver extraction of insulin can limit glucose release from the liver, yet result in low insulin values in peripheral blood. Some hypoxic infants display more persistent hypoglycemia that is associated with hyperinsulinism and responds well to diazoxide.

III. MANAGEMENT

A. Neonatal transient. Newborns with symptoms suggestive of hypoglycemia and all newborns in high-risk groups (Table 46-1) should be screened for hypoglycemia via a point of care testing (Chemstrips™; Dextrostix™) and have low values confirmed by formal laboratory glucose determination. If low glucose values are confirmed, start treatment with an intravenous infusion of glucose at *6 to 8 mg/kg/min*. Low glucose values tend to occur during the first 6 to 10 hours of life, especially if feeding is delayed, there is associated illness (such as respiratory distress), or the mother has diabetes

mellitus. Hypoglycemia **usually resolves over 2 to 3 days**, when intravenous glucose can be gradually tapered and then discontinued. Although transient hyperinsulinism may resolve in a few days, long-term follow-up reports indicate that **neonates with transient hypoglycemia may be at high risk for neurodevelopmental abnormalities**, making prompt recognition and treatment of hypoglycemia essential in the newborn period. Three important caveats are as follows:

1. Oral glucose supplementation may not of itself be adequate, but oral feedings should be given as tolerated.

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2. Sudden interruption of hypertonic glucose (10% to 15%) that has been infused can itself trigger hypoglycemia, so all management strategies require gradual tapering of the intravenous glucose delivery rate.
3. During *labor and delivery*, intravenous infusion of glucose to the mother should not produce maternal hyperglycemia in excess of approximately 100 mg/dL. Because this glucose may be transferred to the fetus, its sudden curtailment after separation of the umbilical cord may lead to a precipitous fall in the neonate's glucose concentration.

   In infants of diabetic mothers, it is becoming increasingly apparent that strict antepartum metabolic control minimizes or eliminates newborn hypoglycemia as well as the other characteristics traditionally associated with these infants: macrosomia, respiratory distress, polycythemia, hyperbilirubinemia, hypocalcemia, and congenital malformation. In diabetic mothers who have not been aggressively managed antepartum, these neonatal problems require therapy in addition to management of hypoglycemia.

B. Neonatal persistent hypoglycemia (Table 46-1). When hypoglycemia and symptoms persist beyond 48 hours or recur despite increasing the rates of glucose infusion from the initial 6 to 8 mg/kg/min up to 12 to 16 mg/kg/min (or higher), hormone excess (hyperinsulinism), hormone deficiency (cortisol, growth hormone), or an inborn error of glycogen synthesis or gluconeogenesis is most likely. Rates of glucose infusion of up to 20 to 25 mg/kg/min may be necessary to maintain euglycemia, and this requirement signifies that

the patient likely has hyperinsulinism. Clinical clues to the existence of one of these syndromes are quite helpful if they are present: perinatal asphyxia or large size (macrosomia) in hyperinsulinemia; microphallus, midline facial defects (cleft palate), holoprosencephaly, and/or cholestatic jaundice in hypopituitarism; ambiguous genitalia, hyperpigmentation, and/or hyponatremia/hyperkalemia in primary adrenal insufficiency; macroglossia, earlobe fissures, hemihypertrophy, umbilical hernia/omphalocele, visceromegaly, and/or flame nevus of the face in Beckwith–Wiedemann syndrome; and hepatomegaly in glycogen storage disease. Neonatal persistent hypoglycemia can almost always be precipitated by a period of fasting. At the time of hypoglycemic symptoms, it is essential to collect a "critical sample" to determine the etiology of the hypoglycemia. Table 46-2 summarizes the recommended specimens to obtain at the time of hypoglycemia. If hyperinsulinism is suspected, a glucagon stimulation test following discontinuation of glucose infusion can be diagnostic (Table 46-3). A glycemic response is defined as an increase in blood glucose by 30 mg/dL or more in response to intravenous or intramuscular glucagon (0.5 or 1 mg) at the time of hypoglycemia.

TABLE 46-2 Critical Sample

Blood

Essential:

1. Plasma glucose
2. Bicarbonate
3. *β*-hydroxybutyrate
4. Free fatty acids
5. Reserve additional serum (C-peptide, cortisol, growth hormone)

Desirable:

6. Ammonia
7. Insulin-like growth factor–binding protein 1

Urine

1. Ketones
2. Organic acids (if fatty acid oxidation defect is suspected)

TABLE 46-3 Diagnostic Criteria for Hyperinsulinism

At the time plasma glucose is <50 mg/dL:

- Measurable C-peptide (>0.5 ng/mL) or insulin (>2 mIU/mL)
- Low β-hydroxybutyrate (<1.8 mmol/mL)
- Low free fatty acids (<1.5 mmol/L)
- >30 mg/dL change in plasma glucose 20 minutes following glucagon administration (1 mg IM or IV)

1. **Hyperinsulinism**
   a. **Evaluation.** If the infant is large, requires >12 to 15 mg/kg/min to maintain euglycemia, the *increment* in glucose after glucagon exceeds 30 mg/dL, ketones are absent or low, and FFAs are low, then hyperinsulinism is most likely. The most sensitive and specific indicator of hyperinsulinism is a β-**hydroxybutyrate** <1.8 mmol/mL at the time the plasma glucose is <50 mg/dL. Commonly, levels of insulin are >10 μU/mL, but **any level >2 μU/mL**, or C-**peptide >0.5 ng/mL** at the time of hypoglycemia is strongly suggestive of **hyperinsulinism**. An elevated level of ammonia in the serum (>80 μM/L) suggests **glutamate dehydrogenase** deficiency. Patients with activating **mutations of glucokinase** (Fig. 46-2) often have a family history consistent with autosomal dominant inheritance. Such patients respond favorably to medical measures such as diazoxide (at a modest dose of 5 to 15 mg/kg/day) or long-acting somatostatin. When these medical measures fail after 2 or 3 days, when there is a strong family history consistent with autosomal recessive inheritance, or if the infant was macrosomic at birth, one of the severe forms of defects in the potassium channel (K_{ATP}) governing insulin secretion with variable diffuse or focal islet hyperplasia is likely (Fig. 46-2).
   b. **Etiology.** Whether the infant has some form of diffuse islet cell hyperplasia or focal adenoma can be definitely confirmed only by histologic examination of biopsied tissue. Positron emission tomography (PET) with ^{18}F-L-DOPA imaging is now used to differentiate diffuse from focal disease in hyperinsulinism of infancy and has replaced more invasive procedures, such as arterial stimulation with hepatic venous sampling for detection of a step-up gradient in insulin secretion. These approaches are

available at only a limited number of medical centers around the world for the preoperative localization of the lesion as focal or diffuse.

c. **Management.** Appropriate treatment of hypoglycemic hyperinsulinism of infancy (HHI) is exceedingly important to prevent serious brain damage. Usually, *diazoxide* is the first-line drug, and is used at a dose of 5 to 20 mg/kg/day divided into two to three doses. Side effects include hypertrichosis, hyperglycemia, and fluid retention, which can lead to hyponatremia, pulmonary edema, and congestive heart failure. Addition of **chlorothiazide to diazoxide** has been suggested to avoid water and salt retention. In those unresponsive to diazoxide, *octreotide* (somatotropin release inhibitory factor analog) can be effective in the short-term treatment of HHI, but the development of tachyphylaxis may limit its efficacy with chronic use. (We are unaware of a contraindication to using **both diazoxide and octreotide** at the same time.) The dose range is 5 to 20 μg/kg/day divided every 6 to 8 hours or as a continuous intravenous drip. Side effects include diarrhea, gallstones, and suppression of growth hormone. It has also been associated with a risk for necrotizing enterocolitis, particularly in preterm and small for gestational age infants, in whom octreotide should be avoided. In the short term, an infusion of glucagon at 0.5 to 1.0 μg/minute, not to exceed 1.5 mg/day, may increase blood glucose levels temporarily by promoting glycogen breakdown. It has been suggested that **sirolimus**, a rapamycin inhibitor, may be an alternative in those nonresponsive to diazoxide and octreotide, but this is **not an established form of treatment**. If medical treatment fails, *surgical pancreatectomy* is required. The distinction between

p. 645p. 646diffuse and local lesion is a crucial step in defining the extent of pancreatectomy and the long-term prognosis. A near-total pancreatectomy is required for the diffuse form, whereas only partial pancreatectomy with local excision is needed for the localized form. It is important **not to delay local, subtotal (80%), or near-total (95%) pancreatectomy** when the diagnosis of hyperinsulinism is confirmed and hypoglycemia persists despite administration of

intravenous glucose in excess of 10 mg/kg/min in addition to ongoing treatment with diazoxide, as indicated previously. This group of patients is most likely to suffer permanent neurologic deficits if definitive treatment by surgery is delayed when the patient is not responding to medical management.

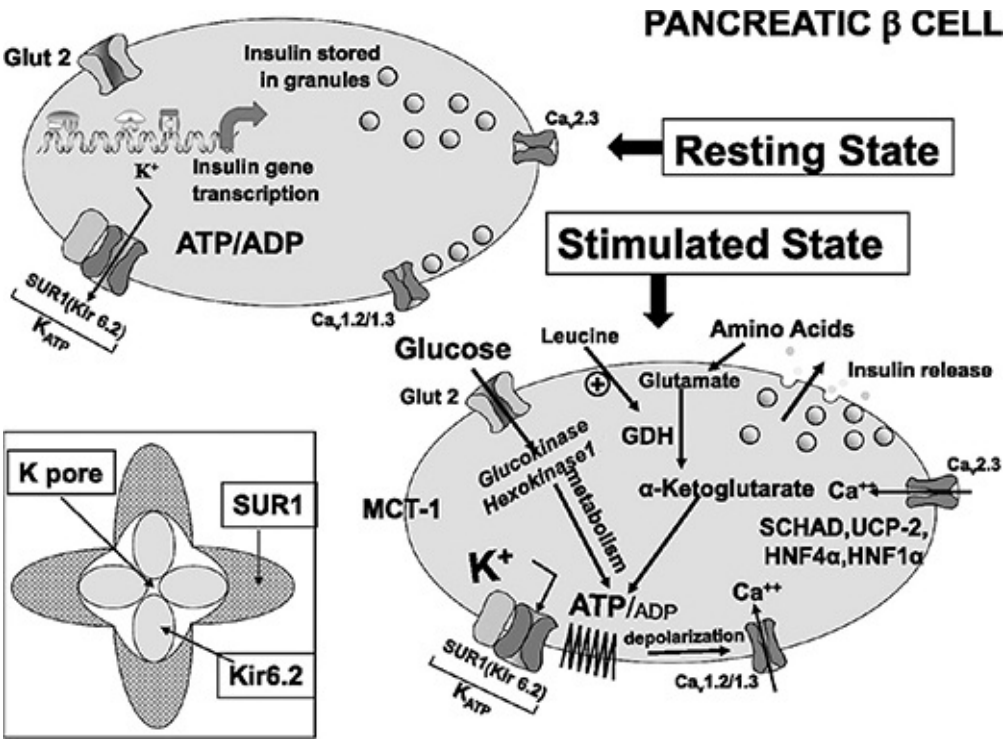

Figure 46-2. Pancreatic *β* cell—regulation of insulin secretion. Glucose and amino acids stimulate insulin release by generating ATP, which leads to closure of ATP-sensitive plasma membrane potassium channels, plasma membrane depolarization, activation of voltage-sensitive calcium channels, an increase of cytosolic calcium, and release of insulin from storage granules. Leucine is an allosteric activator of glutamate dehydrogenase that enables protein metabolism. Inactivating mutations in the K_{ATP} channel lead to closure and hence excessive unregulated insulin secretion causing hypoglycemia—these mutations may respond to diazoxide, an agent that promotes the opening of these channels. GDH, glutamate dehydrogenase; HK1, hexokinase I; HNF4*α*, hepatic nuclear factor 4*α*; HNF1*α*, hepatic nuclear factor 1*α*; Kir 6.2, inwardly rectifying potassium channel 6.2; MCT-1, monocarboxylic acid transporter 1; SCHAD, short-chain 3-OH acyl-CoA dehydrogenase; SUR1, sulfonylurea receptor 1; UCP2, uncoupling protein 2.

2. **Hormone deficiency.** Severe hypoglycemia during the initial hours of life occurs with *multiple pituitary hormone deficiencies* as a result of congenital hypoplasia or aplasia of the pituitary or of functional separation of the hypothalamus and its releasing factors from the anterior pituitary. Because growth hormone is not a primary *in utero* growth factor, infants with growth hormone

deficiency tend to be born at near normal length and normal weight. Isolated growth hormone deficiency has been associated with hypoglycemia. In males, microphallus and undescended testes provide a strong clue to the existence of gonadotropin deficiency. A midline facial defect, such as cleft lip/palate, may occur in some patients and provides a clue to the possibility of pituitary abnormalities.

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Cholestatic jaundice and hepatomegaly are frequently associated with growth hormone deficiency or multiple pituitary hormone deficiencies and resolve with replacement of glucocorticoid, growth hormone, and thyroid hormone. Frequent feedings also help to relieve the symptoms, in contrast to other etiologies associated with jaundice such as *galactosemia*, which may have a similar clinical picture, but in which typically hypoglycemia is associated with severe liver failure. The **critical blood sample** at the time of hypoglycemia reveals low insulin levels (<2 μU/mL) in association with low cortisol and growth hormone. Infants will often also have thyroid-stimulating hormone (TSH) deficiency, associated with a low thyroxine (T_4) and frequently normal range TSH. (Note that the normal TSH does not rule out central hypothyroidism; central hypothyroidism is typically associated with low T_4 and at least one other pituitary hormone deficiency.) The level of growth hormone must be interpreted with the knowledge that newborns normally have a basal concentration of 20 to 40 ng/mL in the initial days of life. Ketones, FFAs, and uric acid are normal, and the glycemic increment after glucagon is within the normal range rather than exaggerated (>30 mg/dL), as occurs in neonates with hyperinsulinism. Infants with multiple pituitary hormone deficiencies, including growth hormone and ACTH deficiency, respond dramatically to *replacement with glucocorticoid and growth hormone*, which may be essential to avoid hypoglycemia during the first year of life. Cortisol replacement in physiologic doses (9 to 12 mg/m^2/day divided every 8 hours) is lifelong. Rarely, isolated growth hormone deficiency or isolated ACTH/cortisol deficiency can be responsible for neonatal

hypoglycemia. Diagnosis is again established based on the screening blood sample. Replacement therapy with the hormone ameliorates the symptoms.

3. **Metabolic defects.** Metabolic defects that cause hypoglycemia in the immediate newborn include *type 1 glycogen storage disease*, *galactosemia*, and *maple syrup urine disease (MSUD)*. Galactosemia, MSUD, as well as fatty acid oxidation cycle defects are most often detected as part of newborn screening programs. Affected infants have metabolic acidosis, hepatomegaly, elevated uric and lactic acid concentrations, ketonemia and ketonuria, and elevated FFAs. Galactosemia can be screened for by testing the urine for reducing substances with Clinitest, which will be positive, but testing with Clinistix, which is specific for glucose, is negative. They may also have reducing substances. Plasma levels of hormones are normal and the **glycemic increment after glucagon is markedly diminished or absent** (<30 mg/dL). If not fed, profound hypoglycemia in the first days of life can be present in infants with **type 1 glycogen storage disease** (glucose 6-phosphatase deficiency [G6PD]), because both glycogen breakdown and gluconeogenesis are curtailed by the deficiency of this enzyme at the final critical step for liberating free glucose. **Galactosemia** should also be considered in an infant with jaundice, hepatomegaly, and nonglucose reducing substances in the urine, but hypoglycemia need not be present consistently. Apart from galactosemia, most individuals with inborn errors of metabolism present in infancy rather than in the immediate newborn period, because the usual 3- to 4-hourly feeding schedule masks a defect in gluconeogenesis that may require longer deprivation of nutrients. Thus, these inborn errors of metabolism more commonly manifest when the infant has more prolonged periods without food, for example, sleeps through the night or has poor food intake in conjunction with an intercurrent illness.

C. Infancy and childhood

1. **Incidence.** Beyond the newborn period, hypoglycemia in infants and children is distinctly uncommon. An inability to maintain euglycemia during fasting and acquired deficiency of hormones predominate during late infancy and childhood.
2. **Age at presentation.** A common time for presentation of milder

hyperinsulinism and defects in gluconeogenesis is between 3 and 6 months of age, when infants sleep at night for progressively longer periods. Feedings are no longer given at 3- to 4-hour intervals, and the infant is progressively "fasting" for up to 8 hours during the nighttime sleep. **Leucine-sensitive** forms of hyperinsulinism, such as p. 647p. 648hyperinsulinism/hyperammonemia syndrome, may present after the introduction of proteins in the diet (note breast milk is relatively low in leucine).

3. **Signs and symptoms.** Symptoms can result from neuroglycopenia and include seizure activity and coma or may be due to activation of counterregulatory hormones, causing irritability, anxiety, tachycardia, and sweating. A high index of suspicion is required, especially if symptoms recur at regular times of day in relation to feeding and its intervals.
4. **Evaluation.** An adequate blood sample at the time of symptoms can document hypoglycemia and can be used for measurement of substrates or hormones. This "*critical sample*" needs to be drawn when the plasma glucose level is <50 mg/dL (Table 46-2). If the critical blood sample is not obtained at the time of symptoms, it is necessary to admit the child for a 10- to 20-hour fast under observation. A urine sample is also sent to dipstick for ketones. **Glucagon** (1 mg) is given after the critical sample is drawn, and the glucose level is checked at 15 and 30 minutes after glucagon to assess for the rise in glucose; a **rise in glucose of** >**30 mg/dL** above baseline glucose is **consistent with hyperinsulinism**. Worth noting is the importance of making sure that the glucose level is truly hypoglycemic before glucagon is given, because once it is administered, the fasting test cannot continue. Therefore, if the child is *symptomatic* and/or the meter reading is well below 50 mg/dL, the critical sample is drawn and glucagon is given while awaiting the formal laboratory glucose determination. If the child is not *symptomatic* and the point of care glucose is not below 50 mg/dL, we would recommend waiting for the formal laboratory glucose determination to guide the decision regarding the administration of glucagon. However, it remains at the discretion

of the clinician whether to wait for confirmation of hypoglycemia in the asymptomatic patient with point of care blood glucose that is borderline hypoglycemic (high 40s to low 50s mg/dL). Once glucagon is administered, the fasting test cannot be continued as glycogen stores would be depleted following administration.

5. **Differential diagnosis**
   a. **Hyperinsulinism**
      i. Hyperinsulinism is the *most common* cause of hypoglycemia in the first 6 months of life. The findings in the initial blood sample at the time of symptoms demonstrate low glucose, low FFAs, and low ketones, whereas **insulin values are inappropriately high (>2 μU/mL)** when glucose is inappropriately low (<60 mg/dL). Cortisol and growth hormone levels are normally elevated in response to hypoglycemia, although **false low cortisol and false low growth hormone levels at the time of hypoglycemia** are reported in children with hyperinsulinism. There is no metabolic acidosis. Glutamate dehydrogenase deficiency is associated with leucine-sensitive hyperinsulinism/hyperammonemia syndrome (Fig. 46-1). At the time of spontaneous symptoms, or if provoked by fasting, glucagon challenge results in an exaggerated response of blood glucose (change of >30 mg/dL).
      ii. **Management** differs from that for the neonate in that affected infants do not require continuous infusion with glucose. A more prolonged *trial of diazoxide,* at a dose of 5 to 15 mg/kg/day divided every 8 to 12 hours (up to 20 mg/kg/day in some instances), is warranted. Frequently, diazoxide in these dosages can maintain euglycemia in these patients so that, if successful, diazoxide therapy can be continued for months to years. *Octreotide* can be of benefit in this circumstance but **tachyphylaxis may occur**. However, if hypoglycemia recurs despite adequate doses of diazoxide, or if side effects such as hypertrichosis, edema, hypertension, and hyperuricemia become intolerable, partial pancreatectomy may be indicated.

Endogenous insulin production may come from a focal insulin-producing lesion or diffuse pancreatic excessive, nonregulated insulin production. Finding a focal lesion in

cases planned for pancreatectomy may be helpful, thus allowing for a partial resection to be therapeutic. Distinguishing focal and diffuse types may be done using PET scanning with *^{18}F-L-DOPA*.

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Factitious or **exogenous hyperinsulinism** resulting from deliberate injection of insulin as a form of Münchausen syndrome, child abuse, or Münchausen by proxy can mimic spontaneous hypoglycemia due to endogenous hyperinsulinism and lead to repeated episodes of symptomatic hypoglycemia. Suspicion is raised by the presence of inappropriately high insulin levels (>100 μU/mL), requiring measurement of **C-peptide** concentration in the same sample. Because **C-peptide** concentrations reflect endogenous insulin secretion, they **are low, whereas insulin levels are high in factitious hypoglycemia**. By contrast, a high C-peptide level along with a high insulin level indicates endogenous insulin secretion, the result of an insulinoma or an insulinotropic drug such as a sulfonylurea given inadvertently as a pharmaceutical error or another manifestation of Münchausen syndrome.

b. Hormone deficiency. Deficiency of **growth hormone** or **cortisol** can *rarely* cause hypoglycemia after the first months of life, but if it does occur, it is likely to occur during prolonged fasting. The diagnosis is established on the basis of the results of the critical sample at the time of symptoms; the glycemic increment following glucagon administration is diminished or near normal (<30 mg/dL). During fasting, glucose also declines, whereas FFAs and ketones increase, thereby simulating so-called **ketotic hypoglycemia**. In older children, there may be clinical clues of deficiency of either hormone, such as short stature, poor height velocity, or symptoms associated with a space-occupying intracranial lesion indicative of pituitary pathology; there also may be hyperpigmentation, salt craving, hyponatremia, and hyperkalemia in progressive adrenal insufficiency. Treatment involves replacing the deficient

hormone as clinically indicated. Investigations will be needed to assess for other possible associated deficiencies that may be present.

c. **Ketotic hypoglycemia.** This is the **most common cause** of hypoglycemia in infants and children aged 6 months to 6 years without diabetes mellitus.
    i. **Etiology.** The cause appears to be an *inability to adapt to fasting*. Apart from the nonidiopathic ketotic hypoglycemia associated with hormone deficiency, specific mechanisms are not understood. Hypoglycemia, occasionally with severe symptoms such as seizures, may occur after limited glucose (food) intake during intercurrent infection, or gastrointestinal disturbances combined with a relatively long fast after prolonged sleep, when resources for glycogenolysis and gluconeogenesis have been consumed.
    ii. **Evaluation.** In the critical diagnostic blood sample, glucose and insulin are low, whereas ketones are high, and there may be ketonuria. There is a low glycemic increment with glucagon challenge (<30 mg/dL), and the syndrome can be produced by a fast of 14 to 24 hours. Because the syndrome can be simulated by adrenal insufficiency, and to a lesser extent growth hormone deficiency in older children, the levels of **cortisol and growth hormone should always be measured** as outlined in Table 46-2. Children with glycogen storage disease type 0, VI, and IX, and fructose bisphosphatase deficiency will also present with ketotic hypoglycemia, and these conditions should also be excluded prior to confirming diagnosis of idiopathic ketotic hypoglycemia.
    iii. **Management.** Management consists of a high-carbohydrate, high-protein diet, with frequent daily feedings. During intercurrent illness, high glucose–containing drinks are encouraged and the urine is checked for ketones. The appearance of ketonuria despite high-carbohydrate feeding or administration of high carbohydrate–containing liquids warrants admission for temporary intravenous glucose at a rate of 6 to 8 mg/kg/min to avoid a serious hypoglycemic reaction. Most patients *spontaneously resolve* the tendency for hypoglycemia by

age 7 years.

d. **Carnitine deficiency.** Systemic **carnitine deficiency** and **acylcarnitine transferase deficiency** are rare causes of hypoglycemia *provoked by fasting* p. 649p. 650and are sometimes associated with muscle *hypotonia and cardiomyopathy*. Carnitine and its enzyme transferase are essential for the transport of FFAs across the mitochondrial membrane, where metabolism of FFAs produces energy for gluconeogenesis and where ketogenesis occurs. Hypoglycemia in these conditions is characterized by low to absent blood ketones, low insulin and growth hormone levels, and a normal cortisol level; there is negligible glycemic response to glucagon. Definitive diagnosis can require measurement of carnitine levels in liver and blood.

   i. **Nonketotic hypoglycemia and low carnitine** levels sometimes associated with hypotonia are also features of the increasingly recognized fatty acid oxidation disorders, **medium-chain acyl coenzyme A (acyl-CoA) dehydrogenase deficiency (MCADD), and long-chain acyl-CoA dehydrogenase deficiency**. MCADD is not an uncommon entity, with an incidence as high as 1 in 10 000 births. Hence, this entity should be considered in a child presenting with seizure and hypoglycemia during an intercurrent illness with vomiting and inability to retain ingested food. *Dicarboxylic acids* in the urine and other special tests are necessary to confirm the diagnosis. *Note that these conditions and all forms of hyperinsulinism are associated with low ketones* and can easily be distinguished from each other on the basis of the insulin level and the glycemic response to glucagon, which is high in hyperinsulinism (>30 mg/dL) and low in carnitine deficiency (<30 mg/dL). *In all other forms of hypoglycemia, ketones are high. Because of the relative frequency of MCADD, this condition forms part of the expanded **neonatal screening programs** of many states. Knowledge of this fact permits checking with relevant state offices whether the entity has been excluded or diagnosed by neonatal screening.*

e. Enzyme deficiencies

i. Glycogen storage disease (see Chapter 49)

a) G6PD (*type 1* glycogen storage disease) rarely presents in the first days or weeks of life. This is because babies are fed every 3 to 4 hours, hence masking the defect in glucose production during fasting. More typically, G6PD presents in infancy and childhood with poor growth, protuberant abdomen, hepatomegaly, eruptive xanthomas, chronic acidosis, and hyperlipidemia; levels of FFAs, triglycerides, lactate, pyruvate, and uric acid are high, and insulin levels are low. **Bleeding tendencies** are caused by abnormal platelet function but not abnormal platelet numbers. **In response to glucagon injection, lactate levels rise but the glycemic response is absent**. Definitive diagnosis can be made with molecular testing or liver biopsy for histologic examination together with in vitro measurement of enzyme activity. Continuous intragastric nighttime feeding of glucose, glucose polymer (4 to 6 mg/kg/min), or cornstarch (so as to provide approximately one third of total daily calories) together with frequent high-carbohydrate feedings during the day will markedly ameliorate the biochemical abnormalities and result in catch-up growth as well as marked reduction of liver size. In the untreated child, symptoms of hypoglycemia spontaneously improve with age. However, with institution of intensive therapy by intragastric feeding and normalization of several of the abnormal biochemical indices, the sensitivity to hypoglycemic symptoms and signs, including seizures, returns. Meticulous monitoring is therefore necessary once intensive therapy is started.

b) The clinical features of fasting hypoglycemia and hepatomegaly (but usually without acidosis) occur in a much milder degree in *type III* glycogen storage disease (amylo-1,6-glucosidase deficiency; debrancher deficiency) and *in type VI* glycogen storage disease (liver phosphorylase deficiency). Both require tissue biopsy and enzyme measurement for definitive

diagnosis, and both types respond to frequent high-carbohydrate feeding, although continuous intragastric nocturnal feeding can be beneficial in some cases of type 3 glycogen storage disease.

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c) *Glycogen synthase deficiency*, a rare enzyme deficiency, causes severe *hypoglycemia with fasting* because no accumulation of glycogen is possible. Paradoxically, affected children have **hyperglycemia** *after meals*, because the ingested glucose cannot be deposited as glycogen in the liver. **Fasting produces a "ketotic" hypoglycemia** and can be distinguished from the usual ketotic hypoglycemia described earlier by the presence of hyperglycemia after meals in the case of glycogen synthase deficiency.

ii. Disorders of gluconeogenesis

a) Fructose 1,6-diphosphatase deficiency is associated with severe hypoglycemia during prolonged fasting or with infections. *Hepatomegaly* is present, as is **chronic lactic acidosis** exaggerated by fasting. Episodes of hypoglycemia can be treated acutely with glucose and bicarbonate; **fructose should be avoided** at all times because it, as well as various metabolic intermediates (alanine, glycerol, lactate), acutely inhibits glucose production, and hence provokes hypoglycemia. Definitive diagnosis requires enzyme assay in a liver biopsy or in leukocytes.

b) With **hereditary fructose intolerance (fructose 1-phosphate aldolase deficiency)**, hypoglycemic episodes are provoked **only after ingestion of fructose**. Symptoms can be severe and associated with acute vomiting; poor feeding and failure to thrive are present at other times. Affected infants learn to avoid fructose-containing foods and sweets. *A fructose-free diet must be instituted.*

c) In **phosphoenolpyruvate carboxykinase deficiency** (PEPCK deficiency), fasting hypoglycemia results from an inability to initiate gluconeogenesis at

the key entry point of several intermediates. Diagnosis requires a demonstration that infusion of lactate or alanine has no glycemic effect because they require PEPCK to enter gluconeogenesis, whereas glycerol infusion results in a normal glycemic response because PEPCK is bypassed. This cause is extremely rare. Molecular diagnostic techniques are becoming available for glycogen storage diseases and may eliminate the need for liver biopsy or other tissue enzymatic assays.

d) **Alcohol and other drugs.** An important cause of hypoglycemia due to acute **interruption of gluconeogenesis** in infants and children is alcohol ingestion. The metabolism of alcohol to acetaldehyde requires cofactors that are also essential for gluconeogenesis. However, hepatic alcohol metabolism seems to take preference, thereby **depleting the cofactors essential for gluconeogenesis**. Consequently, **alcohol-induced hypoglycemia** occurs only when liver glycogen stores are depleted after 6 to 8 hours of fasting. The inadvertent swallowing of alcohol left unattended (Sunday morning syndrome) or the deliberate feeding of alcohol such as wine or beer to infants and young children deprived of food (e.g., during a long car trip) can provoke a hypoglycemic reaction. The response to intravenous glucose is dramatic. No investigation for this isolated episode of hypoglycemia is necessary if the history of alcohol ingestion is elicited. Similarly, isolated episodes of hypoglycemia caused by inadvertent use of **oral hypoglycemic drugs**, such as sulfonylureas, in children do not require investigation. **Valproic acid**, used for seizure disorders, interferes with fatty acid oxidation and, indirectly, gluconeogenesis. Hence, its toxic effects include nonketotic hypoglycemia, especially during fasting. **Propranolol** has also been reported to cause hypoglycemia in infants treated for hemangiomas and it is thought that the mechanism is through β-adrenergic blockade leading to decreased glycogenolysis, gluconeogenesis, and lipolysis.

e) **Reactive hypoglycemia.** This form of postprandial hypoglycemia is frequently suspected in children and adolescents but is actually quite uncommon. Diagnosis requires demonstration of blood glucose levels <50 mg/dL between the third and fifth hour of an oral glucose tolerance test performed in the prescribed manner (1.75 g/kg with a maximum of 75g p. 651p. 652after 3 days of normal carbohydrate intake). This may be preceded by hyperglycemia during the first 2 hours. Measurements in the critical sample during hypoglycemia will show results consistent with hyperinsulinism (as above). This is commonly seen in children who have had a *Nissen fundoplication* because there is a rapid gastric emptying, and so a **rapid absorption of glucose** (hyperglycemia), followed by a rapid (excessive) release of insulin (hypoglycemia), which is thought to be **mediated by glucagon-like peptide 1 (GLP-1;** and hence hypoglycemia may be **treatable with GLP-1 receptor antagonists**). This may be off-label for children. Treatment involves changes in the feeding regimen to give feeds more slowly, or using lower osmolarity feeds. **Acarbose**, prior to meals has been used as well because it slows the conversion of oligosaccharides to monosaccharides, and so leads to a slower rise in glucose and slower insulin release as well.

IV. SUMMARY

An approach to the diagnosis of hypoglycemia in infants beyond the immediate newborn period and in children is outlined in Table 46-4. The clinical features and differential diagnosis of the most common forms of childhood hypoglycemia are outlined in Table 46-5. Management is discussed for each cause in the text.

TABLE 46-4 Diagnosis of Acute Hypoglycemia in Infants and Children

Acute symptoms present	

1. Obtain blood sample before and 30 min after glucagon administration.
2. Obtain urine first void after hypoglycemic event. Examine for ketones; if not present and hypoglycemia confirmed, suspect hyperinsulinism or carnitine deficiency; if present, suspect ketotic hypoglycemia, hormone deficiency, inborn error of glycogen metabolism, or gluconeogenesis.
3. Measure glucose in original blood sample. If hypoglycemia confirmed, proceed with substrate-hormone measurement as in Table 35-2.
4. If glycemic increment after glucagon is 30 mg/dL or greater above basal, suspect hyperinsulinism.
5. If insulin level at time of confirmed hypoglycemia is >100 μU/mL, suspect factitious hyperinsulinism (exogenous insulin injection). Admit to hospital for provocative testing.
6. If cortisol is <10 μg/dL and growth hormone is <5 ng/mL, suspect adrenal insufficiency or pituitary disease. Admit to hospital for provocative testing.

History suggestive: acute symptoms not present

1. Careful history for relation of symptoms to time and type of food intake, bearing in mind age of patient (Table 32-1); exclude possibility of alcohol or drug ingestion; assess possibility of insulin injection; salt craving; height velocity; intracranial pathology.
2. Careful examination for hepatomegaly (glycogen storage disease; defect in gluconeogenesis); pigmentation (adrenal failure); stature and neurologic status (pituitary disease).
3. Admit to hospital for provocative testing via:
   a. 24-hour fast under careful observation; when symptom provoked, proceed with steps 1 through 4 as when acute symptoms present.
   b. Pituitary–adrenal function via appropriate growth hormone or ACTH stimulation test if indicated.
4. Consider molecular testing or liver biopsy for histology and enzyme determination if indicated.
5. Oral glucose tolerance test (1.75 g/kg; max 75 g) if reactive hypoglycemia suspected in an adolescent.

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TABLE 46-5 Clinical and Differential Diagnoses in Childhood Hypoglycemia

Condition	Hypoglycemia	Ketones (K) or reducing substances (S)	Hepatomegaly	Serum		Glycemic response to glucagon		Effect of 24- to 36-hr fast on plasma/serum				
				Lipids	Uric acid	Fed	Fasted	Glucose	Insulin	Ketones	Alanine	Lactate
Normal	None	0	0	N	N	↑↑	↑	N	↑	↑	↓	N
Hyperinsulinism	Recurrent severe	0	0	N or ↓	N	↑↑	↑↑	↓↓	↑↑	↓↓	↓↓	N
Ketotic hypoglycemia	Severe with missed meals	K+++	0	N	N	↑	0–↑	↓↓	↓	↑↑	↓↓	N
Hypopituitarism	Moderate with missed meals or stress	K++	0	N	N	↑	0–↑	↓↓	↓	↑↑	↓	N
Adrenal insufficiency	Severe with missed meals or stress	K++	0	N	N	↑	0–↑	↓↓	↓	↑↑	↓	N
Glycogen storage disease type I	Severe constant	K+++	+++	↑↑	↑↑	0	0	↓↓	↓	↑↑	↑	↑↑
Glycogen storage disease type III	Moderate with fasting	K++	+	N or ↑	N	↑	0	↓↓	↓	↑↑	↓	N or ↑
Glycogen storage disease type VI	Mild with fasting	K++	+	N or ↑	N	↑	↑	↓	↓	↑↑	↓	N
Glycogen storage disease type IX	Mild with fasting	K++	+	N or ↑	N or ↑	↑	↑	↓	↓	↑↑	↓	N
Glycogen storage disease type XI	Mild to moderate	K++	+	N	N	0–↑	0	↓	↓	↑↑	↓	N

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Glycogen storage disease type 0	Mild to moderate with fasting (postprandial hyperglycemia)	K++	0	↑	N	↓	↓	↓	↓	↑↑	↓	N
Fructose 1,6-diphosphatase deficiency	Severe with fasting	K+++	+++	↑↑	↑↑	↑	0	↓↓	↓	↑↑	↑	↑↑
Galactosemia	After milk or milk products	0–S+++	+	N	N	↑	0	↓	↓	↑	↓	N
Fructose intolerance	After fructose	0–S+++	+	N	N	↑	0–↑	↓	↓	↑	↓	N
Fatty acid oxidation defects	Moderate to severe with fasting	0	0–+	↓	↑	↑	0	↓	↓	↓	N	N–↑
Phosphoenolpyruvate carboxykinase deficiency	Severe hypoglycemia	K0-+	0-+	↑	N	↓	↓	↓	↓	↑	↑	↑
Pyruvate carboxylase deficiency	Mild hypoglycemia	K++	Type B++	N	N	↓	↓	↓	↓	↑	↑	↑

N, normal; 0, absent; ↑, low increase; ↑↑, great increase; ↓, some decrease; ↓↓, marked decrease; +, slight; ++, small; +++, moderate-high.

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47 Congenital Hyperinsulinism

Amanda M. Ackermann and Diva D. De Leon

Congenital hyperinsulinism (HI) is a group of genetic disorders characterized by dysfunctional β-cells that secrete insulin inappropriately, resulting in recurrent hypoglycemia. The hypoglycemia caused by HI is severe and can result in seizures, neurological damage, and even death. Therefore, early recognition, diagnosis, and intervention are recommended. HI is an orphan disease with an estimated incidence of 1:50 000 live births in nonconsanguineous populations.

I. CLINICAL PRESENTATION

As a congenital genetic disorder, HI is present from birth, and most patients present immediately after birth with hypoglycemia. Typical signs of HI in this age group include being large for gestational age, poor feeding, lethargy, and seizure. However, signs of hypoglycemia may escape detection during the neonatal period, so HI should be considered in children of any age with recurrent hypoglycemia. Older children will often describe classic neurogenic and neuroglycopenic symptoms of hypoglycemia including hunger, diaphoresis, irritability, and altered mental status.

II. PATHOPHYSIOLOGY

A. Hyperinsulinism (Fig. 47-1)

1. Insulin secretion is normally inhibited when plasma glucose is <80 mg/dL (<4.4 mmol/L). When plasma glucose rises above this level, glucose is transported into β-cells and phosphorylated by glucokinase (GK) to glucose-6-phosphate, which then enters the glycolysis and tricarboxylic acid cycle (TCA) pathways and produces adenosine triphosphate (ATP). The resulting increase in ATP/adenosine diphosphate ratio closes the ATP-sensitive potassium (K_{ATP}) channels on the plasma membrane of the β cell. This, in turn, depolarizes the cell membrane and opens voltage-gated calcium channels, causing calcium to enter the cell and

activate insulin granules to fuse to the plasma membrane and release their contents. HI is caused by mutations in genes involved in the insulin secretion pathway, resulting in dysregulated insulin secretion without regard for the plasma glucose level.

B. Molecular genetics (Table 47-1 and Fig. 47-1)

1. *ABCC8* and *KCNJ11* encode for the SUR1 and KIR6.2 subunits of the K_{ATP} channels on the *β*-cell plasma membrane. Inactivating mutations in either of these genes result in absent or nonfunctional K_{ATP} channels and persistent *β*-cell depolarization and insulin secretion. This is the most common and severe type of HI. In addition to fasting hypoglycemia, patients are also typically **protein sensitive**, meaning that eating protein stimulates increased insulin secretion and triggers hypoglycemia. Different subtypes of HI are observed depending on the inheritance pattern of the *ABCC8* or *KCNJ11* mutation(s).

a. Biallelic recessive mutations inherited from both parents result in **Diffuse HI**, in which all *β*-cells in the pancreas are affected. This is the **most severe** form of HI.

b. Monoallelic recessive mutations inherited from the father are associated with **Focal HI**, in which *β*-cells within only a portion of the pancreas are affected. Focal HI results from a paternally-inherited heterozygous mutation in *ABCC8* or *KCNJ11* that is duplicated only in a distinct region of the pancreas due to duplication of the paternal, and loss of the maternal, chromosome 11p15 p. 656p. 657region where the *ABCC8* and *KCNJ11* genes are located (for more information, see the Beckwith–Weidemann Syndrome section). Even a small number of dysfunctional *β*-cells is sufficient to cause severe HI, although some of these cases may be less severe than Diffuse HI.

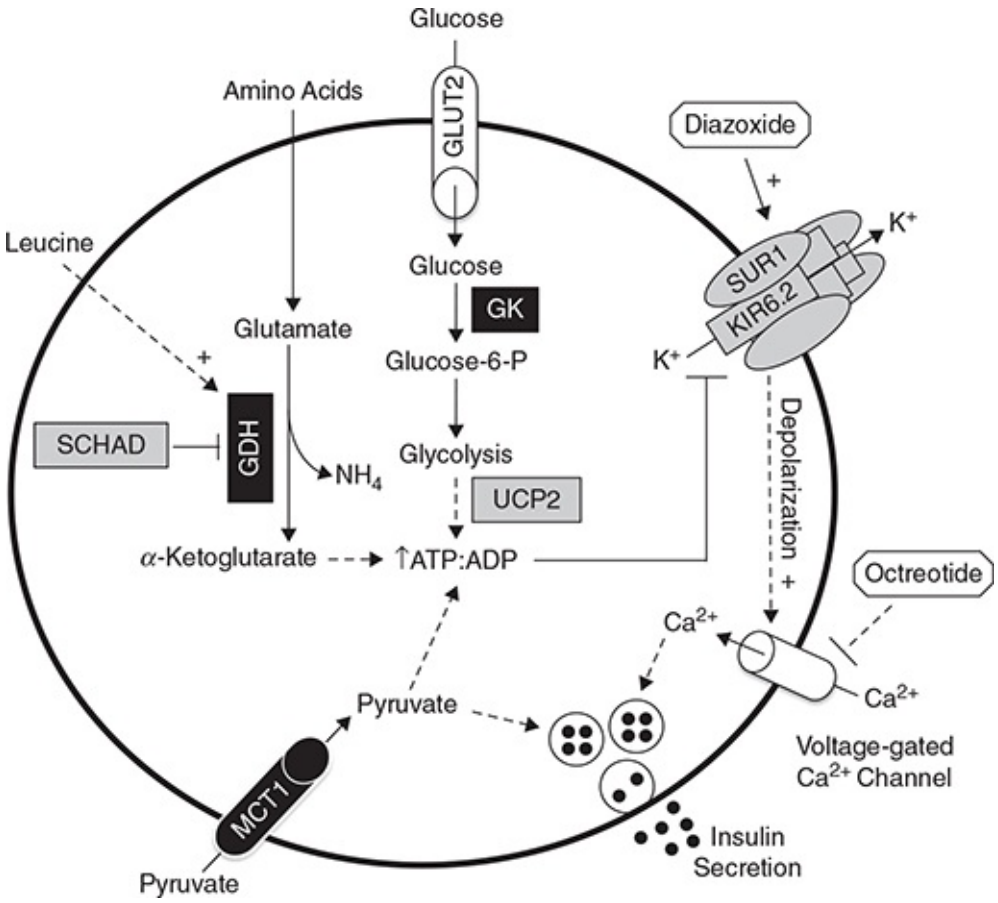

Figure 47-1. Multiple genetic mutations affect β-cell insulin secretion in hyperinsulinism. Proteins with activating mutations are indicated by black boxes, and those with inactivating mutations are in gray boxes. Medications used to treat congenital hyperinsulinism are in hexagons. ADP, adenosine diphosphate; ATP, adenosine triphosphate; GDH, glutamate dehydrogenase; GK, glucokinase; GLUT2, facilitated glucose transporter member 2; MCT1, monocarboxylate transporter 1; SCHAD, short-chain 3-hydroxyacyl-CoA dehydrogenase; SUR1, sulfonylurea receptor 1; UCP2, uncoupling protein 2.

c. Monoallelic-dominant mutations may be inherited from either parent. These heterozygous mutations often produce hypofunctioning, rather than nonfunctioning, K_{ATP} channels, resulting in less severe and more easily manageable HI. However, severe inactivating dominantly inherited mutations have also been described.

2. *GCK* encodes glucokinase (GK). Activating mutations act in a monoallelic-dominant fashion to lower the plasma glucose threshold that stimulates insulin secretion. The severity of the hyperinsulinism and the responsiveness to treatment is highly variable.

3. *GLUD1* encodes glutamate dehydrogenase (GDH), which converts

glutamate to α-ketoglutarate and increases ATP production through the TCA cycle. Activating mutations in *GLUD1* act in a monoallelic-dominant fashion and cause **hyperinsulinism hyperammonemia (HIHA)** syndrome. These patients are highly protein sensitive and have elevated plasma ammonia levels.

4. *HADH* encodes short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD), which normally inhibits GDH. Inactivating mutations inherited in a biallelic recessive fashion result in increased GDH activity, resulting in protein-sensitive HI. The p. 657p. 658phenotype can be distinguished from HIHA syndrome because **plasma ammonia levels are normal and the plasma acylcarnitine profile is abnormal**.

TABLE 47-1 Genetic Mutations That Cause Congenital Hyperinsulinism

Protein	Gene	Inheritance	Clinical features
SUR1, KIR6.2	*ABCC8*, *KCNJ11*	Biallelic recessive	Not diazoxide-responsive Protein-sensitive
		Monoallelic recessive (usually paternal)	Not diazoxide-responsive Protein-sensitive Focal pancreatic lesion (usually)
		Monoallelic dominant	May be diazoxide-responsive or unresponsive Protein-sensitive
GK	*GCK*	Monoallelic dominant	Lower glucose threshold for insulin secretion May be diazoxide-responsive or unresponsive
GDH	*GLUD1*	Monoallelic dominant	Hyperammonemia Protein-sensitive Diazoxide-responsive
SCHAD	*HADH*	Biallelic recessive	Protein-sensitive Abnormal plasma acylcarnitine profile Diazoxide-responsive
MCT1	*SLC16A1*	Monoallelic dominant	Exercise-induced hypoglycemia
UCP2	*UCP2*	Monoallelic dominant	Diazoxide-responsive Transient, resolves within 6 mo to 6 yr
HNF1α	*HNF1A*	Monoallelic dominant	Diazoxide-responsive Transient, resolves by 6 yr Causes MODY3 later in life

HNF4*α*	*HNF4A*	Monoallelic dominant	Diazoxide-responsive Transient, resolves by 4 yr Causes MODY1 later in life

MODY, maturity-onset diabetes of the young.

5. *SLC16A1* encodes monocarboxylate transporter 1 (MCT1), which transports pyruvate into cells. The pyruvate can then enter the TCA cycle and produce ATP, resulting in increased insulin secretion. MCT1 is normally not expressed in *β*-cells, but activating mutations in the promoter region of this gene cause inappropriate expression in *β*-cells. Patients typically have **exercise-induced hyperinsulinism (EIHI)** because of increased circulating pyruvate levels with anaerobic metabolism, which can then enter the *β*-cell and stimulate insulin secretion.
6. *UCP2* encodes uncoupling protein 2, which plays a role in mitochondrial production of ATP. Monoallelic-inactivating mutations in this gene result in **transient HI** that typically resolves by 6 months to 6 years of age.
7. *HNF1A* and *HNF4A* encode hepatocyte nuclear factors 1*α* and 4*α*, respectively. Inactivating mutations in either of these genes can cause transient HI that typically resolves by 4 to 6 years and then can cause maturity-onset diabetes of the young **(MODY)** types 3 or 1, respectively.

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C. Beckwith–Weidemann syndrome (BWS) is caused by either abnormal methylation or paternal uniparental isodisomy (UPD) of the imprinted chromosome 11p15 region. Altered expression of multiple genes within this region results in increased *β*-cell proliferation and increased insulin secretion. Part or the entire pancreas may be affected, depending on the level of genetic mosaicism. Patients with BWS have characteristic features including **macrosomia, macroglossia, hemihypertrophy, omphalocele, and increased tumor risk**, although the phenotype is highly variable. Patients with 11p15 methylation abnormalities typically have mild and transient HI, whereas patients with 11p15 UPD typically have persistent and more severe HI.

III. DIAGNOSIS

A. Laboratory evaluation (Table 47-2)

1. The diagnosis of HI is made based on evidence of increased insulin secretion at the time of hypoglycemia (plasma glucose <50 mg/dL [<2.8 mmol/L]). **Insulin is not always detectable at the time of hypoglycemia in HI**, likely as a result of hepatic metabolism and degradation from sample hemolysis. Thus, the sensitivity of a detectable insulin concentration at the time of hypoglycemia is 82.2%, but the specificity is 100%. Because of the low sensitivity of insulin, the diagnosis is frequently based on other manifestations of excessive insulin secretion, such as suppression of glycogenolysis, lipolysis, and ketogenesis, which are inferred by the findings of a glycemic response to glucagon and the **suppression of plasma free fatty acids and *β*-hydroxybutyrate** (BOHB) during hypoglycemia. Furthermore, an indirect correlation between insulin and insulin-like growth factor binding protein-1 (IGFBP-1) levels has been established. Although some of these laboratory results may be delayed for days, the ability to measure BOHB at the bedside using a ketone meter and to measure glucose at the bedside during the glucagon stimulation test, makes diagnosis at the bedside with some degree of certainty possible. Additional tests may help in the diagnosis of the specific type of HI, for example, plasma ammonia concentration, which is elevated in HIHA and increased concentrations of 3-hydroxybutyryl-carnitine in a plasma acylcarnitine profile and 3-hydroxyglutaric acid in a urine organic acid profile in SCHAD HI. Other causes of hypoglycemia should be ruled out p. 659p. 660by measuring growth hormone (GH), cortisol, lactate, carnitine, acylcarnitines, and urine organic acids.

TABLE 47-2 Diagnosis of Hyperinsulinism

Test at time of hypoglycemia (plasma glucose < 50 mg/dL)	Result	Sensitivity for HI (%)	Specificity for HI (%)
Plasma insulin	≥2 *μ*U/mL	82.2	100
Plasma C-peptide	≥0.5 ng/mL	88.5	100
Plasma *β*-hydroxybutyrate	<1.8 mmol/L	100	100

Plasma free fatty acids	<1.7 mmol/L	86.9	100
Insulin-like growth factor binding protein-1 (IGFBP-1)	≤110 ng/mL	85	96.6
Glucagon stimulation	Increase of plasma glucose by ≥30 mg/dL within 40 min	88.9	100

Ferrara C, Patel P, Becker S, et al. Biomarkers of insulin for the diagnosis of hyperinsulinemic hypoglycemia in infants and children. *J Pediatr* 2016;168:212–219.

B. Fasting evaluation

1. If labs are unable to be drawn during an episode of spontaneous hypoglycemia, then the patient should undergo a formal fasting evaluation. Feeds should be discontinued, and IV glucose support weaned off while plasma glucose levels and vital signs are monitored closely. Once the plasma glucose level is <50 mg/dL (<2.8 mmol/L), then the critical sample can be obtained followed by the glucagon stimulation test.

C. Genetic testing

1. **Gene sequencing panels** are available for testing the genes known to be associated with HI. Specific panels may be indicated based on the patient's history and presentation, as described above. For patients in whom surgery is being considered, genetic testing should be performed by a laboratory that can provide prompt results and reflexive parental genetic testing.
2. If a mutation in *ABCC8* or *KCNJ11* is identified in the patient, then specific genetic testing should be performed on samples from both biological parents because of the different inheritance patterns associated with different forms of K_{ATP} channel HI, as described above.
3. Genetic testing for BWS should be performed in consultation with a trained geneticist. Deletion/duplication and methylation analyses should both be performed, keeping in mind the mosaic nature of BWS means that **findings from a blood sample are not necessarily representative of abnormalities in the pancreas or other tissues**.

D. Imaging

1. If there is concern for Focal HI, based on the finding of a monoallelic *ABCC8* or *KCNJ11* mutation that is not diazoxide-

responsive, then noninvasive imaging with ^{18}fluoro-l-dihydroxyphenylalanine positron emission tomography and computed tomography (^{18}F-DOPA PET/CT) should be performed to identify the location of the focal abnormality. This test has a sensitivity and specificity of 85% and 96%, respectively, which is superior to other imaging modalities, and it is less invasive than calcium arterial stimulation with venous sampling. 18F-DOPA PET/CT is almost 100% accurate in localizing focal lesions.

2. Ultrasound of the pancreas can be performed intraoperatively to aid in localization of focal lesions, but transabdominal ultrasound is not useful to localize focal lesions.

E. Pathology

1. If pancreatectomy is indicated, based on the diagnosis of Focal HI and/or failure of medical management, then pancreatic biopsies should be obtained to aid in diagnosis and management. Diffuse HI is characterized by normal islet number and appearance, with the exception of islet cell nucleomegaly. In contrast, Focal HI is characterized by a discrete region of islet hyperplasia with islet cell nucleomegaly. Histopathology in BWS is quite variable, with the extent of abnormalities correlating with the level of genetic mosaicism in the pancreas; increased islet cell number with or without nucleomegaly is typically observed.

IV. MANAGEMENT (Fig. 47-2)

The goal of treating children with HI is to **maintain plasma glucose concentration >70 mg/dL (>3.9 mmol/L).** This can be achieved by medical and/or surgical therapies, depending on the underlying genetic cause of HI. Often, a combination of therapies is indicated.

A. Acute

1. **Glucose** can be administered as an IV bolus (0.2 g/kg) for acute severe hypoglycemia. Continuous IV glucose is typically required to maintain euglycemia in patients with HI until other therapies are implemented. Glucose infusion rate (GIR) up to 20 to 30 mg/kg/min may be necessary, for which a central line is indicated.
2. **Glucagon** counteracts insulin action, and it can be administered as either 1 mg IV or IM for acute severe hypoglycemia or as a continuous IV infusion of 1 mg/24 hours for patients requiring high GIR.

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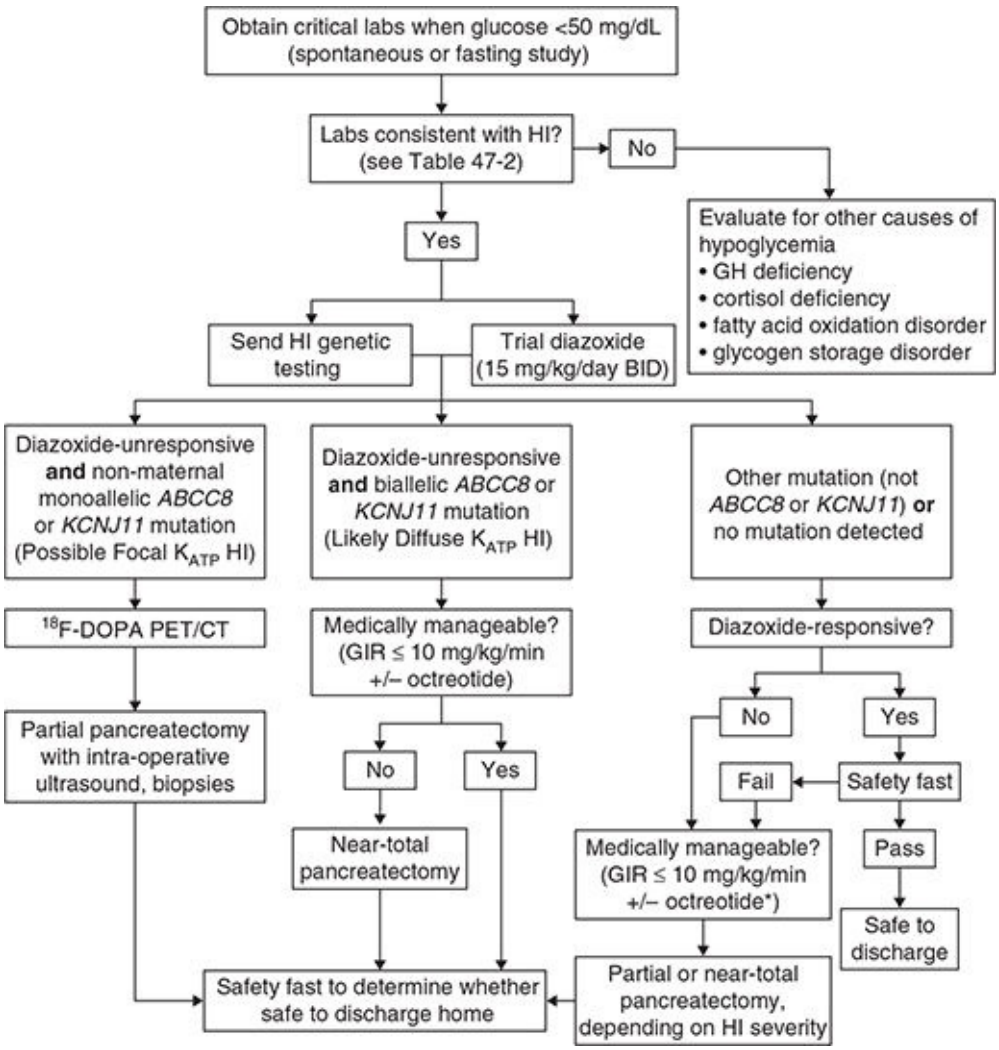

Figure 47-2. Management of hyperinsulinism. *Octreotide is relatively contraindicated in young neonates and those with risk factors for NEC, due to increased risk of NEC. BID, two times a day; F-DOPA PET/CT, fluoro-l-dihydroxyphenylalanine positron emission tomography and computed tomography; GH, growth hormone; GIR, glucose infusion rate; HI, hyperinsulinism; NEC, necrotizing enterocolitis.

B. Long term

1. **Diazoxide** is a **K_{ATP} channel agonist;** it binds to and opens K_{ATP} channels, preventing membrane depolarization and insulin secretion. Therefore, it is only **effective in patients with functioning K_{ATP} channels** (i.e., not patients with Diffuse or Focal HI). Diazoxide is effective in some patients with

monoallelic-dominant *ABCC8* or *KCNJ11* mutations, *GCK* mutations, and *SLC16A1* mutations and in patients with *GLUD1*, *HADH*, *UCP2*, *HNF1A*, and *HNF4A* mutations. Therefore, diazoxide responsiveness may be utilized as a diagnostic tool to distinguish those patients that may have a K_{ATP} channel defect, of which 50% may have Focal HI. Because of its long half-life (~22 hours), a trial of maximum dose diazoxide for 5 days is typically recommended for patients with HI. Typical dose range is 5 to 15 mg/kg/day divided every 12 hours.

2. **Octreotide** is a **somatostatin** analog that inhibits voltage-gated calcium channels and thus decreases insulin secretion (and secretion of other hormones from other endocrine cells). It can be administered IV or subcutaneously. Various dosing regimens often need to be tried before finding the best dose(s) and schedule for

p. 661p. 662each patient. Typically, 5 to 17 μg/kg/day is divided evenly or unevenly into 2 to 4 doses. Continuous subcutaneous infusion may also be used. Long-acting somatostatin analogs are now available and have been used with some success in diazoxide-unresponsive cases.

3. **Glucose infusion** by an enteral route can be used in combination with other therapies in patients with recurrent hypoglycemia. Typically, we recommend **limiting the enteral glucose infusion to <10 mg/kg/min** due to increased gastrointestinal distress with higher osmolality infusions. Combination therapy with enteral glucose infusion and octreotide (see below) is often effective in controlling the hypoglycemia in children with persistent hypoglycemia after pancreatectomy.
4. **Surgical resection** is indicated in most cases of Diffuse and Focal HI and in some cases of BWS.
    a. **Diffuse HI** that cannot be medically managed is an indication for near-total (95% to 98%) pancreatectomy. This results in approximately 23% of patients being euglycemic and not requiring any medical support, 41% requiring some type of medical support to maintain euglycemia, and 36% rapidly developing diabetes requiring insulin therapy.
    b. **Focal HI** can be cured by resection of the abnormal pancreatic region. Typically, this requires removal of a much smaller

portion of the pancreas compared to Diffuse HI. The median extent of pancreatectomy at our center for Focal HI is 27%, ranging from 1% to 100%, with a cure rate of 94%.

c. **BWS** may require partial pancreatectomy if the HI is severe and persistent. Intraoperative biopsies are particularly useful for guiding the extent of resection.

5. **Repeat fasting studies** are required (1) to determine whether the patient is safe on their current therapeutic regimen and (2) to determine whether the patient is cured after resection if they have Focal HI. These fasting studies should be performed similarly to the diagnostic fasting study (see above), with feeds and glucose being held but other therapies continued, close monitoring of plasma glucose and vital signs, and laboratory evaluation and a glucagon stimulation test if/when plasma glucose is <50 mg/dL (<2.7 mmol/L) or at the end of the study. The goal is for patients to be able to maintain plasma glucose >70 mg/dL (>3.9 mmol/L) for 8 to 12 hours if <1 month of age or for 12 to 18 hours if >1 month of age. These safety goals are based on children's feeding and fasting/sleeping schedules. Fasting studies should be performed routinely (we recommend annually) so that therapy adjustments can be made if indicated as the patient grows.

V. COMPLICATIONS

A. Neurological development

1. Children with HI have increased prevalence of developmental delays and disability compared to the normal population. In some studies, the prevalence of developmental deficits is as high as 48% and includes not only children with permanent forms of HI but also children with transient and focal forms of HI, suggesting that the initial insult from hypoglycemia prior to treatment contributes to the poor outcomes.
2. Routine evaluation by a developmental/behavioral pediatrician is recommended for all patients with HI at 12 to 18 months and at 5 years prior to school initiation.

B. Hypertrophic cardiomyopathy

1. Approximately **15% of patients** with Diffuse or Focal HI have associated hypertrophic cardiomyopathy at the time of HI diagnosis, which is likely due to insulin's growth promoting effect in utero and postnatally.

2. Baseline cardiology evaluation should be considered in all patients with Diffuse or Focal HI.

C. Feeding aversion

1. Feeding aversion is very common in children with HI, particularly in infants with severe HI requiring high rates of dextrose infusion to maintain euglycemia and prolonged hospitalizations.
2. To prevent feeding aversion, it is important that oral feedings (bottle or breastfeeding) are kept as normal as possible, allowing the infant to feed on demand, p. 662p. 663rather than practicing force feeding or feeding by nasogastric tube to control the hypoglycemia. We strongly advise against using feedings to control the hypoglycemia.

D. Medication side effects

1. **Diazoxide**
   a. **Fluid retention** is one of the most common and rapidly developing side effects of diazoxide, particularly in young infants. Attention should be paid to signs and symptoms of hypervolemia (rapid weight gain, edema, respiratory distress).
      i. All young infants started on **diazoxide should also be given hydrochlorothiazide diuretic**, particularly those receiving intravenous fluids.
      ii. Older children on diazoxide should be given a diuretic if clinically indicated.
   b. **Hypertrichosis** occurs within months of continued diazoxide use and directly correlates with dose.
   c. **Appetite suppression** occurs frequently, especially in young patients. Enteral tube feeds are often needed temporarily.
   d. **Hyperuricemia** may occur due to decreased urinary excretion of uric acid and typically does not warrant intervention unless clinically significant.
   e. **Bone marrow suppression** is a rare but serious side effect of diazoxide therapy and can occur at any time.
      i. If this occurs, the diazoxide should be discontinued. It can be restarted at a lower dose once cell counts have recovered.
   f. **Screening** with complete blood count with differential, basic metabolic panel, and uric acid level every 6 months is recommended.

2. **Octreotide**
    a. **Transaminitis** (elevated liver enzymes) occurs in at least 40% of patients on octreotide. This is typically mild, transient, and does require further workup; however, severe hepatitis has been reported.
    b. **Biliary sludging and cholecystitis** occurs in approximately 30% of patients on octreotide and may require medical therapy with **ursodiol** or invasive intervention with percutaneous or endoscopic drainage or cholecystectomy.
    c. **Hypothyroidism and/or growth retardation** may occur due to inhibition of secretion of thyroid stimulating hormone and/or GH, respectively, from the pituitary gland. This is more commonly seen in patients on high doses of octreotide.
    d. **Necrotizing enterocolitis (NEC)** is a rare but serious side effect of octreotide that is thought to be due to decreased splanchnic blood flow. This occurs more frequently in young infants and patients with other risk factors for NEC (preterm, prior abdominal surgery, cardiac anomaly); therefore, octreotide use in these populations is relatively contraindicated.
    e. **Screening** with hepatic function panel, thyroid function tests, and growth factors (IGF-1, IGFBP-3) is recommended every 6 months, and liver/gallbladder ultrasounds are recommended every 6 to 12 months.

E. Surgical outcomes

1. **Diabetes** presents acutely in approximately 36% of patients with Diffuse HI who undergo near-total pancreatectomy, but this prevalence increases to over 90% by 14 years. Patients with subtotal (<60%) pancreatectomy are at significantly lower risk of developing diabetes, although extent of pancreatectomy, family history, and obesity risk factors should always be considered.
2. **Pancreatic exocrine insufficiency** occurs in 50% to 72% of patients with Diffuse HI who undergo near-total pancreatectomy. Similar to patients with pancreatic-insufficient cystic fibrosis, these patients may experience weight loss, poor growth, and frequent infections associated with malnutrition. Treatment with pancreatic enzyme replacements and fat-soluble vitamin supplementation is indicated for these patients.
3. **Screening** with annual hemoglobin A_{1c}, fecal elastase level, stool

fat, and fat-soluble vitamin (A, D, E, K) levels is recommended for all patients who underwent near-total pancreatectomy.

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SECTION 8

Inborn Errors of Metabolism

48

Introduction to Inborn Errors of Metabolism

Stephen D. Cederbaum and Derek A. Wong

I. GENERAL PRINCIPLES

Genetically determined inborn errors of metabolism are individually rare, but collectively they affect more than **1 in 500** individuals in the population. An abnormality in deoxyribonucleic acid (DNA) is expressed by the production of an enzyme that is deficient in its function of catalyzing and modulating the conversion of substrate to product. Each DNA abnormality results in a uniquely different protein product, some retaining full enzymatic potency, others retaining none, and others something in between. The resulting clinical picture ranges from normal to severely affected; the former can differ significantly in nature as well as severity from the most profound expression of the mutation. The severity of the clinical illness is influenced by other genetic characteristics and environmental circumstances of the patient. Many affected individuals have mental retardation and neurologic damage as cardinal features, but visceral organs may be affected, particularly in disorders of energy metabolism.

A. Inheritance. Inborn errors of metabolism are generally inherited in an autosomal recessive or, less frequently, in a sex-linked recessive manner. Some disorders of energy metabolism are caused by mutations in the mitochondrial genome and are maternally inherited. Instances of dominantly inherited inborn errors are rare, largely because 50%

residual enzymatic activity appears to be sufficient for the retention of a normal phenotype. Some female carriers of sex-linked disorders can express the abnormal biochemical phenotype, probably because of the effect of skewed X-chromosome inactivation.

B. Categories. Inborn errors of metabolism can be divided into different categories (Table 48-1). The disorders of smaller, water-soluble substrates such as amino acids, organic acids, and sugars and disorders that impair energy generation in particular can cause acute disease, whereas those in the remaining categories cause more insidious disorders in which the onset of organ damage is slower and more indolent. Newer categories of disease are emerging as well; these are included in the list but are not discussed in detail. This discussion focuses on the first three categories because they are the most common, best understood, and most amenable to therapy. A number of inborn errors may present with hypoglycemia, but this is discussed elsewhere (see Chapter 46).

C. Newborn screening. No discussion of inborn errors of metabolism would be complete without a consideration of the expanding palette of disorders for which newborn p. 665p. 666screening has either been implemented or is contemplated. All US jurisdictions and most in Canada test for the majority of inborn errors of amino, organic, and fatty acid metabolism and encompass virtually all those for which effective intervention is available, except disorders of ammonia metabolism, energy metabolism, and blood sugar regulation (see Chapter 46). With an entire group of intoxicating metabolic disorders screened at birth, the probability of metabolic disorders in a sick newborn who has screened-negative is greatly diminished. Every newborn intensive care unit needs to know how to obtain the newborn screening results as quickly as possible. The palette of disorders that are screened at birth is expanding rapidly.

TABLE 48-1 Classification of Inborn Errors of Metabolism

Small molecules
- Amino acids
- Organic acids
- Sugars

Lysosomal storage diseases
- Mucopolysaccharidoses

- Sphingolipidoses
- Mucolipidoses

Disorders of energy metabolism

- Oxidation defects
- Disorders of fatty acid mobilization and metabolism
- Glycogen storage diseases

Peroxisomal disorders

Disorders of cholesterol synthesis

Transport disorders

Carbohydrate-deficient glycoprotein disorders

Defects in purine and pyrimidine metabolism

Disorders of neurotransmitter metabolism

Receptor defects

D. DNA. The explosion in the application of recombinant DNA methods to inborn errors of metabolism has altered our approach to these disorders in a number of diagnostic and therapeutic ways (e.g., utilizing DNA probes for prenatal diagnosis). Even now, the workup of an inborn error of metabolism has moved away from liver biopsy and other invasive studies in favor of DNA diagnosis. In the future, sick newborns will be diagnosed with rapid genetic panels or exome or whole genome analysis rather than require a battery of biochemical and other tests.

II. DIAGNOSIS

A. Patient population and clinical features. Except for that special category of disorders whose diagnosis is made, often pre-emptively, by population-wide newborn screening, the diagnosis of inborn errors of metabolism is established by recognizing a population of patients at higher risk, ascertained as a result of the presence of specific clinical features (Table 48-2). The clinical features can vary from neonatal collapse to a chemical abnormality lacking any clinical correlate. The early onset of symptoms or the profound metabolic derangements of later or intermittent occurrence are medical emergencies that require immediate therapeutic intervention. Examination of this list of clinical and laboratory findings in inborn errors clearly demonstrates that they are not unique to this group of diseases. The choice of patients to study further is based on one of three criteria:

1. A single sign or symptom persisting without adequate explanation

Several of the clinical findings coexisting without any other known basis

3. A clinical crisis compatible with an inborn error, making wholly rational and stepwise evaluation dangerously impractical

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TABLE 48-2 Clinical and Laboratory Clues Suggesting the Presence of an Inborn Error of Metabolism

Signs and symptoms
- Neonatal catastrophe
- Developmental retardation
- Failure to thrive
- Gastrointestinal disorders
- Hyperpnea
- Neurologic and behavioral abnormalities including coma
- Peculiar odors
- Organomegaly
- Ocular and/or hearing abnormalities
- Cutaneous changes
- Skeletal abnormalities

Laboratory clues
- Urine: ketones, reducing substances
- Blood: pancytopenia, acidosis, hypoglycemia, ketonemia

Course
- Developmental arrest or regression

Family history
- Consanguinity
- Similar illness

B. Diagnostic tests

1. **Inborn errors of small molecules and energy metabolism.** Table 48-3 lists those tests that are part of the complete, short-term, evaluation for inborn errors of intermediary metabolism. The routine tests listed are available in all but the smallest hospitals, whereas the specialized tests are sometimes available in tertiary centers for the study of inborn errors and, more prevalently, in some commercial clinical laboratories. The most commonly used specialized studies are the plasma amino acid, plasma acylcarnitine, and urinary organic acid analyses. Urinary

p. 667p. 668organic acids and plasma acylcarnitines are most revealing in instances of acute, chronic, or intermittent **metabolic acidosis**. Spot specimens are usually adequate except in those instances in which the course is clearly intermittent. As we have become more aware of disorders of fatty acid oxidation as causes of inherited metabolic disease, plasma carnitine levels are more frequently obtained. With the advent of expanded newborn screening, virtually all children in developed countries will have been screened for disorders of amino acids, organic acids, fatty acid oxidation, and galactosemia. The previously used metabolic profile testing is most effectively deployed when reserved for children with a higher index of suspicion for an inborn error, and less as a routine procedure.

TABLE 48-3 Laboratory Evaluation of Patients Suspected of Having an Inborn Error of Metabolism

Generally available studies • Blood sugar • Plasma and urine ketones • Blood pH and true bicarbonate • Blood lactate (and pyruvate) • Plasma ammonia Specialized studies • Plasma amino acids • Urine organic acids • Plasma carnitine • Blood (or plasma) acylcarnitines • Mitochondrial DNA analysis • Whole exome analysis and other DNA studies
DNA, deoxyribonucleic acid.

2. **Lysosomal storage diseases.** These disorders are characterized by relatively more normal levels of metabolites in the body fluids and more significant abnormality within affected cells. The diagnosis is often suggested by the physical characteristics of the patients, which include coarsened physical

features, abnormalities of the bones (described as dysostosis multiplex), and visceral enlargement. Standard laboratory approaches are listed in Table 48-4. Urine studies can indicate some lysosomal enzyme disorders through the detection of partially hydrolyzed, endogenous cellular constituents. Biopsy can expose abnormal material accumulation in cells, but is now being replaced by gene studies described previously. In centers with experience in reading conjunctival biopsies, this material is preferred to skin because of the wide variety of cell types represented and its diagnostic sensitivity. The plasma "lysosomal enzyme screen" is an ill-defined, and variable battery of lysosomal enzyme assays that is variable between laboratories. This approach carries a risk of misleading the clinician into believing, falsely, that all lysosomal enzyme abnormalities have been ruled out. More precise urine and blood testing is available in highly specialized laboratories, but gene panels or whole exome testing is likely to become the "screening" approach of choice. Newborn screening for many of these disorders is on the horizon.

3. Careful **neurologic and ophthalmologic evaluation** had been crucial to the diagnosis of a number of inborn errors of metabolism. Specialized tests might have included auditory and somatosensory evoked responses, nerve conduction times, electromyograms, electroretinograms, and visual evoked responses. A lumbar puncture would have been performed in any patient with undiagnosed neurologic disease, and glucose, amino acids, neurotransmitter, and lactate levels obtained. Nuclear magnetic resonance spectroscopy (MRS) is still a powerful tool to measure brain levels of creatine, lactate, and glutamine, among others, and data for this analysis should be obtained whenever a neurologically handicapped child is having magnetic resonance imaging (MRI). If no diagnosis is made on MRI, then the MRS data should be analyzed. Nevertheless, as next generation tests, such as whole exome analysis, have a more rapid turnaround, clinicians may bypass many of the above-mentioned, older invasive studies.
4. **Enzymatic confirmation.** Some disorders of intermediary metabolism involve the only known enzyme responsible for the metabolism of a substrate, and in that case enzyme assay is redundant. In other instances, the substrate accumulation can be

due to a deficiency in one of several enzymes, so that appropriate therapy and an accurate prognosis depend on laboratory confirmation of the precise defect. For the most part, enzymatic or DNA confirmation of a putative p. 668p. 669defect should be the goal in every instance of an inborn error of intermediary metabolism, especially if prenatal diagnosis is contemplated.

TABLE 48-4 Diagnosis of Lysosomal Diseases

Urinary mucopolysaccharide studies
Urinary oligosaccharide chromatography
Histologic examination of skin or conjunctival biopsy
Plasma “lysosomal enzyme screen”
Gene panels, Whole exome analysis or other deoxyribonucleic acid (DNA) studies

5. **DNA studies.** The availability of DNA probes for many of the abnormal genes involved in inborn errors of metabolism has led to a definition of the primary genetic abnormality and to relatively simple means of diagnosis of those frequently seen in certain disorders. DNA studies might be preferable for those disorders in which the enzymatic diagnosis is difficult or not readily available, especially in prenatal diagnosis, where substrate accumulation can also fall short as a diagnostic indicator. Mitochondrial DNA studies were used frequently as a screen for disorders of the electron-transport chain, but the efficiency of this approach was open to question, particularly in patients in whom the prior probability is low. With advancing technology, the cost of sequencing DNA is falling and its ease is increasing. It is probable that whole exome DNA diagnosis, which probes both the mitochondrial and nuclear genomes will replace some enzyme assays as the confirmatory diagnostic method of choice, especially for those conditions that require invasive procedures, such as a liver biopsy or muscle biopsy, for diagnosis. The practitioner must remember, however, that DNA studies are not 100% accurate, and patients with “normal” sequencing whose clinical and biochemical features match a specific disorder may not be able to avoid enzyme assay or

biopsy.

III. TREATMENT

A. General approaches

1. **Small molecules and disorders of energy metabolism.** Management of these inborn errors is directed at alleviating the substrate accumulation or replacing the missing products of the reaction. There are two approaches to this: direct environmental manipulation of the metabolites, and augmentation or stabilization of the enzymatic levels. Gene and stem cell therapy are under investigation but are not yet ready to be used to treat inborn errors of metabolism. The different strategies for accomplishing these goals are given in Table 48-5.

   a. The most common treatment for disorders of intermediary metabolism is the **elimination diet** pioneered for **galactosemia** two generations ago and probably best associated with **phenylketonuria** (PKU). Whereas one can still constitute the galactose-poor diet for galactosemia from natural foods, that for PKU and for most other disorders is partially semisynthetic and derived from proprietary products. In the United States, a variety of dietary components are available from a number of companies, now too numerous to mention. These products can cause malnutrition if improperly used, and treatment is best carried out with the assistance of an expert in these disorders, at least until the pitfalls are p. 669p. 670clearly understood. Unlike in antibiotic therapy, the composition and amount of different components of the diet must be individualized for each patient because of the principles outlined at the beginning of this chapter. Therapy for an acute life-threatening episode is a unique instance in the application of these principles and is outlined in Section III.B.

TABLE 48-5 Therapeutic Strategies for Inborn Errors of Intermediary Metabolism

Metabolite manipulation • Substrate limitation • Product supplementation

- Substrate diversion
- Inhibition of proximal enzyme

Enzyme augmentation

- Coenzyme (vitamin) supplementation
- Enzyme induction
- Enzyme replacement
  - Allotransplantation
  - Direct enzyme administration
    - “Chaperone treatment”

Gene replacement

b. Product supplementation is well illustrated by the administration of glucose in glycogen storage diseases or excess lipid in pyruvate dehydrogenase deficiency. Several disorders, such as pyruvate dehydrogenase and pyruvate carboxylase deficiency, involve highly regulated enzymes in which moment-to-moment modulation of substrate-to-product transformation is mandatory. In these instances, external efforts to regulate metabolite levels are at best approximations of circumstances in the normal population, and only suboptimal results can be expected.

c. More recently, a new approach has been brought to bear on the **control of substrate or precursor levels**. This involves augmenting precursor restriction with pharmacologic doses of chemicals that divert the poorly metabolized compounds into auxiliary pathways, diminishing the load on the defective enzymatic function. This is best illustrated by the use of **benzoate and phenylacetate** (or phenylbutyrate) in the management of **hyperammonemia due to urea cycle disorders**. Benzoate is excreted as benzoylglycine (hippurate) and phenylacetate as phenylacetylglutamine, removing, respectively, 1 and 2 moles of nitrogen for each mole of drug added. Glycine and glutamine, when resynthesized in the body, divert ammonia that would have gone into the urea cycle. Similar approaches can prove useful with carnitine and glycine in organic acid disorders such as methylmalonic or isovaleric acidemia and with betaine in homocystinuria.

2. Vitamin or cofactor supplementation is usually useful only for those disorders in which the deficient enzymatic phenotype is

vitamin responsive and refers only to the augmentation of the vitamin specifically involved in that reaction. Several types of inborn errors are involved.

a. In the first, exemplified by vitamin B_{12}–responsive **methylmalonic acidemia,** the vitamin normally undergoes five or more genetically controlled processing steps prior to its function as cofactor in the enzymatic reaction converting methylmalonyl coenzyme A (methylmalonyl-CoA) to succinyl-CoA. Inherited deficiencies in these processing steps can be partially bypassed by administering huge doses of **vitamin B_{12}** (1 000 times the normal requirement, daily or several times a week).

b. In the second type, the deficient enzyme is the catalytic one, which in some instances of specific mutations responds to augmented doses of its normal vitamin cofactor. This is best exemplified by vitamin B_6 (pyridoxine)–responsive **homocystinuria**. The concordance of B_6 responsiveness in affected siblings in individual families confirms the site of the abnormality in the cystathionine synthase enzyme protein.

c. In a third type, a vitamin cofactor or a compound mimicking a substrate or an inhibitor can act as a "chaperone" or stabilizing element for a mutant enzyme that has a shortened half-life in the cell. An example of this is **tetrahydrobiopterin (BH_4)**, a normal cofactor in the phenylalanine hydroxylase reaction. In some instances of missense mutations in the gene, it can stabilize the enzyme and allow better phenylalanine control and/or a more relaxed diet in patients with PKU.

d. There are a number of proposals or protocols extant that suggest a cocktail of vitamins for treatment of disorders of the mitochondrial respiratory chain. Some of these are rational, but none has been proven efficacious.

e. Variations on the theme of molecular chaperones have been developed for some lysosomal disorders. Other therapies for these complex disorders of catabolic enzymes involve diminution of the biosynthesis of the essential biologic compound in the body.

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3. **Enzyme replacement** with newer preparations of enzyme has proven to be effective for the palliation of **adenosine deaminase deficiency** and for **Gaucher disease** and an enlarging number of lysosomal storage disorders. The treatment costs are high, organ penetration is variable, and treatment is time intensive, but the approach represents a new and hopeful modality for patients who suffer from disorders that were previously untreatable.
4. **Bone marrow and renal transplantation** seems to be effective in some cases of **lysosomal storage diseases,** whereas liver transplantation has been effective in disorders of intermediary metabolism, such as **hepato-renal tyrosinemia, Wilson disease, maple syrup urine disease,** and **urea cycle disorders,** in which activity of the missing enzyme is largely confined to the liver. Continued excitement and progress in this area are likely because all of the reagents and animal models are available for a number of disorders.
5. 2-(Nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione has been proven to be very efficacious in **hepatorenal tyrosinemia**, presumably by starving the pathway of its toxic metabolite. Small-molecule inhibitors of glycosaminoglycan and sphingolipid biosynthesis are being studied as substitutes for or augmenters of enzyme replacement therapy in lysosomal storage disorders. Unlike the enzymes, they are usually accessible to the central nervous system. Eliglustat (Cerdelga) has U.S. Food and Drug Administration approval for the treatment of type 1 **Gaucher disease**.
6. **Gene therapy** was much discussed at the time of the last edition of this book and while creeping toward maturity, large-scale clinical trials are just beginning. Stem cell therapy seems still further from practical application, and except for some eye disorders, is not in clinical trials.

B. Therapy of acutely ill patients

1. **Diagnosis unknown.** The acute catastrophic presentation of an inborn error of metabolism requires **prompt** and decisive therapeutic **intervention,** even when the diagnosis is unknown. Therapy for these acutely ill infants must begin at once and then be modified when the diagnosis becomes known.

   a. At birth, the **signs and symptoms** are those of general

multiorgan failure and cannot be distinguished from other neonatal emergencies, such as sepsis. They include lethargy, somnolence, irritability, rapid shallow respirations, jitteriness or seizures, poor temperature control, metabolic acidosis, hypoglycemia, and hypocalcemia. In older patients, the symptoms appear as an exaggerated response to minor infection or other stress and include neurologic signs, somnolence, acidosis, and, in some instances, hypoglycemia. The patients are often considered to have the Reye syndrome, as a result of lethargy or coma, hepatomegaly with fat infiltration, hyperammonemia, hypoglycemia, and elevated plasma transaminase levels.

b. Specimens for positive **diagnosis** must be obtained before the initiation of therapy, if possible. In case, the patient's life cannot be saved, a rapid autopsy freezing liver, kidney, and brain at −70°C is advisable.

c. The principles of **therapy** at any age are similar, but the application requires modification according to the age and physiologic constraints of the patient.

If the situation is sufficiently serious, and death or permanent brain damage seems imminent, peritoneal dialysis, at least, must be undertaken. Exchange transfusion is ineffective for disorders in which metabolite binding to plasma protein is not a problem. At least one exchange per hour of a twice-normal-osmolality dialysate should be used. However, peritoneal dialysis is considerably less effective than hemodialysis or extracorporeal membrane oxygenation. If deterioration continues and death seems possible, massive doses of all water-soluble vitamins (up to 1 000 times normal) are given. **In cases of lactic acidosis, this vitamin mixture should include biotin.** Once a definite or probable diagnosis has been made, more specific therapy can be instituted. Whenever possible, the treatment should be undertaken in consultation with a metabolic specialist and, if feasible, transfer to an appropriate tertiary center is desirable.

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i. Temporary **elimination of protein** intake is mandatory in most instances and harmful in none. To minimize

endogenous protein catabolism and gluconeogenesis, adequate calories in the form of carbohydrate and fat must be administered intravenously or intragastrically, with insulin if hyperglycemia occurs.

ii. If metabolic acidosis is present, **blood lactate levels** must be ascertained, because at least one form of lactic acidosis is made worse by excessive glucose administration. In these instances, minimizing glucose intake to that needed to maintain blood glucose in the normal range and increasing fat is desirable.

iii. **Bicarbonate** may be considered in cases of severe metabolic acidosis.

2. **Diagnosis known.** Although a protein-free diet is appropriate for the acute, **short-term care of patients in virtually all metabolic catastrophes**, soon plasma amino acid depletion causes protein breakdown and excessive levels of any amino acid whose catabolic pathway is impaired. Adequate regulation of plasma metabolite levels involves either intravenous or nasogastric repletion with an amino acid mixture properly constituted for the particular disorder.

   a. In **maple syrup urine disease,** a branched-chain-free amino acid mixture is used, with frequent plasma amino acid analyses to determine the appropriate amount of leucine, isoleucine, and valine added, usually from natural sources. Supplemental isoleucine and valine is usually required.

   b. In **urea cycle defects,** an essential amino acid mixture is used, and lower amounts may be required to keep ammonia levels near or in the normal range.

      In most instances, specific or adaptable amino acid mixtures are unavailable for intravenous use, and enteral therapy with the amino acids alone is required. Fortunately, an adequate enteral amino acid intake can be provided in extremely low volume. Amino acid preparations for a number of these disorders are available from commercial sources, but expect a delay of several days to acquire them. These are not typically available in community, or even tertiary care hospitals.

   c. **Hyperammonemia** in which a primary organic acidemia is probably not the cause, calls for special measures. In most instances, a sustained ammonia level of 250 μM (~400 mg/dL)

constitutes a serious threat to the central nervous system and, unless transient, should stimulate a heroic therapeutic response. The linchpin of this response, as noted, is dialysis. Because **increased intracranial pressure** is a common and threatening complication, efforts to ascertain and follow it are in order. Therapy consists of mannitol, extracellular volume depletion (difficult, but not impossible with dialysis), phenobarbital coma (efficacy not proven), central hypothermia (not proven), and hyperventilation. Sodium benzoate and sodium phenylacetate in a combined preparation (Ammonul) are available and are given as a loading and maintenance dose.

d. One product of the urea cycle is **arginine,** and this ordinarily semiessential amino acid can be deficient in most of these disorders. It is used in supplementing patients with most forms of urea cycle disorders other than arginase deficiency. In the case of **citrullinemia** and especially **argininosuccinic acidemia,** arginine can correct the hyperammonia. Fortunately, arginine hydrochloride is readily available as an intravenous preparation for growth hormone studies. Its use can induce hyperchloremic acidosis, and patients must be closely monitored for this.

C. Long-term therapy. This form of treatment is the heart of the management of inborn errors of metabolism and embodies the same principles enumerated for the acute management of this class of disorders. Patients may require restriction of the substrate and provision of the product. They must be adequately nourished. Enzyme levels must be maximized, and catabolism is best avoided. In this circumstance, when immediate intervention is not required, therapy is best supervised by individuals trained in the management of these disorders.

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1. The hyperphenylalaninemias

a. No family of disorders better epitomizes the problems and principles in the approach to the inborn errors of metabolism than the hyperphenylalaninemias, the **most common family of the intoxicating amino acid disorders**. They will be used to illustrate the principles of long-term therapy in inborn errors. The majority of patients with hyperphenylalaninemia (in

the Western developed countries) have a partial or complete deficiency of the apoenzyme phenylalanine hydroxylase. About 1% or fewer of patients are deficient in the ability to synthesize or reduce the cofactor dihydrobiopterin. The reduced form, tetrahydrobiopterin, also participates in the hydroxylation of tyrosine and tryptophan to L-DOPA and serotonin. The enzyme deficiency leads to deficiency of these neurotransmitters and a quite different and less readily treatable disorder. The primary enzyme defect in all hyperphenylalaninemic patients must be inferred from specific testing for cofactor abnormalities.

b. The object of therapy is to bring phenylalanine levels to <350 μM if possible. Treatment consists of reducing phenylalanine intake from natural sources and supplementing the diet with amino acid products containing little or no phenylalanine. Practically speaking, the diet is a vegetarian one with focus on those fruits and vegetables that are particularly low in protein. Unlike a natural vegetarian diet, other essential amino acids are provided from synthetic products largely distributed through the commercial sources noted previously.

c. Effective treatment has produced a population of intellectually normal affected women of child-bearing age. Such women, with various degrees of hyperphenylalaninemia, have heterozygote offspring that are at risk of having serious abnormalities, such as mental retardation, microcephaly, and cardiac malformations. **Dietary treatment during pregnancy** appears to improve the chances of delivery of a normal infant. And these woman should be placed on therapy before and during pregnancy, at least.

d. In the last decade, a fraction of phenylalanine hydroxylase-deficient patients (10% of those with severe enzyme deficiency and a larger proportion of those with lesser deficiencies) have been shown to have deficient enzyme stabilized by tetrahydrobiopterin (e.g., Kuvan) and thus increasing the residual activity and requiring a less stringent diet. Enzyme replacement therapy is in phase 3 clinical trials and may be available in the foreseeable future.

D. Newborn screening. Until recently, newborn screening was limited, at best, to a few disorders of amino acid metabolism, to hypothyroidism, and, on a more limited basis, congenital adrenal

hyperplasia and hemoglobinopathies. With the advent of high-throughput, automated screening of newborn blood spots, particularly, the menu of disorders screened has expanded greatly, although it differs from state to state and internationally. Most disorders of amino acids, organic acids, and fatty acids and others can be diagnosed at birth with a high degree of probability using tandem mass spectrometry. In the near future, it is likely that still more conditions, such as most lysosomal storage disorders, adrenoleukodystrophy, and immunodeficiencies, will prove amenable to screening as well, and in fact are in use in some jurisdictions. The list of primary and secondary screening targets currently recommended by the American College of Medical Genetics can be found on their web site, http://www.acmg.net. Although not apparent so far, once integrated into our diagnostic algorithms, newborn screening will alter the way that we approach symptomatic individuals.

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49 Glycogen Storage Diseases

Joseph I. Wolfsdorf and Paulina Ortiz-Rubio

I. GENERAL PRINCIPLES

The glycogen storage diseases (GSDs) or glycogenoses comprise several inherited diseases caused by deficiencies of the enzymes that regulate the synthesis or degradation of glycogen resulting in increased storage of glycogen in several tissues, especially the liver and muscle.

A. The structure of glycogen. Glycogen is the storage form of carbohydrate in humans. It is a highly branched polymer of glucose residues, most of which form straight chains linked by α-1,4-glycosidic bonds. Branches are created by α-1,6-glycosidic bonds, which occur on the average of once in 10 residues. The two major sites of glycogen storage are the liver and skeletal muscle. During carbohydrate feeding, the concentration of glycogen in the liver is 5 g/100 g wet weight; its concentration in muscle is 2 g/100 g wet weight. Because of the greater mass of skeletal muscle, more glycogen is stored in muscle than in the liver; however, because skeletal muscle lacks the enzyme **glucose 6-phosphatase (G6Pase)**, it is unable to release glucose into the systemic circulation.

B. Glycogen synthesis, degradation, and conversion to glucose

1. **Glycogen synthesis and degradation** in the liver follow distinct pathways that begin and end with glucose 1-phosphate (Fig. 49-1). The liver is freely permeable to glucose, which is first converted to G6P before it can enter one of several metabolic pathways. G6P can be reversibly converted to glucose 1-phosphate, which is the starting point for glycogen synthesis. Alternatively, G6P can be hydrolyzed to glucose by G6Pase or it can be metabolized via the glycolytic pathway to pyruvate and lactate or, via the pentose phosphate pathway, to ribose 5-phosphate, a precursor of nucleotide synthesis. Glycogen synthase catalyzes the formation of α-1,4-linkages. A branching enzyme

forms the α-1,6-linkages that make glycogen a branched polymer (Fig. 49-1).

2. **Glycogen breakdown** requires the sequential interaction of several enzymes. First, phosphorylase successively cleaves the 1,4 links to within four glucosyl units of the branch point. Then 4-α-glucanotransferase exposes the 1,6-linked branch points by transferring three glucosyl residues elsewhere on the glycogen molecule. Amylo-1,6-glucosidase, the debranching enzyme, then splits the 1,6-linked glucosyl units. Thus, the sequential action of phosphorylase and the debrancher enzymes liberates the stored glucose units; the action of phosphorylase yields glucose 1-phosphate, and the debranching enzyme liberates free glucose. During fasting, the debrancher enzyme mobilizes approximately 8% of hepatic glycogen as free glucose; the remainder requires activity of hepatic G6Pase.

C. Clinical features of the hepatic glycogenoses.

The types of hepatic glycogenoses, the specific enzyme deficiencies, affected tissues, their modes of inheritance, and the chromosomal localization of the relevant genes are shown in Table 49-1. Table 49-2 lists the major biochemical characteristics of the hepatic glycogenoses (types 0, I, III, VI, and IX); their hallmark is **fasting hypoglycemia**.

II. GLYCOGEN STORAGE DISEASES

A. Glycogen synthase deficiency (type 0 GSD)

1. **The nature of the defect.** Lack of liver glycogen synthase activity due to mutations in the glycogen synthase gene (*GYS2*) on chromosome 12p12.2 is a p. 674p. 675rare autosomal recessive disorder characterized by an inability to store hepatic glycogen. There is a marked decrease in liver glycogen content (0.5 g/100 g wet weight 4 to 6 hours after a meal) and a preferential conversion of glucose to lactate. Less than 30 cases have been reported worldwide; however, the disorder may be underdiagnosed.

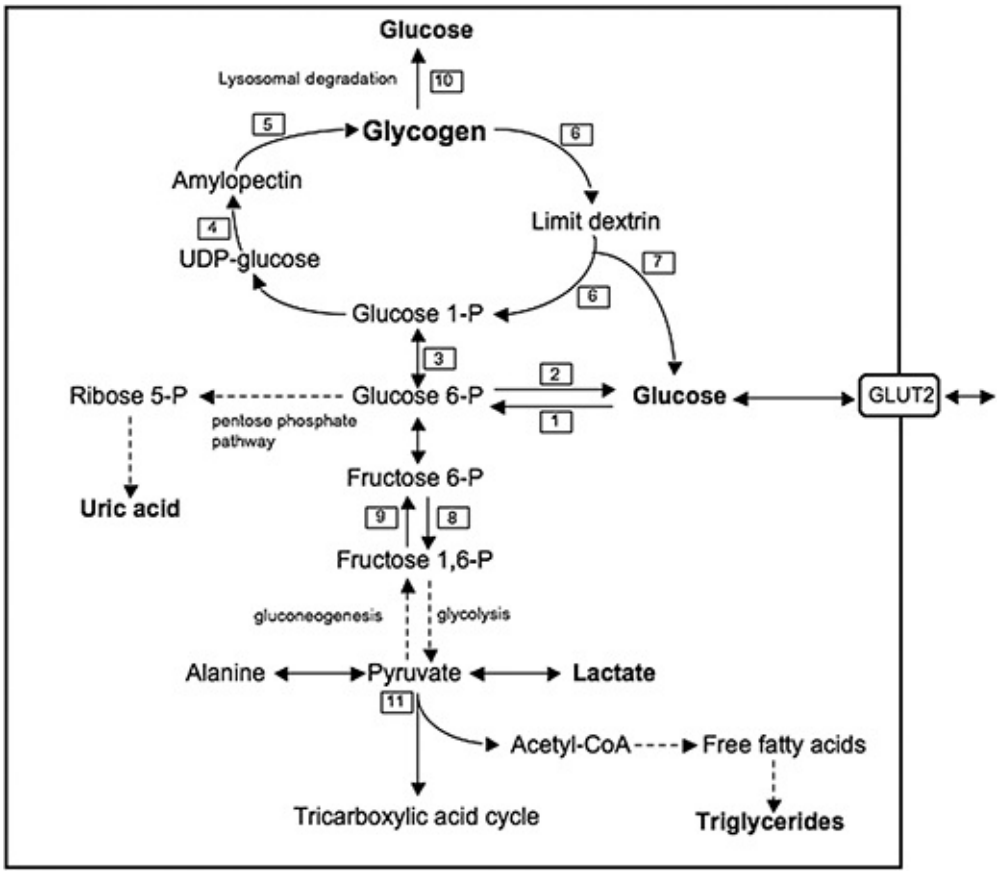

Figure 49-1. Simplified scheme of glycogen synthesis and degradation in the liver. UDP-glucose is uridine diphosphoglucose; GLUT2 is glucose transporter 2; 1, hexokinase/glucokinase; 2, glucose 6-phosphatase; 3, phosphoglucomutase; 4, glycogen synthase; 5, branching enzyme; 6, glycogen phosphorylase; 7, debranching enzyme; 8, phosphofructokinase; 9, fructose 1,6-bisphosphatase; 10, acid maltase; 11, pyruvate dehydrogenase.

2. **Clinical manifestations.** Symptoms of morning hypoglycemia appear when nocturnal feeding ceases. The disorder has a characteristic biochemical pattern of fasting hypoglycemia and hyperketonemia alternating with daytime hyperglycemia and hyperlacticacidemia after meals. Unlike the other GSDs that cause hypoglycemia, the liver is not enlarged. The disorder should be considered in **the differential diagnosis of "ketotic hypoglycemia."**
3. **Laboratory findings**
   a. **General laboratory tests.** Fasting hypoglycemia with ketosis and postprandial hyperglycemia and hyperlacticacidemia.
   b. **Provocative laboratory tests.** (See Section II.B.3.b for a general approach to defining the metabolic consequences of

enzymatic deficiencies.) After an overnight fast, oral glucose (1.75 g/kg) causes hyperglycemia and hyperlacticacidemia, whereas glucagon (0.03 mg/kg IM) typically has no appreciable effect on the plasma glucose (PG) level.

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TABLE 49-1 Hepatic Glycogen Storage Diseases

Disorder	Affected tissue	Enzyme	Inheritance	Gene	Chromosome	OMIM
Type 0 GSD	Liver	Glycogen synthase	AR	*GYS2*	12p12.2	240600
Type Ia GSD	Liver, kidney, intestine	G6Pase	AR	*G6PC*	17q21	613742
Type Ib GSD	Liver	Glucose 6-phosphate transporter (T1)	AR	*SLC37A*	11q23	602671
Type IIIa GSD	Liver, muscle, heart	GDE	AR	*AGL*	1p21	232400
Type IIIb GSD	Liver	GDE	AR	*AGL*	1p21	232400
Type VI GSD	Liver	Glycogen phosphorylase	AR	*PYGL*	14q21–22	613741
Type IXa GSD	Liver, erythrocytes, leukocytes	Liver isoform of α subunit of PHK	X-linked	*PHKA2*	Xp22.1–p22.2	306000
Type IXb GSD	Liver, muscle, erythrocytes, leukocytes	β subunit of liver and muscle PHK	AR	*PHKB*	16q12–q13	261750
Type IXc GSD	Liver	Testis/liver isoform of γ subunit of PHK	AR	*PHKG2*	16p11–p12	613027
Type XI GSD	Liver, pancreas, intestine, and kidney	GLUT2	AR	*SCL2A2*	3q26.1–q26.3	227810

AR, autosomal recessive; GDE, Glycogen debranching enzyme; GLUT2, Glucose transporter 2; G6Pase, Glucose 6-phosphatase; GSD, glycogen storage disease; OMIM, online inheritance in man; PHK, phosphorylase kinase.

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TABLE 49-2 Biochemical Characteristics of the Hepatic Glycogenoses

	At time of hypoglycemia			Response to oral glucose		Response to glucagon 4–8 hr after a meal[a]		Response to glucagon 2 hr after a meal	
Type	Triglyceride	Uric acid	Lactate	Glucose	Lactate	Glucose	Lactate	Glucose	Lactate
GSD-0	N	N	N	↑↑	↑↑	0-↑	0	↑	↓
GSD-I	↑↑↑	↑↑	↑↑↑	↑	↓↓	0	↑↑↑	0	↑↑
GSD-III	↑	N	N	↑	↑	0	0	↑	0
GSD-VI, IX	0-↑	N	N	↑	↑	0-↑	0	↑	0

Subjects with suspected GSD-I should not be permitted to fast for more than 4 hr.
[a]After a meal that provides glucose.
GSD, glycogen storage disease; N, normal; 0, no increase; 0-↑, variable increase; ↑, mild increase, ↑↑, moderate increase; ↑↑↑, marked increase; ↓, mild decrease; ↓↓, moderate decrease.

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c. **Specific laboratory tests.** Genetic testing for mutations in *GYS2* is commercially available (refer to www.genetests.org for laboratory listing).

4. **Treatment.** The goal of treatment is to prevent hypoglycemia and ketosis during the night and hyperglycemia and hyperlacticacidemia during the day. Fasting hypoglycemia and

ketosis are prevented by bedtime feedings of uncooked cornstarch (UCS), 1 to 1.5 g/kg. During illness, administration of a similar dose of cornstarch every 6 hours is used to prevent hypoglycemia. During the day, patients are fed frequently (e.g., every 4 hours). The diet should contain an increased amount of protein to provide substrate for gluconeogenesis, and a decreased amount of carbohydrate to minimize postprandial hyperglycemia and hyperlacticacidemia. The diet should contain predominantly complex, low-glycemic-index carbohydrates. Such a diet and feeding schedule relieves symptoms, reverses the biochemical abnormalities, and improves growth.

B. Glucose 6-phosphatase deficiency (*type I GSD*; Von Gierke disease; hepatorenal glycogenosis)

1. The nature of the defect

a. von Gierke first described the disease in 1929. It is an autosomal recessive disorder resulting from lack of activity of the hepatic enzyme **G6Pase**, either due to a deficiency of the G6Pase enzyme itself, discovered by Cori and Cori in 1952, or due to a deficiency of the transporter enzyme G6P translocase (G6PT), described by Narisawa et al. in 1978. G6Pase catalyzes the final step in the production of glucose from G6P. Deficiency of this enzyme **impairs glucose production** from both glycogenolysis and gluconeogenesis. Decreased production of glucose results in interprandial hypoglycemia and increased production of lactate, uric acid, and triglyceride. Glycogen and triglyceride accumulate in the liver, resulting in marked hepatomegaly; glycogen also accumulates in the kidney and intestinal mucosa.

b. The **G6Pase enzyme system** is located in the endoplasmic reticulum (ER) membrane and consists of several subunits. The catalytic subunit, which converts G6P to glucose, faces into the ER. Three transport systems transport the substrate, G6P, and the products, phosphate, inorganic orthophosphate, and glucose, across the ER membrane. G6P transporter transports G6P into and phosphate out of the ER; glucose transporter 2 (GLUT2) transports glucose out of the ER.

c. Approximately 80% of patients with GSD-1 have deficient catalytic activity of the G6Pase system leading to **type Ia GSD (GSD-Ia)**. Approximately 100 different mutations have been

found in the G6Pase gene, *G6PC*, located on chromosome 17q21.

d. These mutations have not been found in patients **with type Ib**, which is caused by failure to transport G6P into the lumen of the ER owing to a mutation (about 80 mutations have been described) in the G6PT gene, *SLC37A4*, on chromosome 11q23.

2. Clinical manifestations

a. The estimated incidence of GSD-1 is 1 in 100 000 births in the general population; its prevalence is 1 in 20 000 in **Ashkenazi Jews**. It affects the sexes equally.

b. The presenting **symptoms** vary according to age. Symptomatic **hypoglycemia** may appear soon after birth; however, most patients are asymptomatic as long as they receive frequent feedings that contain sufficient glucose to prevent hypoglycemia. Symptoms of hypoglycemia typically appear only when the interval between feedings increases, such as when the infant starts to sleep through the night or when an intercurrent illness disrupts normal feeding.

c. The condition may not be recognized until the child is several months old and an **enlarged liver and protuberant abdomen** are noted during a routine physical examination. Patients may present with hyperpnea (from lactic acidosis) and a low-grade fever without a demonstrable infection. Untreated patients may have a cushingoid appearance (round face and full cheeks), growth failure, and delayed motor development. Social and cognitive development is not affected unless the infant suffers cerebral damage from recurrent severe hypoglycemia.

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d. During infancy, the blood glucose concentration typically drops to <40 mg/dL within 3 to 4 hours of a feeding. Longer intervals between feedings cause more severe hypoglycemia accompanied by **hyperlacticacidemia** and metabolic acidosis. Fructose-1-6-bisphosphatase deficiency may present like GSD-I, with recurrent hypoglycemia and lactic acidosis in infancy. Hepatomegaly is due to fatty infiltration (not glycogen accumulation). In contrast to GSD-I, glucagon administration elicits a brisk glycemic response. Genetic testing for *FBP1* confirms the diagnosis.

e. The serum of untreated patients may be cloudy or milky, with extremely **high triglyceride concentrations** (typically >500 mg/dL) and moderately increased levels of phospholipids, total and low-density lipoprotein cholesterol; the high-density lipoprotein cholesterol concentration is low. High triglyceride concentrations result from increased hepatic synthesis (mobilization of fatty acids from adipose tissue in response to hypoglycemia), impaired ketogenesis, and reduced clearance of triglycerides secondary to decreased lipoprotein lipase activity. The circulating concentration of free fatty acids is markedly increased. Eruptive xanthomata may appear on the extensor surfaces of the extremities and on the buttocks. Severe hypertriglyceridemia (>1 000 mg/dL) is associated with an increased risk of acute pancreatitis.

f. Although hypoglycemia becomes less severe with increasing age, without adequate therapy **growth is stunted and puberty is delayed**. However, when continuous glucose therapy is started early in life and long-term good metabolic control is maintained, patients can grow and develop normally.

g. A **bleeding tendency** manifested as recurrent epistaxes or oozing after dental or other surgery is caused by impaired platelet function. Reduced platelet adhesiveness, abnormal platelet aggregation, and impaired release of adenosine diphosphate in response to collagen and epinephrine have been observed. The platelet defects are secondary to the systemic metabolic abnormalities and are corrected by improving the metabolic state.

h. **Anemia** has been reported in up to 81% of adults and in 17% to 60% of children with GSD-I. The etiology of the anemia is multifactorial and includes iron and other nutritional deficiencies, chronic lactic acidosis, blood loss from menorrhagia, end-stage renal disease (ESRD), and enterocolitis (in patients with GSD-Ib). Patients with liver adenomas may have iron refractory anemia secondary to aberrant hepcidin expression.

i. **Nephromegaly** is readily demonstrated by ultrasonography in GSD-1, although it is not severe enough to be identified on physical examination. Deficiency of G6Pase leads to glycogen deposition in the kidneys and disturbs the metabolism of renal

tubular cells, resulting in a relative energy deficiency. Increased renal blood flow and glomerular filtration rate may be a compensatory mechanism for the intracellular energy deficit. Renal manifestations include proximal and distal renal tubular dysfunction as well as glomerular injury that can lead to ESRD requiring transplantation. Proximal tubular dysfunction (glucosuria, phosphaturia, hypokalemia, and a generalized aminoaciduria) is reversible when biochemical control of the disease improves. Some patients have a distal renal tubular acidification defect associated with hypocitraturia and hypercalciuria, which predisposes to nephrocalcinosis and renal calculi. Increased urinary albumin excretion may be observed in adolescents. More severe renal injury with proteinuria, hypertension, and decreased creatinine clearance due to focal segmental glomerulosclerosis and interstitial fibrosis may be seen in young adults. Patients with persistently elevated blood lactate, serum lipid, and uric acid concentrations appear to be at increased risk of developing nephropathy. Normalization of metabolic parameters decreases proteinuria, and optimal therapy instituted at or before age 1 year may delay, prevent, or slow the progression of renal disease.

j. Development of **hepatic adenomas** is a common complication occurring in up to 75% of patients by the time they reach adulthood. Although they are usually first observed in the second and third decades of life, adenomas p. 679p. 680may appear before puberty. They may undergo malignant degeneration or hemorrhage. Ultrasonography is the preferred method of screening for hepatic adenomas. When malignancy is suspected, magnetic resonance imaging (MRI) and measurement of serum alpha-fetoprotein should be performed.

k. Radiographic studies have demonstrated **osteopenia**, and pathologic studies have shown pure osteoporosis without evidence of abnormalities in calcium, phosphate, parathyroid, or vitamin D metabolism. Bone mineral content is decreased compared to age-matched normal children. Endocrine and

metabolic disturbances, including hypercortisolemia, resistance to growth hormone, delayed puberty, and lactic acidosis, may account for decreased bone mineralization.

l. **Menstrual irregularities** and hirsutism are uncommon; however, in all types of hepatic GSDs, ultrasonography has shown a high prevalence of morphologically polycystic ovaries (even in prepubertal children), the clinical significance of which is still unclear.

m. Although the heart itself is not affected in GSD-I (unlike GSD-II or GSD-III), **hypertension** may develop in association with renal disease. **Pulmonary hypertension** presenting in the second or third decade of life and leading to death from progressive heart failure has also been described.

n. Patients with **GSD-Ib** have similar symptoms, typically, with the addition of either constant or cyclic **neutropenia** of variable severity, ranging from mild to complete agranulocytosis, and associated with recurrent bacterial infections. Neutropenia is a consequence of disturbed myeloid maturation and is accompanied by functional defects of circulating neutrophils and monocytes. A recent case series suggests that *vitamin E supplementation may improve neutropenia* and reduce infection rates in these patients. Patients frequently develop an **inflammatory bowel disease** resembling Crohn's disease, which is responsive to treatment with granulocyte colony-stimulating factor (G-CSF). Children with GSD-Ib are prone to **oral complications**, including recurrent mucosal ulceration, gingivitis, and rapidly progressive periodontal disease. Patients with GSD-Ib may have an increased prevalence of thyroid autoimmunity and primary hypothyroidism.

3. **Diagnostic studies**

a. **General laboratory tests.** During infancy, PG typically falls to <40 mg/dL 3 to 4 hours after a feeding and is accompanied by hyperlacticacidemia and metabolic acidosis. The serum may be cloudy or milky with very high triglyceride and moderately increased levels of cholesterol. Serum uric acid, aspartate aminotransferase, and alanine aminotransferase levels are usually increased.

b. **Provocative laboratory tests**

i. **Fasting study.** The simplest means of determining the probable nature of the enzymatic deficiency in a child suspected of having a glycogenosis is to obtain **serial blood samples for measurement of metabolites** (glucose, lactate, free fatty acids, ketones, and uric acid) for up to 6 hours (or until the PG falls to ≤50 mg/dL) following oral glucose (1.75 g/kg) or 30 minutes after stopping a continuous overnight intravenous or intragastric infusion of glucose.

ii. **Glucagon challenge.** Administration of glucagon may lead to worsening acidosis and decompensation in GSD-I and is *no longer recommended to make the diagnosis.*

c. **Specific laboratory tests. Mutational analysis** of *G6PC* (GSD-Ia) and *SLC37A4* (GSD-Ib) genes is recommended to confirm type I GSD. Because GSD-Ia is more common, unless neutropenia is present, complete *G6PC* sequencing is recommended first. Note that although neutropenia suggests GSD-Ib, neutrophils can be normal in patients with GSD-Ib in the first years of life and neutropenia can also be seen in occasional GSD-Ia patients. A **liver biopsy** for measurement of G6Pase activity may be necessary in the rare patient who does not have an identifiable gene mutation. Lack of G6Pase activity is diagnostic of GSD-Ia. The glycogen itself has a normal appearance.

d. **Imaging studies. Ultrasound** of the abdomen shows hepatomegaly and nephromegaly without splenomegaly. Nephromegaly is characteristic of GSD-I.

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4. **Treatment** consists of providing a continuous dietary source of glucose to prevent the PG from falling below the threshold for glucose counterregulation or <70 to 75 mg/dL. When hypoglycemia is prevented by providing an appropriate amount of glucose throughout the day and night, the biochemical abnormalities are ameliorated, liver size decreases, the bleeding tendency is reversed, and growth improves. **Recommended biochemical targets:** PG >70 to 75 mg/dL, triglycerides <500 mg/dL, and uric acid <7.5 mg/dL.

a. **Supply of glucose**

i. Various methods may be used to provide a continuous source of glucose at a rate sufficient to satisfy glucose requirements in the intervals between meals: intravenously, via the gastrointestinal tract by intragastric infusion (either nasogastric or gastrostomy tube), or by use of low-glycemic-index foods. Of these, uncooked cornstarch (UCS) has the most suitable properties described to date. The *minimum* amount of glucose required may be obtained by using the formula for calculating the basal glucose production rate: $y = 0.0014^3 - 0.214x^2 + 10.411x - 9.084$ where y = mg glucose per minute and x = ideal body weight in kilograms. The amounts and/or schedule of glucose or UCS administered is modified, if necessary, based on the results of clinical and biochemical monitoring.

ii. In **infants**, we recommend feedings every 2 to 3 hours of a formula that does not contain either lactose or sucrose. The formula must contain a polymer of glucose (corn syrup solids, maltodextrins) that will yield, after digestion, an amount of glucose equal to the calculated glucose production rate. If nighttime feedings are challenging, continuous overnight feedings using the same formula may be given via nasogastric or gastrostomy tube with the rate controlled by an infusion pump.

iii. Orally administered **UCS** acts as an intestinal reservoir of glucose that is slowly absorbed into the circulation. In many centers, UCS has replaced frequent daytime feedings of glucose or glucose polymers and overnight continuous intragastric infusion of glucose. It has been used successfully in infants as young as 8 months of age. The UCS is given in a slurry of water or an artificially sweetened beverage (e.g., Kool-Aid) or in formula for infants, at 3- to 5-hour intervals during the day and 4- to 6-hour intervals overnight. The amount given is determined by multiplying the time interval between feedings by the calculated hourly glucose requirement for ideal body weight. One tablespoon (8 g) of UCS contains 7.3 g of carbohydrate. The optimum schedule and amounts of intermittent UCS feedings for patients of different ages is determined empirically by metabolic monitoring to ensure

that the biochemical goals are being achieved.

iv. **Extended release waxy maize cornstarch** (Glycosade; Vitaflo, International Ltd, Liverpool, England) was approved in England in 2009 for the management of GSD-I and was released in the United States as a medical food in 2012. Efficacy studies in children as young as 5 years have shown prolongation of fasting tolerance from an average of 4.1 to 7.8 hours using extended release cornstarch as compared to standard UCS. Biochemical markers of metabolic control reportedly remained stable while on the extended release formulation. Gastrointestinal intolerance and exacerbation of inflammatory bowel disease are common side effects of the extended release formulation.

b. When adequate exogenous glucose is provided, significant **hyperuricemia** and **hyperlipidemia** are usually restored to near normal. If severe hyperuricemia persists, allopurinol, a xanthine oxidase inhibitor (5 to 10 mg/kg/day as a single daily dose or divided q12 hours), effectively lowers serum uric acid to normal levels. Lipid-lowering agents (gemfibrozil or fenofibrate) are indicated when persistent severe hyperlipidemia despite optimal glucose therapy poses a significant risk of acute pancreatitis.

c. **Dietary fat** should be restricted to <20% of the total energy intake, equally distributed among monounsaturated, polyunsaturated, and saturated fats. p. 681p. 682Dietary cholesterol is restricted to <300 mg/day. Carbohydrate typically provides 60% to 65% of the daily calories. Of the total daily calories, 30% to 45% is prescribed (both the amount and schedule) in the form of UCS. Most of the remaining dietary carbohydrate should, ideally, be low-glycemic-index starches. With the glucose requirements prescribed, the total caloric intake is determined by the child’s appetite as long as the rate of weight gain is not excessive. The dietitian must ensure that the patient is consuming an adequate amount of protein, fat, minerals, and vitamins to support

optimal growth. When adequate glucose is prescribed to maintain normoglycemia, milk products and fruit, despite their content of galactose and fructose, respectively, may be used sparingly to supply essential nutrients, minerals, and vitamins.

d. Other therapeutic considerations

i. **Renal disease.** Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been reported to improve glomerular filtration rate in patients with hyperfiltration. Thiazide diuretics and oral citrate can help prevent nephrocalcinosis and renal calculi. Loop diuretics should be avoided because of the risk of hypercalciuria.

ii. **Anemia.** Iron, vitamin B_{12}, and folic acid intake should be optimized. Erythropoietin supplementation may be required in patients with ESRD.

iii. **Neutropenia.** G-CSF is efficacious for the treatment of neutropenia and infections in patients with GSD-Ib; monitoring for splenomegaly should be performed as it is the most serious complication of G-CSF therapy in this population.

e. Monitoring

i. **Glucose meter.** Frequent PG monitoring is needed to establish good metabolic control and identify asymptomatic hypoglycemia. PG levels should be monitored before meals, before cornstarch administration, and before and after exercise. If the cornstarch dose is changed, PG should also be monitored frequently after cornstarch administration to establish the effective duration of action.

ii. **Continuous glucose monitors (CGMs).** New-generation CGMs have improved accuracy and ability to detect hypoglycemia. Clinical studies in both adults and children show that they can be used safely and reliably in patients with GSD-I, and can help reduce duration of hypoglycemia as well as detect asymptomatic hypoglycemia.

iii. **Routine monitoring.** Guidelines from the European Study on GSD-I recommend laboratory monitoring based on age: 0 to 3 years every 2 months; 3 to 30 years every 3

months, and every 6 months in adults. Testing should include: complete blood count with differential white cell count, serum uric acid, triglycerides, cholesterol, and venous blood gases. Triglyceride concentrations are considered the most useful parameter of metabolic control given the rapid fluctuations in the levels of PG, lactate, and liver enzymes. Significantly increased *adenoma progression has been reported in patients with mean triglyceride >500 mg/dL*.

iv. Screening for complications

a) Creatinine, urea, electrolytes, calcium, phosphate, liver function tests, protein, and albumin should be evaluated every 6 months.

b) Urine microalbumin, protein, creatinine, calcium, and citrate should be checked every year if 0 to 5 years old and every 6 months if >5 years old.

c) Creatinine clearance (GFR estimate) should be performed yearly for those >5 years old.

d) Abdominal ultrasound to evaluate liver, kidneys, spleen, and ovaries should be performed once a year if younger than 10 years and every 6 months thereafter.

e) Bone densitometry should be done every 1 to 2 years for those older than 5 years.

f) Periodic echocardiography (ECHO) and electrocardiogram (EKG) should be performed to screen for pulmonary hypertension starting at 10 years of age and repeated at least every 3 years.

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C. Amylo-1,6-glucosidase deficiency (type III GSD; debranching enzyme deficiency; limit dextrinosis; Cori disease; Forbes disease)

1. Nature of the defect

a. The disorder results from deficient activity of the glycogen debranching enzyme (GDE), leading to impaired glycogen degradation, reduced glycogenolysis, and accumulation of abnormal glycogen. It is an autosomal recessive disease due to mutations of the *AGL* gene on chromosome 1p21, which encodes four GDE isoforms. Isoform 1, the most widely distributed and the predominant form in the liver, is defective in

GSD-IIIa. Isoforms 2, 3, and 4 are exclusively located in skeletal and cardiac muscle. Mutations in exon 3 of the *AGL* gene are associated with GSD-IIIb, which has a milder phenotype characterized by isolated liver involvement.

b. GDE has two enzymatic functions: a transferase that exposes the 1,6-linkage and amylo-1,6-glucosidase, which produces free glucose. Without GDE, glycogen breakdown cannot proceed past the outermost branch points, resulting in abnormal glycogen with short side chains (referred to as limit dextrin). In the United States, 80% to 85% of patients with GSD-III lack GDE activity in both liver and muscle (GSD-IIIa), 15% lack GDE activity in the liver alone (GSD-IIIb), and rarely patients lack activity in muscle alone (GSD-IIIc). In contrast, in Israel, the majority of patients lack enzyme activity only in the liver.

2. Clinical manifestations

a. Clinical and enzymatic variability is a feature of GDE deficiency. During infancy and childhood, the disease may be indistinguishable from GSD-I. Hepatomegaly, fasting hypoglycemia with ketosis, hyperlipidemia, and growth retardation are the predominant features. About 70% of patients have muscle weakness, but this is usually not clinically significant in childhood.

b. Biochemical distinctions between GSD-III and GSD-I

i. Because glucose can be produced from 1,4-segments beyond the outermost glycogen branch points and from gluconeogenesis, patients with GDE deficiency may be able to tolerate longer periods of fasting, and **hypoglycemia usually is less severe** than in those with G6Pase deficiency. Infants with GSD-III may be asymptomatic on their usual frequent feeding schedules and typically do not become as severely ill with infections and other stresses that disrupt feeding as do children with GSD-1.

ii. Infants with GSD-III develop **fasting hyperketonemia** as a result of an accelerated transition to the fasting state. **Blood levels of lactate and uric acid are normal** because the gluconeogenic pathway is intact and hepatic glycolysis is not increased.

iii. **Hyperlipidemia** is less marked in GSD-III than in GSD-I.

c. Physical characteristics. The presenting clinical finding

may be hepatomegaly and growth failure. An **enlarged spleen** may be seen at 4 to 6 years of age in patients who have hepatic fibrosis. The kidneys are not enlarged; renal dysfunction does not occur. Untreated infants and children have a decreased rate of linear growth, and puberty is delayed. In patients who lack the debrancher enzyme in muscle, weakness is usually minimal and not clinically significant in childhood.

d. Chronic conditions

i. **Myopathy.** With the exception of myopathy, symptoms and signs characteristically ameliorate with increasing age. Myopathy, however, usually becomes prominent in the third or fourth decade of life, manifesting as slowly progressive muscle weakness involving the proximal muscles. Some patients also have involvement of the small muscles of the hands.

ii. **Cardiac.** Abnormal glycogen (limit dextrin) may accumulate in the heart, resulting in the development of a cardiomyopathy that resembles idiopathic hypertrophic cardiomyopathy. Significant concentric left ventricular hypertrophy usually develops after puberty. Evidence of cardiac involvement is common and manifests as ventricular hypertrophy on EKG and increased left ventricular mass and wall thickness on ECHO. Ventricular

p. 683p. 684changes are more commonly seen in patients with GSD-IIIa but have also been reported in patients with GSD-IIIb. Ventricular function, however, is usually relatively normal. Severe cardiac dysfunction is an uncommon cause of cardiac mortality. Sudden death in patients with GSD-III has raised concern about cardiac arrhythmias, and glycogen accumulation in the cardiac conduction system has been observed at autopsy.

iii. **Hepatic.** The size of the liver tends to decrease during puberty. Biopsy usually shows hepatic fibrosis, and some adult patients develop cirrhosis. Hepatic adenomas have been found in 4% to 25% of patients, compared to 22% to 78% of GSD-I patients. The development of hepatocellular carcinoma (HCC) is rare, but has recently been described in six patients, all of whom were more than 30 years old.

Transaminases and AFP were not reliable markers of HCC in these patients.

3. **Laboratory findings**
   a. **General laboratory tests.** There is fasting hypoglycemia with ketosis, but without elevation of blood lactate or serum uric acid concentrations. Prevalence of hypertriglyceridemia and hypercholesterolemia is estimated to occur in approximately two-thirds and one-third, respectively, of patients. Hypertriglyceridemia is most commonly found in younger children (<3 years old) and does not reach levels high enough to cause pancreatitis. Liver transaminases are consistently elevated (at least twice the upper limit of normal, and often >500 IU/L) in children but decline at puberty and may be normal in adults. Creatine kinase (CK) is often markedly elevated in patients with GSD-IIIa.
   b. **Provocative laboratory tests.** (See Section II.B.3.b for general approach.) After an overnight fast, blood glucose and lactate concentrations do not increase after administration of glucagon (30 μg/kg, maximum 1 mg IM or IV). When the test is repeated 2 hours after a high-carbohydrate meal (which lengthens the outer branches of glycogen), a glycemic response is elicited.
   c. **Specific assays.** Diagnosis of GSD-III is made by mutation analysis of the *AGL* gene or, alternatively, by liver and/or muscle biopsy. Biopsy results show a three- to fivefold elevation of structurally abnormal glycogen content in the involved tissue. Definitive subtyping of GSD-III requires a biopsy of both liver and muscle. Although muscle involvement can be inferred from the presence of high levels of serum CK, a normal level does not rule out muscle enzyme deficiency. At the time of diagnosis, muscle biopsy is the only way to predict accurately whether skeletal muscle disease or heart muscle involvement is likely to develop in the future, unless a GSD-IIIb-specific mutation is identified.
4. **Treatment.** Because only a limited amount of glucose can be mobilized from glycogen, hypoglycemia develops during an overnight fast in infancy and early childhood. This occurs despite increased gluconeogenesis and enhanced hepatic uptake of gluconeogenic amino acids, which results in low plasma levels of

several amino acids.

a. As in GSD-I, continuous provision of an adequate amount of glucose, using UCS (see Section II.B.4), combined with a normal intake of total calories, protein, and other nutrients, corrects the clinical and biochemical disorder and restores normal growth. UCS 1 to 1.75 g/kg at 6-hour intervals (e.g., at midnight, 6 A.M., etc.) maintains normoglycemia, increases growth velocity, and decreases serum aminotransferase concentrations. Infants younger than 12 months may not produce sufficient amylase to digest UCS and experience bloating, flatulence, and diarrhea. If these side effects occur, a slow rate of introduction of UCS or addition of pancrelipase may improve tolerance. UCS can be mixed in any beverage, although addition to milk or yogurt is preferable as it adds protein and fat. Addition of whey protein is recommended to prolong normoglycemia. Excessive UCS should be avoided as it leads to excess glycogen deposition and weight gain.

b. For patients who have significant **growth retardation and myopathy**, continuous nocturnal feeding of a nutrient mixture composed of glucose, glucose p. 684p. 685oligosaccharides, and amino acids combined with intermittent feedings during the day of meals with a **high protein** content may be beneficial.

c. Adolescents and adults with GSD-IIIa should aim for a high-protein (25% of total calories) and low-complex-carbohydrate (<50% of total calories) diet and should avoid simple sugars and fasting. Patients with GSD-IIIb may be able to transition to a regular well-balanced diet.

d. Blood glucose monitoring should be performed before meals or UCS, before bedtime and breakfast, with addition of extra monitoring during times of illness.

e. Liver function tests should be performed every 6 months. As in patients with GSD-I, annual measurement of **serum α-fetoprotein** and **hepatic ultrasound examinations** should be performed to screen for hepatic adenomas. MRI of the liver should be performed every 6 to 12 months in older patients and

in children when an ultrasound examination shows that an adenoma has increased in size. Routine EKG and ECHO should be performed to evaluate for dysrhythmias, ventricular hypertrophy, and systolic or diastolic dysfunction. ECHO should be done every 12 to 24 months in patients with GSD-IIIa and every 5 years in those with GSD-IIIb. An EKG should be done every other year in patients with GSD-IIIa.

f. No exercise restrictions are recommended for patients with GSD-III unless they have developed significant cardiac disease. Exercise helps prevent worsening myopathy and low bone mineral density. Physical therapy evaluation is recommended every 6 months.

D. Hepatic phosphorylase complex deficiency (type VI GSD, hepatic phosphorylase deficiency, Hers disease; type IX GSD, phosphorylase kinase [PHK] deficiency)

1. Nature of the defect

a. Hepatic phosphorylase, the rate-limiting enzyme of glycogenolysis, is activated by a cascade of enzymatic reactions. First, adenylate cyclase catalyzes the formation of cyclic adenosine monophosphate (cAMP), which then activates a cAMP-dependent protein kinase. Protein kinase then phosphorylates a phosphorylase kinase (PHK), which converts inactive hepatic phosphorylase to its active form. Active phosphorylase hydrolyzes the α-1,4-linkages and mobilizes glucose from glycogen. This cascade of reactions is triggered primarily by glucagon.

b. The GSDs caused by a reduction in liver phosphorylase activity are a heterogeneous group of disorders (Table 49-1). The most common disorder in this group is deficiency of hepatic PHK *or type IX GSD*. It occurs in approximately 1 in 100 000 births and accounts for about 25% of all cases of GSDs. Deficiency of hepatic phosphorylase (type VI GSD) itself is rare.

c. PHK of liver and muscle is a complex enzyme consisting of four subunits: α, β, γ, δ. The enzyme is regulated by phosphorylation of specific serine residues of the α and β subunits and by calcium through the δ subunit, a member of the calmodulin family. Calmodulin (a *calcium*-binding messenger *protein*) is a multifunctional *intermediate messenger* protein that transduces calcium signals by binding calcium ions and

then modifying its interactions with various target proteins.

d. The γ subunit is catalytically active. Mutations in three different genes of PHK subunits (*PHKA2*, *PHKB*, and *PHKG2*) can result in deficient activity of hepatic phosphorylase. GSD-IXa, due to mutations in *PHKA2*, is the most common variant (Table 49-1).

2. Clinical manifestations. These patients seldom have symptomatic hypoglycemia during infancy unless they fast for a prolonged period. They can develop hyperketosis similar to, but usually milder than, that seen in type III GSD. Metabolic acidosis is rare. The disorder is usually discovered when an **enlarged liver** and protuberant abdomen are noted during a physical examination. Physical growth can be impaired, and motor development may be delayed as a consequence of hypotonia. With increasing age, clinical and biochemical abnormalities gradually ameliorate, and most adult patients are asymptomatic. GSD-IXc, due to *PHKG2* mutations, tends to have a more severe phenotype that includes liver fibrosis and p. 685p. 686cirrhosis in childhood. Recent case reports indicate that liver fibrosis can also occur in GSD-IXa. Cardiomyopathy can develop in GSD-VI and IXb.

3. Laboratory features. Hypoglycemia is unusual and blood lactate and uric acid levels are normal. Mild hypertriglyceridemia, hypercholesterolemia, and elevated transaminase levels may be present. Ketosis occurs with fasting. Functional tests are not especially useful in evaluating these patients. After an overnight fast, blood lactate level is normal and administration of glucagon elicits a brisk glycemic response without a rise in the blood lactate concentration. The glycemic response to glucagon cannot be used to distinguish between PHK deficiency and lack of phosphorylase itself. Thus, the definitive diagnosis of *type IX GSD* requires genetic testing or determination of PHK activity in erythrocytes or leukocytes. A liver biopsy is usually not necessary. The diagnosis *of type VI GSD* can also be established by genetic testing or, alternatively, by assaying the activity of phosphorylase in purified blood cell fractions and usually does not require a liver biopsy. Muscle phosphorylase activity is normal; muscle histology and glycogen content are normal.

4. **Treatment.** In the past, specific treatment other than avoidance of prolonged fasting was considered unnecessary. Recent research, however, suggests that therapy with a high-protein diet and UCS in patients with GSD-IX improves linear growth and general well-being, decreases hepatomegaly, and may be associated with regression of ultrasound findings of liver fibrosis. UCS 2 g/kg at bedtime typically prevents hypoglycemia and ketosis in these patients.
5. **Monitoring.** Blood glucose and ketone monitoring should be done routinely. Growth and pubertal progression should be carefully monitored. Annual liver ultrasound examinations should be performed starting at age 5 years. Bone densitometry is recommended once growth is complete as there is increased risk of osteoporosis.

E. Fanconi–Bickel syndrome (type XI GSD)

1. **Nature of the defect.** GSD-XI is a rare autosomal recessive disorder characterized by hepatorenal glycogen accumulation caused by deficiency of the facilitative GLUT2 protein that mediates the bidirectional transport of glucose and galactose in hepatocytes, β-cells of the pancreas, enterocytes, and proximal tubules of the kidney.
2. **Clinical manifestations.** Patients usually present in infancy with hepatomegaly, failure to thrive, chronic diarrhea from carbohydrate malabsorption, and hypoglycemia as the interval between feeds increases. A general renal proximal tubulopathy with severe glucosuria and hypophosphatemic rickets are characteristic features. Older patients have a moon-shaped face, a protuberant abdomen, short stature, and delayed puberty. Kidneys are enlarged (detectable by ultrasound) as a result of glycogen accumulation.
3. **Laboratory findings.** Fasting ketotic hypoglycemia and postprandial hyperglycemia and hypergalactosemia (caused by impaired hepatic uptake of the two sugars) are characteristic biochemical features. Decreased insulin secretion (due to an impairment of β-cell glucose sensing) may also contribute to impaired hepatic glucose uptake and postprandial hyperglycemia. Other laboratory findings include hypergalactosemia, glucosuria, renal bicarbonate wasting, proteinuria, phosphaturia, generalized aminoaciduria, and elevated serum alkaline phosphatase level.

Mutation analysis of the *GLUT2* gene confirms the diagnosis.

4. **Treatment.** Frequent feeds using slowly absorbed carbohydrates and restriction of galactose are recommended. Supplementation with UCS has a beneficial effect on metabolic control and growth. Fructose metabolism is not affected; therefore, this monosaccharide may be used as an alternative carbohydrate source. Water and electrolytes must be replaced. Alkali may be necessary to compensate for renal tubular acidosis, and hypophosphatemic rickets requires supplemental phosphate and vitamin D.

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50 Hypokalemic Paralysis

Chih-Jen Cheng and Shih-Hua Lin

I. INTRODUCTION

Hypokalemia, defined as a plasma potassium (K^+) concentration **lower than 3.5 mEq/L**, is the most commonly encountered electrolyte disorder. The homeostasis of extracellular K^+ is tightly regulated by the K^+ exchange between extracellular fluid (ECF) and intracellular fluid (ICF), primarily mediated by the sodium pump (Na^+, K^+ ATPase) and various K^+ channels in the skeletal muscles, and the K^+ excretion, mainly through kidneys and guts. Hyperactive Na^+, K^+ ATPase and inactive K^+ channels result in net K^+ shift into cells. In kidneys, distal renal tubular K^+ secretion is driven by lumen-negative electric potential via apical K^+ channels (renal outer medullary potassium channel). More lumen-negativity can be generated by the enhanced active sodium (Na^+) reabsorption ("fast Na^+") as in the state of mineralocorticoid excess or accumulated luminal anions ("slow chloride [Cl^-]") as in the salt-losing tubulopathy or gastrointestinal disorders. These two major mechanisms of hypokalemia are demonstrated in Figure 50-1.

Hypokalemia can manifest diverse cardiac, neuromuscular, gastrointestinal, renal, and endocrine symptoms and signs. Muscle weakness to paralysis induced by hypokalemia is p. 689p. 690named hypokalemic paralysis (HP) and the leading presentation of hypokalemia-related medical emergency. A prompt diagnosis of the underlying etiologies of HP often leads to more appropriate treatments and less dire complications and recurrence.

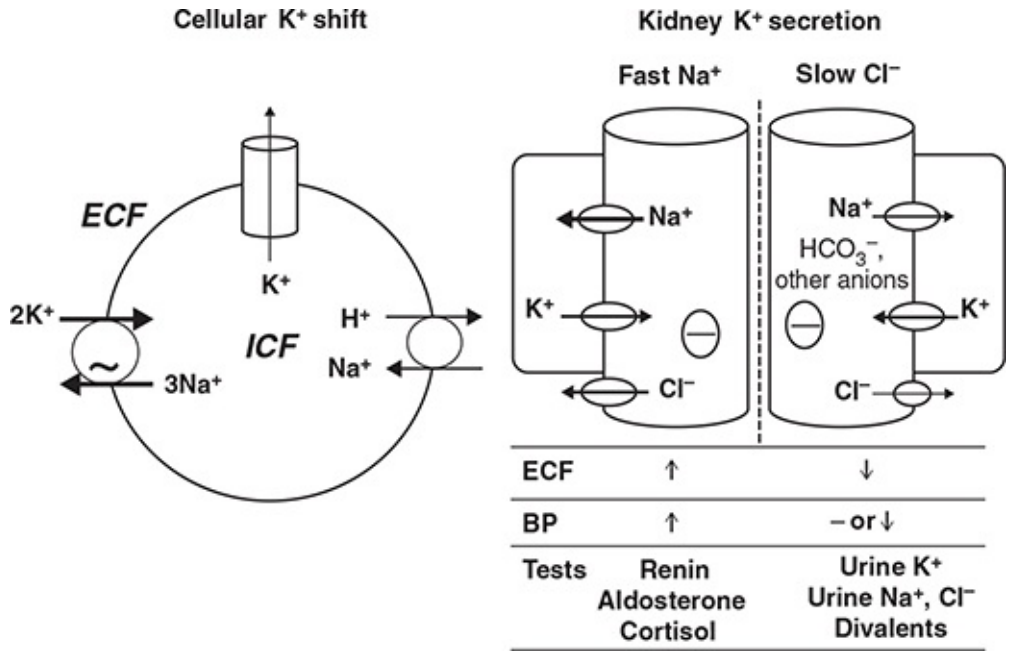

Figure 50-1. Mechanisms of hypokalemia. **Left:** hyperactive K^+ uptake via Na^+, K^+ ATPase, and/or suppressive K^+ efflux via K^+ channels leads to K^+ shift into cells. **Right:** in aldosterone-sensitive distal nephron, enhanced Na^+ reabsorption via electrogenic Na^+ channel (fast Na^+) and reduced Cl^- reabsorption due to increased delivery of HCO_3^- and nonabsorbable anions both enhance luminal negativity (slow Cl^-), and thus high urinary K^+ excretion. The corresponding changes in extracellular fluid, blood pressure, and diagnostic tests are listed.

II. ETIOLOGY

Although the causes of hypokalemia are more diverse, the etiology of HP is much narrower. According to the mechanism of hypokalemia, the etiologies of HP can be classified into hypokalemic periodic paralysis (hypoKPP) due to abrupt K^+ shift into ICF (Fig. 50-2) and hypokalemic nonperiodic paralysis (non-hypoKPP) due to loss of K^+ via urine or feces (Fig. 50-3). In general, hypoKPP and non-hypoKPP disorders are responsible for approximately three-fourths and one-fourth of all HP patients, respectively.

A. hypoKPP: The hallmark of hypoKPP is acute hypokalemia and unexpected muscle paralysis. The muscular symptoms of hypoKPP stem from hypokalemia-related **failure of muscle excitability**. Unlike hyperkalemic periodic paralysis and paramyotonia congenita, hypoKPP does not cause enhanced muscle excitability and myotonia. The paralytic attacks in hypoKPP are often evident at midnight or early morning and **last from hours to days** with spontaneous full recovery. Most attacks involve proximal muscles of the limbs and

spare respiratory, swallowing, and extraocular muscles. Some stressful events including vigorous exercise, cold exposure, emotional stress, carbohydrate feast, and a high Na^+ meal can provoke K^+ shift and paralytic attacks. Based on the family history of periodic paralysis, the hypoKPP disorders can be divided into familial hypoKPP (FPP) and nonfamilial hypoKPP (non-FPP).

1. **FPP:** It includes hypoKPP disorders with clear family history of periodic paralysis. FPP and Andersen–Tawil syndrome (ATS), both inherited in an autosomal dominant pattern, are the major causes.
    a. **hypoKPP:** This is the most popular cause of FPP, especially in Caucasians, with an estimated prevalence of 1 per 100 000 people. The recurrent episodes of muscle weakness to paralysis in the setting of acute hypokalemia begin from childhood to adolescence. Mutations in *CACNA1S* (voltage-gated calcium channel Cav1.1) and *SCN4A* (voltage-gated Na^+ channel Nav1.4) genes are responsible for 60% and 20% of these patients, respectively. The Cav1.1-mutated and Nav1.4-mutated hypoKPP patients displayed similar presentations but still have subtle differences, which may guide the genetic tests (Table 50-1). Female Cav1.1-mutated (especially R528H) hypoKPP patients have lower frequency of paralytic attacks. Permanent vacuolar myopathy often occurs in the fifth or sixth decade. Patients with hyperkalemic periodic paralysis or paramyotonia congenita also carry mutations in the *SCN4A* gene, which, however, cause gain-of-function Nav1.4 channel. Mutation hotspots (R/X substitutions in S4) in *SCN4A* and *CACNA1S* genes are predictive to FPP patients.
    b. **ATS:** It typically presents with the clinical triad of skeletal deformities (craniofacial dsymorphies, syndactyly, etc.), ventricular arrhythmia (especially prolonged QT interval and prominent U wave), and periodic paralysis since infancy. However, the manifestation could be highly variable even within the same kindred. The skeletal deformities and periodic paralysis can be found in the majority of patients, whereas cardiac arrhythmia is observed in approximately 40% of patients and is rarely fatal. About 60% of paralytic attacks in these patients are associated with hypokalemia. Approximately 60% of these patients carry heterozygous mutations in *KCNJ2*

gene (type 1 ATS) encoding hypofunctional inward-rectifying K^+ (Kir) Kir2.1 channel. The remaining 30% to 40% patients (type 2 ATS) have not been linked to a specific gene. A mutation in *KCNJ5* gene encoding Kir3.4 channel was recently found in an ATS patient without *KCNJ2* mutation.

2. **non-FPP:** This group of disorders is clinically indistinguishable from FPP but does not have a positive family history of periodic paralysis. Among non-FPP disorders, thyrotoxic periodic paralysis (TPP) and sporadic periodic paralysis (SPP) are the most common causes, which accounts for three-fourths and one-fourth of all hypoKPP patients in Asians, respectively. TPP and SPP are no longer confined to certain geographic areas because of globalization and immigration.

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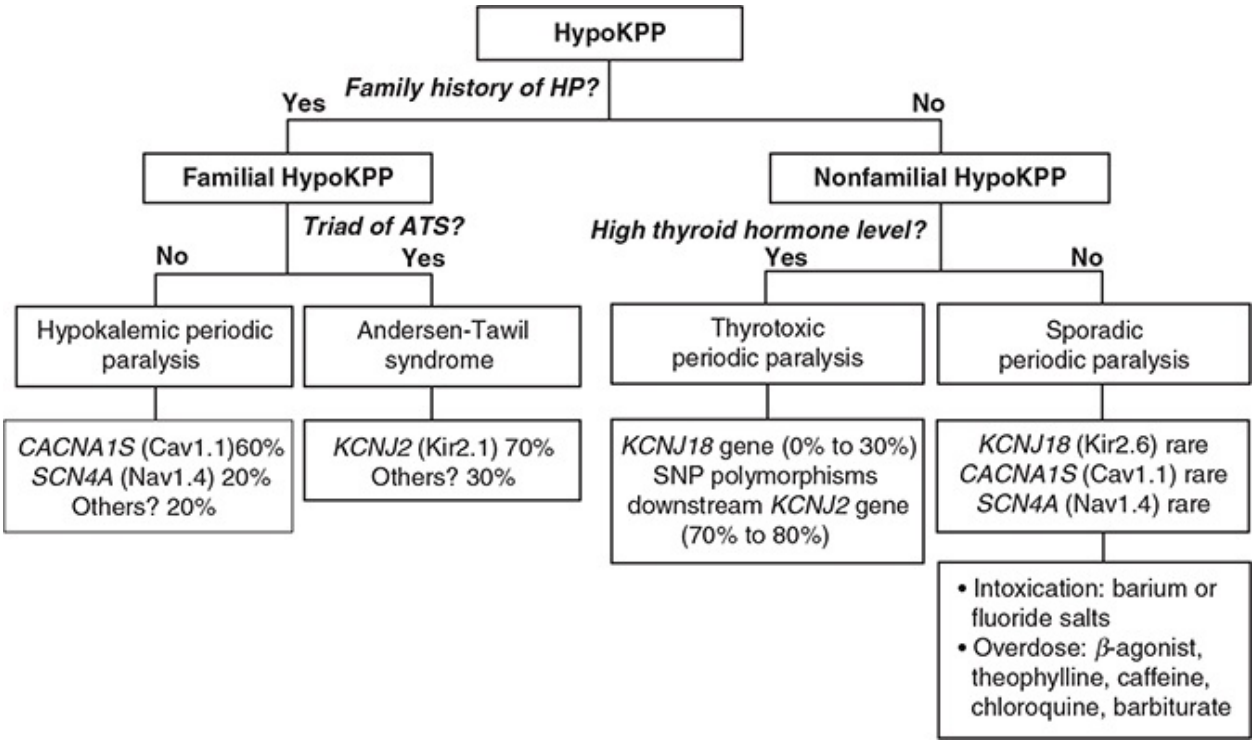

Figure 50-2. Diagnostic approach to hypoKPP.

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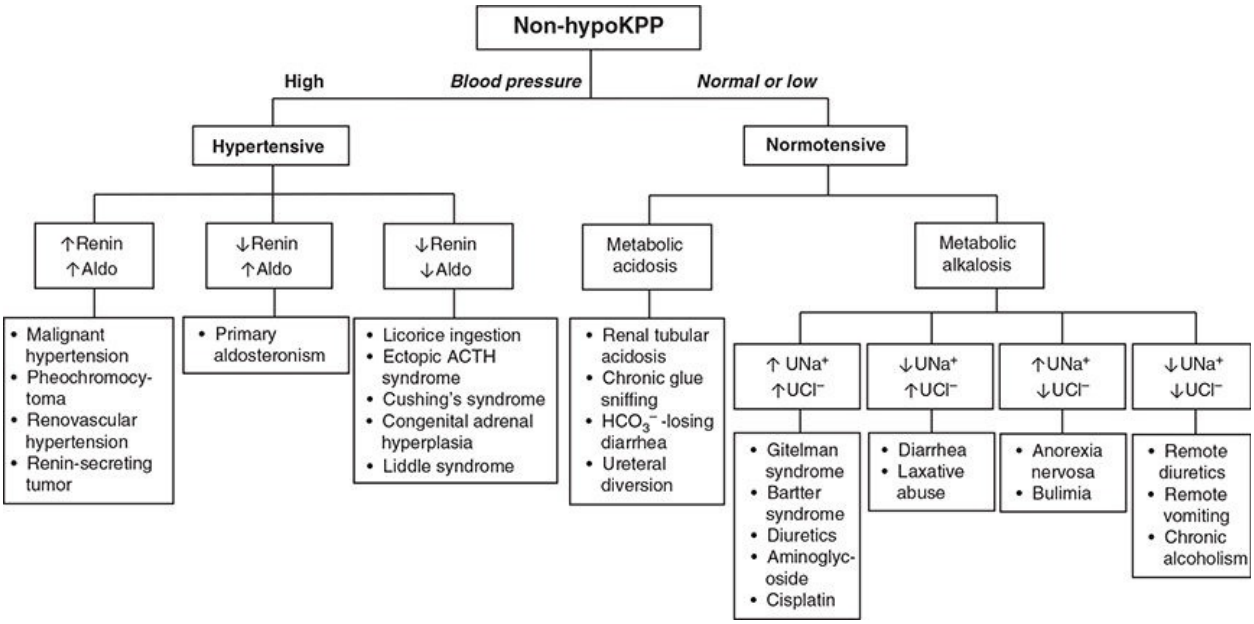

Figure 50-3. Diagnostic approach to non-hypoKPP.

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TABLE 50-1 Phenotypic Difference Between Cav1.1- and Nav1.4-mutated hypoKPP

	Cav1.1	Nav1.4
Reduced penetrance	Often in females	No
Severity	Male > female	Male = female
Frequency of attack	High	Low
Myopathy	Frequent vacuolar myopathy	Rare
Myotonia	No	No
CMAP	Late decrease	Initial postexercise increase followed by late decrease
Acetazolamide	Beneficial for 60% patients	Ineffective, even deleterious
Bumetanide	Beneficial	Beneficial

CMAP, compound muscle action potential test.

a. TPP: It is the most common cause of non-FPP and occurs in approximately **2% of hyperthyroidism patients**. The first

attack of HP often happens in patients' early 20s. The attack of TPP is not correlated with the plasma thyroxin level. The risk factors and precipitating events for TPP are similar to FPP in many ways. Although hyperthyroidism is a prerequisite for the diagnosis of TPP, most TPP patients do not have overt symptoms and signs of hyperthyroidism. Using Wayne score rating symptomatology in TPP patients, only approximately 20% of them are clinically thyrotoxic (Wayne's index >19). Additionally, thyroid function tests are often unavailable in a medical emergency. Nevertheless, several clinical important clues favoring the diagnosis of TPP are presented in Table 50-2. Recent genetic studies have shown that genetic variations in two Kir channels, Kir2.1 and Kir2.6, and nearby long noncoding RNA, *CTD-2378E21.1*, are associated with TPP.

b. SPP: It is the second leading cause of non-FPP in Asia. This term was first used to describe periodic paralysis occurring sporadically with a negative family p. 693p. 694background and not associated with other diseases (by Dr Talbott in 1941). Since then, many sporadic attacks have been attributed to various etiologies, such as drugs and de novo mutations in ion channels (~7% of all SPP), including Nav1.4, Cav1.1, and Kir2.1. Compared with FPP, SPP with de novo Nav1.4 or Cav1.1 mutations often have later age of onset, fewer paralytic attacks, and unidentifiable precipitating events. With unclear pathogenesis, the diagnosis of SPP is made by careful exclusion of other hypoKPP disorders.

TABLE 50-2 Clinical Clues to Diagnosis of TPP

A.	Adult male predominance (male to female ratio ~26:1)
B.	Recurrent paralysis without family history of periodic paralysis
C.	Family and/or personal history of hyperthyroidism (in one-third patients)
D.	Symptoms/signs associated with hyperthyroidism (Wayne score > 19)
E.	Systolic hypertension
F.	Electrocardiogram findings Sinus tachycardia or sinus arrhythmia First-degree atrioventricular block Left ventricular hypertrophy with strain pattern

G. Plasma and urine laboratory findings
Hypocreatininemia due to higher glomerular filtration rate
Relatively normal blood acid–base state
Hypokalemia with low urinary K^+ excretion
Hypophosphatemia with low urinary phosphate excretion on attack
Hyperphosphatemia on recovery
Hypercalciuria (urinary Ca^{2+} to creatinine ratio >0.2 mg/mg)

c. Sympathomimetic overdose and K^+ channel antagonists: Sympathomimetics activate Na^+, K^+ ATPase and enhance cellular uptake of extracellular K^+. HypoKPP-inducing sympathomimetics include caffeine-containing beverages (e.g., large amount of cola consumption), ephedrine/pseudoephedrine in cold medicine, and amphetamine, cocaine, and ecstasy. K^+ channel antagonists (barium, fluoride, chloroquine, and barbiturate) cause acute hypokalemia and paralysis by directly inhibiting cellular K^+ exit through K^+ channels.

B. Non-hypoKPP: Non-hypoKPP patients typically have large K^+ deficit with chronic hypokalemia and progressive neuromuscular symptoms. As mentioned earlier, these patients can be categorized into hypertensive non-hypoKPP (Na^+ retention) and normotensive non-hypoKPP (Na^+ loss) based on ECF volume and blood pressure.

1. Hypertensive non-hypoKPP: These disorders cause renal K^+ wasting with hypokalemia as well as Na^+ retention with expanded ECF volume and hypertension, which often requires multiple antihypertensives. Measurements of plasma renin, aldosterone, and cortisol may reveal the underlying causes of an excessive mineralocorticoid state.

a. Primary aldosteronism (low renin, high aldosterone): This prototype disease can be found in approximately 10% of newly diagnosed patients with hypertension and is responsible for approximately 90% of all hypertensive non-hypoKPP patients. Bilateral adrenal hyperplasia (BAH) and aldosterone-producing adenoma (APA) are the two major causes and account for approximately 60% and approximately 40% of all patients with acquired primary aldosteronism, respectively. Although hypokalemia is found in one-fifth of BAH and half of APA patients, the paralytic attack is often accompanied with

severe hypokalemia (<2 mEq/L). Incidental use of K^+-wasting diuretics for hypertension may aggravate hypokalemia and trigger paralytic attack. Aldosterone secretion is physiologically stimulated by angiotensin II and high plasma K^+, which transiently depolarize the membrane potential of adrenal zona glomerulosa cells, increase intracellular calcium (Ca^{2+}) concentration, and then aldosterone synthesis. A series of genetic studies identified *KCNJ5* somatic mutations in 40% to 70% of APA patients, whereas an additional 10% of APA patients carried somatic mutations in *CACNA1D* (Cav1.3), *ATP1A1* (Na^+, K^+ ATPase subunit α-1), or *ATP2B3* (Ca^{2+} ATPase) genes. Most of these mutations caused small cation (e.g., Na^+) leak and persistently depolarized membrane potential of adrenal cells, accounting for the nonsuppressible aldosterone synthesis in APA.

b. **Secondary aldosteronism (high renin, high aldosterone):** This condition rarely causes HP but can be found in pheochromocytoma, malignant hypertension, renovascular hypertension, and renin-secreting tumors due to hyperandrogenism (high adrenergic activity).
c. **Others (low renin, low aldosterone): Licorice**, a sweat extract from the root of *Glycyrrhiza glabra* often used in folk medicine and for a flavoring agent, prevents the conversion of cortisol to cortisone by inhibiting 11β-hydroxysteroid type 2 and has been reported to cause HP in many cases. Overproduction of endogenous cortisol hormones (saturation effect), such as Cushing syndrome, ectopic adrenocorticotrophic hormone (ACTH) syndrome, and congenital adrenal hyperplasia, can also lead to the syndrome of mineralocorticoid excess but rarely causes HP.

2. **Normotensive non-hypoKPP:** These patients lose both K^+ and Na^+ via kidneys or the alimentary tract. Because of losing salt and water, these patients typically have hypovolemia with secondary hyperreninemic hyperaldosteronism and mild p. 694p. 695hypotension. Of note, metabolic alkalosis or acidosis is

usually associated with these patients because K^+ loss is accompanied by bicarbonate (HCO_3^-) or Cl^-.

a. **Salt-losing tubulopathy:** Congenital or acquired salt-losing tubulopathy causes excessive urinary K^+ wasting together with Cl^- (metabolic alkalosis) or HCO_3^- (metabolic acidosis) wasting.
    i. **Hypochloremic metabolic alkalosis: Gitelman syndrome** (GS) and diuretic abuse are the major causes in this group. GS characterized by chronic hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria is the most common inherited renal tubular disorder. It is primarily caused by homozygous or compound heterozygous mutation in the *SLC12A3* gene encoding thiazide-sensitive Na^+ Cl^- cotransporter in the distal nephron. Other than various muscular complaints such as muscle cramps, tetany, numbness, and weakness, muscle paralysis as primary presentation is not infrequent. The reported prevalence of paralytic attack is approximately 6% in patients with GS. Loop diuretics and thiazides that inhibit renal Na^+ transporters are often abused by young females with body image concern or regularly used by elderly patients with hypertension or heart failure. Severe hypokalemia often ensues if concomitant K^+ intake or a supplement is insufficient. Classic **Bartter syndrome** (BS) with *CLCNKB* gene mutations is a variant of GS and may have non-hypoKPP with onset in early adulthood.
    ii. **Hyperchloremic metabolic acidosis:** Renal tubular acidosis (RTA) is the major diagnosis and typically causes chronic hypokalemia and hyperchloremic metabolic acidosis because of impaired tubular proton secretion (type 1) or HCO_3^- reabsorption (type 2). Patients with RTA may also manifest the complications of chronic metabolic acidosis such as osteomalacia and osteoporosis in adults and rickets in children. In HP patients with type 1 RTA, **Sjögren syndrome** is the most common cause. Patients with Sjögren syndrome are usually female and middle-aged with age of onset ranging from 20 to 60 years. The

mechanism of Sjögren syndrome–induced RTA is unclear, but may be related to autoimmune interstitial nephritis or hypergammaglobulinemia. In HP patients with type 2 RTA, proximal tubulopathy with Fanconi syndrome caused by drugs (aristolochic acid, tenofovir, rifampin, lead), Sjögren syndrome, or multiple myeloma should be considered. Hypokalemia and hyperchloremic metabolic acidosis can also be observed in patients with chronic glue (hippurate) sniffing and ureteral diversion, especially those having gastric, ileal, or colonic segments interposed into urinary tract.

b. Gastrointestinal disorders: The etiologies in this group cause chronic K^+ wasting via vomiting or profound diarrhea. Only severe gastrointestinal disorders can cause K^+ deficit huge enough to induce HP. Furthermore, concomitant multiple electrolyte imbalance such as hypophosphatemia, hypomagnesemia, hypocalcemia, and malnutrition is common.

i. **Eating disorders:** Anorexia nervosa and binge eating/purging (subtype, bulimia) are the most common diagnoses and mainly affect young females.

ii. **Chronic alcoholism:** It is the most common cause of HP in patients with alimentary disorders. These patients often develop chronic depletion of multiple electrolytes, including K^+, magnesium (Mg^{2+}), Ca^{2+}, and phosphate. Low electrolyte intake, frequent vomiting, urinary electrolyte wasting, and hypomagnesemia-related hypoparathyroidism are contributory factors.

iii. **Laxative abuse:** Laxatives are most commonly abused by patients with eating disorders, body image concern, or older patients with chronic constipation.

III. DIAGNOSIS

Prompt diagnosis of the underlying etiology of HP is decisive to guide appropriate therapy. The first step of differential diagnosis is to separate hypoKPP from non-hypoKPP disorders based on several easily available quick facts given in Table 50-3.

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TABLE 50-3 Quick Facts to Separate hypoKPP from non-hypoKPP

	HypoKPP	Non-hypoKPP
Onset	Sudden	Progressive
Cause of hypokalemia	K^+ shift	K^+ deficit
Urinary K^+ excretion	Low	Usually high
Divalent abnormalities	Rare	Often
Acid–base state	Normal	Abnormal
Acute therapy	Small K^+ dosage Nonselective β-blockers[a]	Large K^+ dosage $MgSO_4$[b]
Chronic therapy	Acetazolamide[c] Loop diuretics[d]	K^+ citrate[e] KCl[f]

[a]Might be helpful for those with obvious hyperadrenergism and refractory to K^+ supplement.
[b]For patients with coexisted hypomagnesemia.
[c]More helpful for FPP patients with R/X Cav1.1 mutations.
[d]Still require randomized controlled trial to prove the efficacy.
[e]For patients with coexisting metabolic acidosis.
[f]For patients with coexisting metabolic alkalosis.

A. History taking and physical examination: History taking and physical examination gather relevant clinical information for diagnosis.

1. **Family and personal history:** A clear family history of childhood-onset paralysis indicates autosomal dominant inherited FPP or ATS. In contrast, patients with autosomal recessive disorders, such as GS or classic BS, may have negative or obscure family history. The personal medical history should focus on thyroid disorders, hypertension, renal/gastrointestinal disorders, psychological conditions, and bowel surgery. The patient's medications need to be thoroughly scrutinized, especially sympathomimetics, laxatives, or diuretics. It should be noted that patients with habitual or surreptitious behaviors often deny any use of laxatives, diuretics, and self-induced vomiting.
2. **Physical examination:** The clinicians should look for the constellation of symptoms and signs caused by ATS (triad), hyperthyroidism (enlarged thyroid gland, exophthalmos, heat intolerance, weight loss), hyperadrenergism (tachycardia or tachyarrhythmia, tremor, etc.), kidney diseases

(nephrolithiasis/urolithiasis, impaired urine concentration), or gastrointestinal diseases (low body mass index and change of body weight or bowel habit).

B. Clues of K^+ shifting: Some clues of acute K^+ shift indicate the diagnosis of hypoKPP. Relatively normal blood acid–base status is typically found because there is no associated anion lost in the process of K^+ shift. Paired hypophosphatemia is common due to similar factors that drive K^+ and phosphate into cells, especially in TPP. Lower K^+ dosage to achieve muscle recovery is also an important clue.

C. Blood acid–base and electrolyte abnormalities: Unlike hypoKPP, patients with non-hypoKPP have an abnormal blood acid–base state as mentioned earlier. Hypomagnesemia is a hallmark in patients with GS but also found in patients with alcoholism, eating disorders, or profound diarrhea. Multiple electrolyte abnormalities point to the diagnosis of alimentary disorders such as anorexia nervosa or chronic alcoholism, and renal tubular disorders, such as Fanconi syndrome.

D. Renin, aldosterone, and cortisol hormones: The causes of hypertensive non-hypoKPP (mineralocorticoid excess state) can be identified based on the changes in renin activity, aldosterone, and cortisol in plasma (Fig. 50-3). In the condition of relatively low renin and aldosterone, a high plasma cortisol usually indicates ectopic ACTH or Cushing syndrome; low plasma cortisol suggests congenital adrenal hyperplasia; normal cortisol gives a hint of licorice overdose or Liddle syndrome.

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E. Urinary K^+ excretion: A spot urine sample right before the initiation of K^+ supplement and the following 24-hour urine collection are recommended. Urinary K^+/creatinine ratio (urine K^+/Cr), transtubular K^+ gradient, or fractional excretion of K^+ in response to hypokalemia can be evaluated. A low urinary K^+ excretion rate is typically detected in patients with hypoKPP or extrarenal causes of normotensive non-hypoKPP. However, some patients with alimentary disorders may have misleadingly high urinary K^+ excretion due to severe bicarbonaturia or hypomagnesemia. Patients with hypertensive non-hypoKPP or salt-losing tubulopathy usually show high urinary K^+ excretion rate.

F. Urinary Na^+ and Cl^- and divalent: Finding the source of salt (NaCl) loss from urinary Na^+ and Cl^- excretion discriminates the pathophysiologic cause of hypokalemia in normotensive non-hypoKPP disorders featuring salt and fluid wasting and hypovolemia. Unparalleled urinary Na^+ and Cl^- excretion usually points to gastrointestinal disorders. Patients with anorexia/bulimia nervosa lose large HCl via vomiting, then gain and excrete HCO_3^- from the kidney to have a high Na^+ but low Cl^- in urine (high urinary Na^+/Cl^- ratio). Low urinary Na^+ but a high Cl^- excretion (low urinary Na^+/Cl^- ratio) suggests laxative abuse and some chronic diarrhea states, in which the renal ammonium production (ammoniagenesis) and excretion is enhanced by uncorrected hypokalemia. Low excretion of Na^+ and Cl^- could indicate remote vomiting and "yesterday's diuretics." High paralleled urinary Na^+ and Cl^- wasting is universal to renal tubular disorders (GS and BS, RTA, and diuretics). The evaluation of urinary Mg^{2+} and Ca^{2+} is helpful to separate a lesion of the loop of Henle (as in BS) from that of a distal convoluted tubule (as in GS). Hypocalciuria is a keynote footprint for GS. Besides, the calculation of urine anion gap ($U_{Na}{}^+ + U_K{}^+ - U_{Cl}{}^-$) as an index of urinary ammonium excretion distinguishes RTA (positive) from non-RTA (negative).

IV. PATHOGENESIS

A. FPP: R/X mutation hotspots create an aberrant conducting pore for small cation influx, so-called omega current, which is normally counteracted by K^+ efflux and does not cause an anomaly. Whenever acute hypokalemia occurs, the K^+ efflux via various K^+ channels is inhibited and thus allows the omega current to depolarize the resting membrane potential of sarcolemma. This phenomenon is termed hypokalemia-induced paradoxical depolarization and has been a common hallmark in FPP and TPP. There is no omega current but low Kir K^+ current in ATS patients with *KCNJ2* mutations. The indistinguishable phenotypes between FPP, ATS, and barium (a potent Kir channel inhibitor) poisoning indicate that both omega current and low Kir current lead to a common outcome in skeletal muscles.

B. Non-FPP: Recently, genetic studies have identified that mutations in *KCNJ18* gene encoding a skeletal muscle-specific Kir2.6 and genetic variants downstream from the *KCNJ2* gene are highly associated with

non-FPP. These findings indicate that dysregulated Kir channels may be the underlying mechanism of non-FPP. Furthermore, thyroxine, hyperinsulinemia, and hyperadrenergism, which stimulate the activity and expression of Na^+, K^+ ATPase and suppress the Kir current in skeletal muscles, could provide the needed trigger for HP attacks.

C. Other causes: *In vitro*, the characteristic paradoxical depolarization in hypoKPP myofibrils can be recapitulated in normal myofibrils whenever the extracellular K^+ level is extremely low (usually <2.0 mEq/L). This explains the attack in non-hypoKPP with severe hypokalemia.

V. TREATMENTS

A. General principles: The major emergencies in HP are cardiac arrhythmias and respiratory failure due to severe hypokalemia rather than muscle paralysis *per se*. Cardiac monitoring along with frequent plasma K^+ measurements is very crucial. The route of K^+ therapy is usually parental because severe hypokalemia often impairs the bowel movement, so-called pseudointestinal obstruction. Of note, the K^+ solution should not contain glucose or HCO_3^- because this might aggravate the degree of hypokalemia by enhancing K^+ shift into cells. In the preparation of K^+ supplementation, p. 697p. 698KCl is preferred, whereas $KHCO_3$ and K^+ phosphate may provide more benefit to non-hypoKPP with hyperchloremic metabolic acidosis and gastrointestinal disorders with simultaneous phosphate depletion, respectively. The recommended rate of parenteral K^+ treatment is usually <10 mEq/hour in hypoKPP and 20 mEq/hour in non-hypoKPP. However, the K^+ infusion rate must be increased following a bolus of 3 to 6 mmol K^+ when life-threatening arrhythmia or impending respiratory insufficiency is found. Correction of hypomagnesemia is absolutely warranted because it helps in the correction of hypokalemia and prevention of fatal Torsades de pointes.

1. **Therapy for hypoKPP:** K^+ supplementation has been shown to prevent fatal arrhythmia and accelerate the recovery of paralysis in hypoKPP patients. Because of no absolute K^+ deficit, the reason for K^+ supplementation in hypoKPP patients is to raise plasma K^+

level above the threshold of hypokalemia-induced paradoxical depolarization. It is reported that the average K^+ dose to recover the muscle power is 1 mEq/kg for hypoKPP. However, patients with stronger adrenergic activity have longer recovery time and higher risk of rebound hyperkalemia.

2. **Therapy for non-hypoKPP:** Patients with non-hypoKPP disorders usually need larger amount of K^+ (3.5 to 4.0 mEq/kg) and longer time to recover their muscle power in comparison with hypoKPP (Table 50-4). The factors such as initial presentations of lower plasma K^+, associated volume depletion, and the presence of renal K^+ wasting are associated with much higher KCl dosage required for recovery of muscle power.
3. **Therapeutic course:** A decreased (≥0.1 mEq/L) plasma K^+ level during K^+ supplementation, so-called worsening or paradoxical hypokalemia, can be observed in both hypoKPP and non-hypoKPP. This phenomenon typically happens at a median time of 2 hours after the initiation of KCl therapy and is related to a significant force driving extracellular and infused K^+ into cells. It has been reported that approximately one-fourth of TPP patients and half of non-hypoKPP patients could develop paradoxical hypokalemia during therapy. Paradoxical hypokalemia in TPP is often associated with severe hyperthyroidism and higher β-adrenergic activity to continuously activate Na^+, K^+ ATPase. TPP patients who had paradoxical hypokalemia needed a twofold higher KCl dose to achieve recovery and developed more severe rebound hyperkalemia as a result of the K^+ exit to ECF (Fig. 50-4). The blockade of K^+ shift into cells by nonselective β-blockers through suppressing β-adrenergic activity and inhibiting insulin secretion may be an alternative therapeutic option. In non-hypoKPP, patients with paradoxical hypokalemia had significant volume depletion and larger amounts of normal saline with KCl. The increased volume effect of KCl and NaCl may diminish α-adrenergic activity and then release the “inhibition” on Na-K-ATPase activity. Paradoxical hypokalemia in non-hypoKPP truly reflects the much larger deficit of K^+ than initial hypokalemia. More aggressive K^+ supplement with slow volume repletion is warranted to avoid dire complication and delayed recovery because

rebound hyperkalemia rarely happens in this setting.

TABLE 50-4 Therapeutic Comparison Between hypoKPP and non-hypoKPP

	HypoKPP (TPP)	Non-hypoKPP
Recovering plasma (K^+)	Higher	Lower
Recovery time	Shorter	Often longer
Required K^+ dosage	Smaller	Larger
Paradoxical hypokalemia (%)	One-fourth	Half
Rebound hyperkalemia (%)	40–60	~0
Associated factors for paradoxical hypokalemia	Severe hyperadrenergism	True hypovolemia

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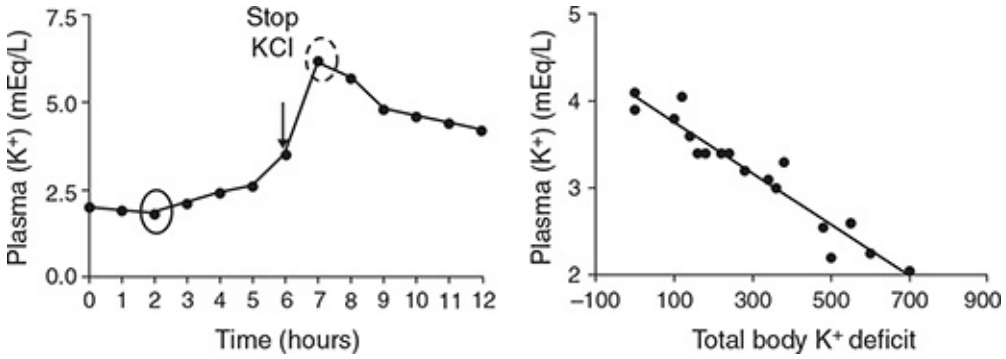

Figure 50-4. Acute K^+ therapy in hypoKPP and non-hypoKPP. **Left:** the demonstrated paradoxical hypokalemia (*solid circle*) and rebound hyperkalemia (*dotted circle*) happened even with short-term K^+ supplement (10 mEq/hour) in a hypoKPP patient; **right:** compared with hypoKPP, non-hypoKPP patients need much larger K^+ supplementation, especially when the initial plasma K^+ level is extremely low (>600 mEq KCl is required when plasma K^+ level is lower than 2.5 mEq/L) (modified from Sterns RH, Cox M, Feig PU, Singer I. Internal potassium balance and the control of the plasma potassium concentration. *Medicine* 1981;60:339–354.).

B. Specific treatments for hypoKPP: The definitive treatments for hypoKPP patients aim to control the underlying etiology, to prevent hypokalemia, and to avoid precipitating events.

1. **FPP**
   a. **Carbonic anhydrase inhibitors:** The most commonly used treatment for FPP is carbonic anhydrase inhibitor, especially **acetazolamide**. Of note, only half of FPP patients benefit

from acetazolamide. Most of them carry R/X mutations (R528H and R1239H) in the *CACNA1S* gene. Like TPP, acetazolamide treatment is ineffective or even deleterious to FPP with *SCN4A* mutation.

b. **Others:** Mineralocorticoid antagonist **spironolactone** and high K^+ meals are advised to lower the risk of hypokalemia in FPP patients. A recent study has demonstrated that **bumetanide**, an inhibitor of Na^+–K^+–$2Cl^-$ cotransporter, completely prevented hypokalemia-related muscle weakness in hypoKPP mouse models, probably through reducing myoplasmic Cl^- concentration. A trivalent cation, 1-(2,4-xylyl) **guanidinium**, has also been shown to block omega current without interfering with the function of normal Nav1.4 channel and could be a potential therapy for FPP.

2. **TPP**

a. **Nonselective *β*-blockers:** Nonselective *β*-blocker (e.g., oral **propranolol** 3 to 4 mg/kg or IV 1 to 2 mg) has been reported to shorten the duration of paralysis in TPP patients, especially those with paradoxical hypokalemia, and even prevent paralytic attacks.

b. **Chronic therapy:** The definitive therapies to hyperthyroidism include thionamides (propylthiouracil, methimazole, etc.), radioiodine therapy, or surgical thyroidectomy. Propylthiouracil inhibits peripheral conversion of T4 to T3 and could be more suitable for patients with more severe thyrotoxicosis. Radioiodine is the preferred therapy for toxic multinodular goiter and those with relapse after thionamides are discontinued. Surgery is recommended for those with a large goiter and severe hyperthyroidism.

C. Specific treatments for non-hypoKPP: For patients with non-hypoKPP, the aim is to stop or diminish K^+ wasting and control the underlying disease.

1. **Diminish K^+ wasting:** The K^+-sparing diuretics, angiotensin inhibitors, or nonsteroidal anti-inflammatory drugs are often used to ameliorate the urinary K^+ wasting in salt-losing tubulopathy. As for patients with gastrointestinal disorders, abstinence from abuse of diuretics/laxatives, electrolyte-rich diet, and appropriate psychosocial interventions involving psychiatrists, dieticians, and

physicians should be applied.

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2. **Control underlying disease:** In the cases of distal RTA caused by Sjögren syndrome, immunosuppressive agents including hydroxychloroquine and prednisolone are often prescribed to control extraglandular involvement. Surgical removal of an adrenal adenoma could be curative for patients with APA.

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SECTION 9

Diabetes Mellitus

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Etiology, Pathogenesis, and Therapy of Type 1 Diabetes Mellitus

David A. Baidal and Jay S. Skyler

I. DEFINITION

Type 1 diabetes mellitus is characterized by pancreatic islet β-cell destruction and absolute insulinopenia. Thus, individuals are ketosis-prone under basal conditions. Onset of the disease is generally in youth (thus, the former name **juvenile-onset diabetes**), but it can occur at any age. Patients are dependent on daily insulin administration for survival (thus, the former name **insulin-dependent diabetes mellitus** or IDDM).

II. OVERVIEW OF PATHOGENESIS

Current formulation of the pathogenesis of type 1 diabetes includes the following:

A. A genetic predisposition, conferred by diabetogenic genes on the short arm of chromosome 6, either as part of or in close proximity to the major histocompatibility complex (MHC) region. There are also protective loci at the same location. When both susceptibility genes and protective genes are present, the protective genes usually confer dominant protection.

B. Putative environmental triggers (possibly viral infections, chemical

toxins, or exposure to cows' milk proteins in early infancy) that in genetically susceptible individuals might play a role in initiating the disease process.

C. An immune mechanism gone awry, either initiation of immune destruction or loss of tolerance, leading to slow, progressive loss of pancreatic islet β cells and eventual clinical onset of type 1 diabetes. The immune destruction appears to be mediated by the TH1 subset of helper CD4 T lymphocytes and cytotoxic CD8 cells, whereas the TH2 subset of CD4 T lymphocytes and T-regulatory cells may confer protection.

III. GENETICS

A. Evidence for genetic predisposition comes from demonstrations that the concordance rate for type 1 diabetes is higher in monozygotic than in dizygotic twins. Moreover, the empirical risk of developing type 1 diabetes is increased in first-degree relatives of individuals with the disease. Among whites in the United States, the overall risk is 0.2% to 0.4%. On the other hand, siblings of probands with type 1 diabetes have a risk of approximately 5%, and offspring of diabetic parents have a 3% risk if the mother has the disease and a 6% risk if the father has the disease. The risk for an identical twin of a proband with type 1 diabetes is 30% to 50%.

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B. The major genetic predisposition appears to be conferred by diabetogenic gene(s), at a locus called *IDDM1* on the short arm of chromosome 6, either within or in close proximity to the MHC region, that is, the human leukocyte antigen (HLA) region. A second locus —*IDDM2*—is on the short arm of chromosome 11 in the region flanking the insulin gene. There are a number of other diabetogenic genes on other chromosomes.

C. The relationship between type 1 diabetes and the HLA system is complex.

1. Within families, there is clearly linkage between type 1 diabetes and the HLA system, regardless of what HLA alleles are manifest in any given family.
2. Across populations, there is clearly an association between type 1 diabetes and certain HLA alleles. This is particularly true of the immune-response genes, also known as Class II MHC alleles.

These include the HLA-DR, DQ, and DP loci.

a. The HLA-DR3 and DR4 alleles of the DR locus occur more frequently in white subjects with type 1 diabetes, with the heterozygote HLA-DR3/DR4 being disproportionately increased (40% of subjects with type 1 diabetes, compared with only 3% of the general population). More than 95% of type 1 diabetic individuals are HLA-DR3, DR4, or DR3/DR4. On the other hand, HLA-DR2 confers protection against the development of type 1 diabetes.

b. Alleles of HLA-DQ-β have a major role in determining relative disease susceptibility or resistance. DQB1*0602 (which is associated with DR2) confers disease protection. On the other hand, DQB1*0201 (which is associated with DR3) and DQB1*0302 (which is associated with DR4) confer increased risk.

c. The structure of the DQ molecule, in particular residue 57 of the B chain, helps specify the immune response against the insulin-producing islet β cells. Alleles in which this residue is aspartic acid appear to have protection against the disease, whereas other amino acids at that site do not offer such protection.

3. Debate exists as to how the immune-response genes alter disease susceptibility. Some could induce an immune response to islets, such as by having a high affinity for peptides that, when presented to the immune system, amplify the cellular immune response. Alternatively, the susceptibility genes could have a low affinity for peptides that establish and maintain tolerance.

4. On the other hand, it should be noted that there are limitations with the HLA type 1 diabetes hypothesis. An all-or-none relationship between type 1 diabetes and the HLA system has not been defined, and diabetogenic gene(s) have not been clearly identified.

D. The search for diabetogenic genes continues. There has been much progress in the last several years in unraveling the genetics of type 1 diabetes, which could lead eventually to identification of specific diabetogenic genes and ultimately their gene products. Such identification might permit better genetic counseling, amniocentesis and fetal diagnosis, identification of susceptible individuals, and possibly even genetic manipulation either to alter susceptibility or to replace gene function.

IV. ENVIRONMENTAL TRIGGERS

A. The degree to which environmental events are important in the pathogenetic sequence is unresolved. There is compelling evidence that they can initiate the pathogenetic processes in genetically predisposed animals, but evidence for their role in type 1 diabetes in human beings is less secure. Although some have argued that the substantial discordance of type 1 diabetes in identical twins indicates that environmental factors must play a role in human type 1 diabetes, this view has been challenged by invoking the potential of genetic diversity between such "identical" twins, an argument that would eliminate the need to necessarily include environmental events in the disease sequence. Nevertheless, most investigators accept that, at the very least, environmental factors influence the probability of an individual developing type 1 diabetes.

B. Viral infections

1. A number of human viruses can infect and damage islet β cells in experimental animals, and some of them have the potential for contributing to the development of type 1 diabetes. In one case, a coxsackie B variant was isolated from the pancreatic tissue of a young boy who died 10 days after the onset of type 1 diabetes, and the isolate produced diabetes in experimental animals.

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2. An unresolved question is whether many different viral infections, such as enteroviral infections, can cause type 1 diabetes in humans; or whether a single unknown diabetogenic virus is responsible for most cases of the disease; or whether viral infections merely serve to bring type 1 diabetes to clinical recognition, without playing any specific role in islet β-cell destruction.
3. Exposure can be remote in time from the onset of type 1 diabetes. This remoteness can even include exposure in utero; for example, congenital rubella can result in type 1 diabetes.

C. Chemical toxins

1. A variety of chemical toxins appear to have the potential of inducing islet β-cell damage. Among these are the nitrosourea compounds. These are ubiquitous in our environment and represent only one class of chemical compounds with the potential for leading to type 1 diabetes.
2. In one animal model of diabetes, a series of environmental insults

(both viral and chemical) results in cumulative β-cell destruction, but only in genetically susceptible animals.

D. Ongoing studies. The Environmental Determinants of Diabetes in the Young

(TEDDY) is an ongoing international, multicenter, observational cohort study which enrolled newborns with high genetic risk for type 1 diabetes. Its primary objective is the identification of infectious agents, dietary factors, or other environmental exposures associated with increased risk of autoimmunity and type 1 diabetes. Eligible children are followed longitudinally at specific intervals until age 15 years, and the study is expected to be completed in 2025. Results obtained from this observational study may allow to clarify the controversy regarding the role of environmental factors in human type 1 diabetes.

V. IMMUNOLOGIC FACTORS

A. Immune involvement. Abundant evidence suggests that islet β-cell destruction is immunologically mediated. The exact immunologic mechanisms involved in the pathogenetic pathway have not yet been defined, even in animal models. There may be several different pathogenetic sequences that eventuate in immune destruction of β cells. For example, the pathways involved in typical type 1 diabetes may be different from those involved when type 1 diabetes is only one component of a polyendocrine autoimmune syndrome. It appears that type 1 diabetes may be a group of clinically similar conditions that eventuate in β-cell failure.

1. It has been argued that the immune destruction is “autoimmune” in nature, which might be the case if environmental factors are not involved. Nevertheless, it must be emphasized that immune-mediated destruction does not necessarily imply spontaneous autoimmunity.
2. Initiating, or primary, events for the activation of immune destruction are not yet known. Once immune destruction commences, secondary and tertiary immune responses are activated, with virtually the whole immunologic army attacking β cells.
3. It is unclear whether immune activation occurs because of presentation of a diabetogenic peptide to the immune system and activation of an immune response, or because of failure to maintain tolerance to a diabetogenic peptide.

B. Insulitis. Important evidence of cell-mediated immune destruction of islet β cells is the finding of mononuclear cell infiltration of the islets (insulitis or isletitis) in pancreases examined near the time of clinical onset of type 1 diabetes. This lesion is consistent with an immune reaction and is similar to the lymphocytic infiltration encountered in other reputed autoimmune conditions, including endocrinopathies.

1. At diagnosis in human beings, the majority of infiltrating cells are lymphocytes, both activated CD8 T-cytotoxic cells and CD4 T-helper cells, with some B lymphocytes present as well. Macrophages and natural killer (NK) cells are also present.
2. In one series of pancreases obtained near time of onset of type 1 diabetes, there was aberrant expression of MHC molecules. The β cells showed expression of Class II (HLA-DR) MHC, although at the electron microscopic level other workers have shown that Class II MHC expression can be on macrophages that p. 703p. 704have ingested β-cell material. Class I MHC was hyperexpressed by several islet cells, but only in those with some β cells. Islets with hyperexpression of Class I MHC also showed interferon-α, suggesting environmental stimulation of β cells and activation of interferon-α.

C. Cell-mediated immune processes are responsible for the destruction of islet β cells.

1. Lymphocytes, NK cells, and macrophages/monocytes appear to be involved. Cytokines produced by these cells may mediate damage to β cells. In vitro, several cytokines (e.g., interferon-γ, tumor necrosis factor, and interleukin-1) can kill cultured islet cells. The β cells appear to be particularly vulnerable to tissue damage.
2. There is accelerated reenactment of the pathogenetic sequence following pancreatic transplantation in identical twins (from a nondiabetic twin to a diabetic cotwin) in the absence of immunosuppression. The genetic identity precluded rejection (which was also excluded by virtue of the fact that the transplanted kidney from the same donor continued to function, and the histology was not consistent with rejection), yet insulitis (predominantly T lymphocytes) and pancreatic graft failure occurred in a rapid course.

D. Circulating antibodies. A variety of antibodies to islet cells and islet cell markers can be detected at diagnosis of type 1 diabetes, and even several years prior to diagnosis. These include antibodies to islet cells detected by immunofluorescence (islet cell antibodies or ICAs); insulin (insulin autoantibodies or IAAs); glutamic acid decarboxylase; an islet tyrosine phosphatase called IA2 or ICA-512; the zinc transporter ZnT8 (Slc30A8); islet-specific glucose 6-phosphatase catalytic subunit–related protein; and others. **These antibodies only reflect *β*-cell damage and are not responsible for mediating *β*-cell destruction**. The presence of islet autoantibodies in the absence of dysglycemia does not make an absolute diagnosis. The presence of islet autoantibodies confers risk for the development of type 1 diabetes and should be viewed in that context. On the other hand, if a person with diabetes is found to have positive islet autoantibodies, this would establish a diagnosis of autoimmune diabetes. It is postulated that some may be directed against an antigen involved in initiating the immune process, particularly insulin, but more evidence is needed in this regard. These antibodies do serve as useful markers of immune activity and/or as markers of ongoing *β*-cell destruction in type 1 diabetes. In patients at increased genetic risk for type 1 diabetes, the presence of a single islet autoantibody is associated with a 14.5% risk of progression to T1D by 10 years. The presence of multiple autoantibodies (two or more) is associated with a 69.7% risk at 10 years and >90% by 20 years.

E. Evolution of immunopathology. The islet immunopathology can commence several years prior to clinical recognition of type 1 diabetes. The evidence is consistent with the notion that there is a slow, continuing immune process antedating the clinical diagnosis of type 1 diabetes.

1. In prospective studies of first-degree relatives (mostly parents and siblings, sometimes offspring) of probands with type 1 diabetes, there is an increased risk of developing type 1 diabetes. The clinical onset of disease is usually preceded by the appearance of various antibodies, often by many years.
2. In studies involving unaffected monozygotic twins and other first-degree relatives of type 1 diabetes probands, antibodies precede the development of clinical type 1 diabetes. Moreover, such subjects have a progressive decline in islet *β*-cell function, as measured by a decrease in early insulin release after an IV glucose load.

3. Not all islets are involved at the time of diagnosis. Histologically, a few show the classical pathognomonic insulitis lesion, but intact islets with β cells can be found, as well as an occasional hyperplastic islet. The majority of islets are pseudoatrophic (i.e., small islets without mononuclear infiltration and devoid of β cells, but with intact glucagon-secreting α cells and somatostatin-secreting δ cells). Presumably, the inflammatory process has abated, having occurred much earlier in those islets, with type 1 diabetes appearing only when sufficient β cells have been destroyed, so that glucose tolerance can no longer be maintained.

F. Animal models

1. **Spontaneous diabetes.** There are two spontaneous animal models of type 1 diabetes, the BB rat and the NOD mouse. Both of these models have an MHC-related p. 704p. 705genetic predisposition, both have been shown to have immune-mediated β-cell destruction, and both develop insulin deficiency, hyperglycemia, and ketosis.
2. **Induced diabetes.** Using repetitive low doses of streptozotocin, type 1 diabetes can be induced in genetically susceptible strains of mice. Destruction of β cells is immune-mediated. Thus, this is a model of immune-mediated, environmentally triggered disease.
3. **Immune intervention.** Immune intervention results in prevention or reversibility of disease in the BB rat, the NOD mouse, and in the low-dose streptozotocin mouse model.

G. Immune intervention studies in humans

1. If type 1 diabetes is an immunologically mediated disease, then immune intervention should alter the natural history of the disease and potentially abort the syndrome. This would be true whether the disease was due to spontaneous autoimmunity or was simply immune-mediated.
2. In human beings, immune intervention trials have been initiated for at least three reasons: to confirm that the immune system is involved in the pathogenesis of type 1 diabetes; to help clarify and define the immune mechanisms involved in the pathogenetic sequence; and to potentially lead to a clinically applicable intervention. Many of these studies have begun shortly after

diagnosis, when there is still some residual β-cell function.

3. The earliest controlled trials used azathioprine, alone or with glucocorticoids, or cyclosporine. They demonstrated that immune intervention does indeed alter the natural history of the disease. This provided convincing support for the hypothesis that immune mechanisms are important in the etiopathogenesis of type 1 diabetes. Unfortunately, the data are too meager to permit conclusions about clinical utility of an early immune intervention strategy because of small sample sizes and short duration of follow-up of subjects. It is possible that intervention at this stage is effective in halting the destruction of β cells, resulting in milder disease.
4. Many new potential therapies are targeted to patients with new-onset type 1 diabetes. The hope is to find a strategy that permits specific intervention to abort the immune attack on pancreatic islet β cells while leaving the immune system otherwise intact. A few therapies have shown promise in clinical trials:
   a. The more promising to date has been the use of humanized anti-CD3 monoclonal antibodies which demonstrated preservation of β-cell function at 1 year and a milder course of disease in two trials (using two different anti-CD3 antibodies). Ongoing are large confirmatory trials with these antibodies.
   b. Costimulation modulation with abatacept, a CTLA4-immunoglobulin fusion protein, showed a reduction in β-cell function over 2 years with an estimated 9.6 months delay in C-peptide reduction.
   c. Selective B-lymphocyte depletion with an anti-CD20 monoclonal antibody also resulted in a delay in the fall of C-peptide arguing in favor of a potential role of B lymphocytes in the pathogenesis of type 1 diabetes.
   d. More recently, combination therapy with antithymocyte globulin and granulocyte colony-stimulating factor demonstrated preservation of β-cell function in patients with established type 1 diabetes (duration of diabetes >4 months and <2 years). A clinical study using this combination in new-onset type 1 diabetes (<3 months duration) is currently ongoing.
5. Treatment of the prediabetic state is the logical ultimate goal of immune intervention studies. Studies are currently under way in high-risk individuals (i.e., first-degree relatives of probands with

type 1 diabetes, with antibodies and with diminished islet β-cell function, measured by decreased early insulin release after an intravenous (IV) glucose load, or in relatives who have dysglycemia but not yet diabetes). Current ongoing TrialNet studies include:

a. **Oral insulin** for prevention of diabetes in relatives at risk for type 1 diabetes. The rationale for this study was based on data from the oral arm of the Diabetes Prevention Trial—Type 1 diabetes which showed that the subgroup of patients with insulin antibodies >80 nU/mL had a potential beneficial effect of oral insulin. Recruitment for this study has been completed, and results should be available soon.

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b. **Anti-CD3 monoclonal antibody (teplizumab)** for prevention of type 1 diabetes in relatives at risk. Eligible participants for this study are those between ages of 8 and 45 years who are relatives of a proband with type 1 diabetes, have two or more diabetes-related autoantibodies, and have abnormal glucose tolerance. Recruitment is currently ongoing.

c. **CTLA4-Ig (abatacept)** for prevention of abnormal glucose tolerance and diabetes in relatives at risk for type 1 diabetes. Eligible participants are those between ages of 6 and 45 years who are relatives of a proband with type 1 diabetes, have two or more diabetes-related autoantibodies (not including insulin antibodies), and have normal glucose tolerance. Recruitment is currently ongoing.

6. Ultimately, it is possible to project the following sequence:
   a. At birth, routinely screen the population for diabetogenic genes or gene products.
   b. Having identified individuals with the potential of developing type 1 diabetes, follow them longitudinally, seeking evidence of initiation of immune damage to islet β cells.
   c. In such individuals, seek evidence of altered or diminishing β-cell function.
   d. If identified, such individuals become candidates for intervention therapy designed to abort the pathogenetic sequence.

VI. STRATEGIES FOR IMPROVING GLUCOSE CONTROL

A. Contemporary management of type 1 diabetes mellitus has vastly changed over the past three decades. Current management approaches emphasize patient self-direction of daily management under the guidance of the physician. Insulin regimens have multiple components, consisting of several daily injections or the use of an insulin pump. Diets are flexible and individually tailored to the patient's needs. Self-monitoring of blood glucose (SMBG) is an integral component of management, used to guide decision making in an attempt to achieve defined target blood glucose values. Continuous glucose monitoring (CGM) is rapidly emerging as a therapeutic option. The goal of therapy is to incorporate diabetes management into the lifestyle of the patient by being flexible in approach while still striving for excellent glycemic control. This approach permits attainment of meticulous control in many educated, motivated patients.

B. Flexible intensive therapy of type 1 diabetes is a system that uses this contemporary approach. It consists of the following 10 elements.

1. **Defined target blood glucose levels.** Blood glucose targets must be individualized for each patient. They must be explicitly defined if they are to be achieved. For healthy young patients who readily recognize hypoglycemic symptoms and who spontaneously recover from hypoglycemia, such targets can nearly approximate the levels of glycemia seen in nondiabetic individuals, such as preprandial values of 70 to 130 mg/dL (3.9 to 7.2 mM). These targets need to be lower during pregnancy and should be raised in subjects who have difficulty perceiving hypoglycemic symptoms, who do not spontaneously recover from hypoglycemia, or in whom hypoglycemia might be particularly dangerous (e.g., patients with angina pectoris or transient ischemic attacks). Additional factors to be considered when setting glycemic targets include duration of diabetes, age/life expectancy, comorbid conditions, and known cardiovascular disease or advanced microvascular complications. In motivated patients, realistic targets are achievable at least 80% to 90% of the time.
2. **A multiple-component insulin program tailored to the patient's lifestyle.** Ideally, this program separates the insulin components providing basal insulinemia from those providing prandial insulinemia. This is accomplished by the following:

a. Preprandial injections (or pump boluses) of rapid-acting insulin analogs (insulin lispro, aspart, or glulisine) before meals (short-acting insulin [regular insulin] is no longer commonly used for this purpose). The doses should be dictated by planned carbohydrate intake with the meal and prevailing level of glycemia, with many individuals using both **(1)** insulin–carbohydrate ratios and **(2)** correction doses for hyperglycemia, to calculate preprandial insulin dosage.

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b. Basal insulin which can be provided by:

i. Subcutaneous injection of long-acting insulin (insulin glargine, detemir, or degludec) (intermediate-acting insulin [NPH] is no longer commonly used for this purpose). Glargine and detemir are given either at bedtime or twice daily. Degludec is given once daily and gives the flexibility of allowing administration at any time of day granted that at least 8 hours have elapsed from a previous dose;

ii. Insulin infusion pump (continuous subcutaneous insulin infusion or CSII), providing continuous background delivery of insulin.

3. **Careful balance of food intake, activity, and insulin dose.** For this purpose, patients (and their families) learn a system of keeping track of food intake, such as carbohydrate counting or a similar system. This permits them to vary their food intake ad lib and to adapt their insulin dose accordingly. By learning general principles of the influence of various foods and of activity on glycemia, and how to balance these components with activity, patients can achieve their desired glycemic control.
4. **Monitoring of blood glucose.** This is accomplished either by SMBG or by the use of CGM. SMBG involves patient measurement of blood glucose on capillary samples (obtained by using an automated device for pricking the finger) four times per day on most days (before meals and at bedtime), with additional samples obtained in the middle of the night (2 A.M. to 4 A.M.) when the overnight insulin dosage is to be altered. Additional samples are obtained anytime hypoglycemia is suspected, prior to engaging in critical tasks such as driving, and should be considered prior to and at completion of exercise. Periodically, postprandial samples

are obtained as well. It is important to note that studies performing careful analytic testing on various approved blood glucose monitoring systems (BGMSs) have shown that not all fulfill the accuracy requirements set by the International Organization for Standardization (ISO) 151917. This highlights a current limitation in point of care blood glucose monitoring and the need for high quality standards to ensure improved accuracy and precision from BGMS. Alternatively, as noted, the use of CGM is growing. Real time CGM measures glucose in the interstitial fluid (ISF), which correlates with plasma glucose levels. CGM sensors can provide a glucose reading up to every minute allowing for the generation of a tracing that is displayed on a receiver device, greatly improving the understanding of glucose fluctuations. Further, CGM receivers can set off alarms when glucose levels are outside of a patient-determined window, to alert patients to both hyperglycemia and impending hypoglycemia. Advances in CGM technology have led to significant improvements in accuracy, particularly in the hypoglycemic range. To maintain sensor accuracy over time, patients are required to enter blood glucose readings into the CGM receiver (generally every 12 hours), which are used for sensor calibrations. Of note, ISF glucose lags plasma glucose; a study in healthy adults measuring glucose tracers following an overnight fast showed it takes 5 to 6 minutes for glucose to be transported from the vascular to the interstitial space (physiologic delay). In addition, some sensors require a short period of time for signal filtering and data smoothing. Taking into account these delays is an important aspect when interpreting CGM values particularly at times when glycemia is changing quickly. Also, **acetaminophen** use has been shown to lead to pharmacologic interference and sensor error resulting in falsely elevated glucose values; however, new generation sensors are expected to eliminate this interference.

5. **Patient adjustments of food intake and insulin dose and timing, and the use of insulin according to a predetermined plan.** Patients are provided with an action plan to alter their therapy and achieve individual blood glucose targets. These actions are guided by SMBG or CGM determinations and daily records, and are dictated by prevailing blood glucose, meal size, anticipated activity, and previous experience in similar circumstances. Actions dictated by the plan can include altering the

size or content of food intake, activity, insulin dose, and timing of injections in relation to meals.

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6. **Patient education.** Patients must be carefully instructed in all aspects of diabetes management, including the details of meal planning (particularly carbohydrate content), insulin dose adjustment, activity planning, monitoring, recognition and treatment of hypoglycemia, and adapting to other intercurrent events.
7. **Frequent contact between patient and staff.** The patient should have 24-hour access to the diabetes management team and should contact them when there is a question about how to achieve the desired level of glycemia, if an intercurrent illness develops, or when any problem arises that requires consultation.
8. **Motivation.** Successful participation in a flexible but demanding management program requires a committed, motivated patient. The management team often must make extra efforts to help maintain motivation. This is often the most difficult component of treatment.
9. **Psychological support.** Patients with new-onset type 1 diabetes and their families need psychological support to adjust to the diabetes as well as to aid in implementing and maintaining the management program. Regular attendance at diabetes support group meetings may be helpful.
10. **Assessment.** An independent measure of integrated glycemic control, glycated hemoglobin (A_{1c}), is used for metabolic assessment. Thus, SMBG values are part of treatment, not assessment (but should be compared with the A_{1c} value). In addition, patient understanding, commitment, and responsibility for diabetes management should be assessed regularly.

VII. ADJUNCTIVE THERAPIES TO INSULIN IN THE MANAGEMENT OF TYPE 1 DIABETES

A. Pramlintide. Pramlintide is the only agent approved for adjunctive treatment of T1D. It is a synthetic version of the pancreatic β-cell hormone amylin, which, like insulin, is deficient in T1D. It lowers postprandial glucose excursions, improves glycemic control, and often results in weight loss. Of note, a reduction in prandial insulin dosing is

required when introducing pramlintide to reduce the risk of severe hypoglycemia.

B. Metformin. The use of metformin in adolescents and adults with T1D can lead to significant reductions in insulin-dose requirements and body weight. However, studies have not shown a significant improvement in glycemic control.

C. Glucagon-like peptide-1 (GLP-1) receptor agonists. Small studies using liraglutide, a long-acting GLP-1 receptor agonist, have shown significant reductions in weight, HbA_{1c}, and insulin total daily dose. However, the manufacturer recently reported that based on the risk/benefit assessment of two phase three trials (unpublished data), it would not pursue an application for the use of liraglutide in T1D. Nonetheless, other trials are currently evaluating the use of other GLP-1 receptor analogs as adjuvants to insulin in T1D management.

D. Sodium glucose cotransporter-2 (SGLT-2) inhibitors. The SGLT-2 is a protein expressed in the proximal convoluted tubule of the kidney and responsible for 90% of renal glucose reuptake. Inhibition of this protein results in marked urinary glucose excretion. SGLT-2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) are approved for management of hyperglycemia in patients with type 2 diabetes. Small clinical trials in T1D have shown favorable results, namely, significant reductions in HbA_{1c}, insulin doses, glycemic variability, and weight. Phase 3 trials in T1D are currently ongoing. However, recent reports have documented the occurrence of euglycemic diabetic ketoacidosis (DKA) or DKA with lower-than-expected hyperglycemia in conjunction with the use of these agents, particularly in patients with T1D. The Food and Drug Administration (FDA) has issued a safety communication regarding the potential risk of DKA with use of SGLT-2 inhibitors and will assess additional postmarketing reports to determine if changes are needed to the prescribing information.

VIII. FUTURE DIRECTIONS IN IMPROVING GLYCEMIC CONTROL

A. Sensor-augmented external insulin infusion pumps. Several insulin pump manufacturers have integrated the use of CGM into their pumps enabling patients to visualize their CGM-derived glucose trends directly on the pump screen. These are currently available for patient use.

B. Glucose sensor–controlled insulin infusion systems. Rapid technical advances are facilitating the integration of CGM systems with insulin pumps, providing the potential of developing a miniaturized Artificial Pancreas Device System (APDS). An APDS, also known as a closed-loop system, consists of an insulin pump, a CGM, and algorithms designed to drive insulin infusions to achieve specific glucose targets. The first APDS approved by the FDA was the Medtronic MiniMed 530G, which includes a "Threshold Suspend" feature. This feature allows users to set a glucose threshold to automatically suspend insulin delivery (for 2 hours) to prevent hypoglycemia unless the patient responds to an alert to take a corrective action. Although far from being a fully automated closed-loop system, this was a significant initial step in the automation of insulin administration. Clinical trials are currently evaluating more advanced and complex algorithms, which allow testing hybrid closed-loop models where the user needs to provide frequent input (e.g., for meal intake and exercise) as well as fully automated models requiring minimal user input. In addition, taking into account the intricate balance between glucagon and insulin in glucose control, bihormonal closed-loop systems are also being actively explored. Thus, the race for the development of a fully automated closed-loop system is ongoing, and the technology is rapidly advancing.

C. Pancreatic transplantation. This approach is available to individuals with end-stage renal disease undergoing simultaneous kidney transplantation (i.e., simultaneous pancreas kidney [SPK] transplantation). However, it may also be considered in the absence of renal disease in patients with severe metabolic complications (pancreas transplant alone [PTA]). Significant improvements in outcomes have been observed over the past decade attributed mainly to tighter donor criteria, changes in surgical technique and modifications in immunosuppressive regimens. The 5-year graft survival, with the patient free from insulin therapy, has been reported at ~70% for SPK and ~52% for PTA. Patient survival now exceeds 70% with the highest rate observed in PTA recipients (82% at 10 years).

D. Islet replacement therapy. Islet isolation and implantation offers the hope of reversing diabetes. Although clinical islet transplantation is an approved therapy in Canada and several European countries, it

remains an experimental procedure in the United States. Thus, potential candidates need to be enrolled in a clinical trial and fulfill strict inclusion criteria. Recent advances in islet isolation techniques and immunosuppressive regimens have led to substantial improvements in insulin independence rates comparable with those observed in pancreas transplantation at 5 years. The data from a multicenter phase 3 clinical trial of islet transplantation (CIT-07), which included 47 adults with T1D of >5 years duration, have recently been published. The composite primary endpoint comprised achievement of HbA_{1c} <7.0% at 1 year and freedom from severe hypoglycemic events from day 28 to day 365 after the first islet transplant. At 1 year, 87.5% of subjects met the primary endpoint, and hypoglycemia awareness was restored. Following the results of this pivotal study, several US islet transplant centers are expected to pursue a biologic license agreement. However, limitations include the need for long-term immunosuppression (which currently precludes children from undergoing this procedure) and tissue availability, which probably will limit wide-scale application using human islet tissue per se. Protecting islets from rejection by encapsulation or by growing islets on hollow-fiber artificial capillaries might permit the use of animal islets for human implantation. However, such encapsulated islets often have been destroyed by tissue reactions in animal models with spontaneous diabetes. Nonetheless, newer encapsulation techniques allowing for conformal coating of human islets have shown promising results in preclinical models and are currently being explored.

E. Genetically engineered pseudo *β* cells. A potential approach to islet replacement therapy is the use of genetically engineered pseudo *β* cells, which have glucose-mediated insulin secretion. By gene transfer approaches, it is possible to program cells to synthesize and secrete insulin. Recent experiments, also genetically inserting other elements, have demonstrated the potential for programmed cells to sense glucose. The challenge is to develop a cell line that both responds to glucose and secretes insulin in a physiologic manner, and that is nonimmunogenic and will not be rejected.

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F. Development of insulin-producing *β* cells from stem cells. A

potential approach is the development of β cells with glucose-mediated insulin secretion from other cell types, including either adult or embryonic stem cells, cord blood cells, or transdifferentiation of non-β cells into β cells. These approaches have shown some promise in animal models of diabetes (see Chapter 69).

IX. GLUCOSE CONTROL AND COMPLICATIONS

A. Diabetes Control and Complications Trial (DCCT): study design.

In June 1993, the DCCT reported its findings to the American Diabetes Association. This decade-long study involved 1 441 patients with type 1 diabetes, who were randomly allocated to either conventional treatment or intensive treatment (similar to that described in Section VI.B). The intensive group received three to four insulin injections daily or used an insulin pump, performed SMBG at least four times daily, and used the data to make self-adjustments to achieve a treatment target of near-normoglycemia. The conventional group received no more than two insulin injections daily, did not use SMBG data to make self-adjustments, and had a treatment target of avoiding excessive hyperglycemia and ketosis.

B. DCCT results

1. The DCCT demonstrated the dramatic significant impact of intensive therapy in lessening complications of diabetes.
   - **a. Eye disease.** Clinically important progression of retinopathy was reduced by 62% to 76% for those with no retinopathy at entry and by 54% for those with mild retinopathy at entry. Progression to severity requiring referral to an ophthalmologist for treatment was reduced by 46%. Treatment for sight-threatening retinopathy, using laser photocoagulation, was reduced by about 50%.
   - **b. Renal disease.** Clinically important kidney damage (proteinuria >300 mg/24 hours) was reduced by 56%. Incipient (subclinical) nephropathy, or microalbuminuria, was reduced by 46%.
   - **c. Nerve disease.** Clinically important neuropathy was reduced by 61%.
   - **d. Cardiovascular.** Although not statistically significant in the DCCT per se, there was a 44% reduction in cardiovascular events in the intensive-therapy group. Subsequently, in the long-term follow-up of the DCCT, called EDIC (Epidemiology of

Diabetes Interventions and Complications), a 30-year follow-up demonstrated a 30% decrement in the incidence of any cardiovascular event, which was statistically significant.

e. **All-cause mortality.** After a mean of 27-year follow-up, assessment of total and cause-specific mortality showed a lower all-cause mortality risk in the intensive-therapy group (HR 0.67 [95% CI 0.46–0.99]; $p = 0.045$)

2. Some **side effects** were seen more frequent in the intensive-therapy group.

   a. **Hypoglycemia.** Severe hypoglycemia requiring the assistance of another person for treatment was increased 3.3 times in the intensive-therapy group. Hypoglycemia resulting in seizure or coma was also increased threefold. The preponderance of events occurred without warning, either while asleep or while awake without symptoms.

   b. **Weight gain.** There was greater weight gain in the intensive-therapy group, with a relative risk of 1.6 for reaching 120% of ideal body weight. Average weight gain was about 10 lb.

C. Conclusion. The DCCT demonstrates that intensive therapy lessens the risk of complications, but not without extracting a price. Patients must be made aware of the study results, so that an informed choice can be made regarding treatment targets. In general, the benefits seem to far outweigh the side effects.

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52 Diagnosis and Management of Type 1 Diabetes Mellitus in Children, Adolescents and Young Adults

Stuart J. Brink

I. GOALS OF TREATMENT

A. The **primary goals** for the treatment of type 1 insulin-dependent diabetes mellitus (IDDM) are achievement of as near normal blood sugar levels as possible, normal growth and development, and avoidance of severe hypoglycemia. **Secondary goals** include avoidance of the long-term complications: microvascular abnormalities such as retinopathy, neuropathy, and nephropathy as well as macrovascular problems/atherosclerotic events such as heart attacks, stroke, and circulatory blockage.

B. Overall goals of treatment must take into account:

1. How well he or she or the parents understand the management concepts.
2. How much endogenous insulin remains available.
3. Individual caloric needs for normal growth and avoidance of obesity.
4. Activity patterns and their unique fuel requirements.
5. Home glucose and ketone monitoring needs.
6. Insulin options.
7. Psychosocial factors including financial and family issues.

C. Diabetes treatment team. Ideally: a pediatric diabetologist should supervise the team for children and adolescents, an internist diabetologist for adults. The diabetologist should be in charge of the diabetes team (pediatricians, internists, family physicians), nurse specialists, dieticians, social workers, psychologists, psychiatrists, and

often, exercise specialists. If specific complications exist, other subspecialists may be extremely helpful.

II. INITIAL APPROACH TO THE PATIENT

A. Presentation and diagnosis

1. The classic manifestations of type 1 diabetes mellitus include:
   a. **Hyperglycemia** secondary to insulin insufficiency.
   b. **Polyuria.** As high glucose in the bloodstream is filtered through the kidneys, osmotic balance causes excess urination.
   c. **Polydipsia.** As more water is excreted, the body requires more water intake and, because thirst mechanisms are intact, thirst increases.
   d. **Loss of weight.** This occurs more commonly in those with the most acute insulin deficiencies. Loss of water as well as loss of muscle mass and fat mass all contribute to acute or subacute weight loss at the time of diagnosis of type 1 diabetes mellitus.
   e. **Fatigue and weakness** probably occur as a result of decreased glucose utilization and subtle electrolyte and/or mineral abnormalities as well as clinical and subclinical dehydration in addition to muscle catabolism.
   f. **Type 2 versus type 1 diabetes.** With the obesity epidemic around the world, it is important to distinguish between type 1 and type 2 diabetes in children, adolescents, and young adults where type 2 diabetes is also epidemic. Members of US minority populations (i.e., African Americans, American Indians, Latinos, and Asian Americans), and also Caucasian populations, are all at risk, especially if there is concomitant acanthosis nigricans, polycystic ovarian syndrome, irregular menses, or overt hirsutism (hyperandrogenism). p. 713p. 714Type 2 diabetes now occurs at younger ages because they become more obese and more sedentary (indigenous populations such as Canadian First Nation, Australian aboriginal folk, for example). Classical type 2 diabetes in children and adolescents sometimes presents with ketoacidosis, but almost always with moderate to severe insulin resistance because of obesity. This is different than classical maturity onset of diabetes in youth, with a different pattern of

family history, and different pathogenesis. Treatment of type 2 diabetes in younger patients, after any initial diabetic ketoacidosis (DKA) presentation and treatment, focuses on weight loss, and the same host of oral agents classically available for the older patient with type 2 diabetes, that is, Metformin. If insulin is needed initially in type 2 diabetes, it often can be quickly discontinued within several weeks of diagnosis as insulin resistance decreases.

2. **Laboratory findings in type 1 diabetes mellitus**
   a. **Fasting blood glucose.** If the value is greater than 126 mg/dL on 2 or more separate days, the diagnosis of diabetes mellitus can be confirmed according to the latest diagnostic classification. **Random blood glucose** values greater than 200 mg/dL are also diagnostic.
   b. **A_{1c} testing.** Some studies suggest that this can replace blood glucose testing or blood glucose screening and, if abnormally high, utilized for diagnosis per se.
   c. **Glucose tolerance test** (2-hour). If the diagnosis is still in doubt, then use a glucose tolerance test (usually not necessary):
      i. Give at least 150 to 200 g carbohydrate daily for 3 days prior to test.
      ii. Overnight fast.
      iii. Have patient drink 75 g of glucose dissolved in 300 mL of water within a few minutes.
      iv. Measure serum glucose levels at 30-minute intervals for 2 hours.
   d. **Autoantibodies and genetic testing.** A variety of islet-related autoantigens can now be measured commercially or in research laboratories, including islet cell antibodies (ICA), glutamic acid decarboxylase-65 antibodies (GAD-65), insulin antibodies (IA2), and zinc-transporter 8 antibodies (ZnT8). In combination, such autoantibodies are positive at least 60% to 80% of the time in classical cases of children and adolescents with type 1 diabetes mellitus because type 1 diabetes is thought to be an autoimmune disorder. Adults and older teenagers are less likely to have positive antibodies but, if present, make type 1 rather than type 2 diabetes more likely. Very young children are also less likely to be antibody-positive. Other populations

such as those with Asian forebears may frequently be antibody-negative, but require insulin rather than oral agents (i.e., those from China, India, Pakistan, and Bangladesh). Adults with positive antibodies will likely need insulin eventually, but early in the course of what is called latent autoimmune type 1 diabetes (LADA), they may only be treated with typical type 2 diabetes treatment protocols, starting with metformin and then adding other medications. Such autoantibodies may also be helpful in an already diagnosed patient to help distinguish between type 1 and type 2 diabetes. HLA testing and other forms of genetic testing remain research procedures.

e. New genetic tests for **monogenic diabetes** can help identify rare cases of neonatal or early childhood diabetes associated with potassium channel or sulfonylurea receptor abnormalities. Such patients can be elegantly managed later (if diagnosis is confirmed genetically) without insulin but with sulfonylurea medications.

f. C-Peptide is not affected by antibodies to exogenous insulin, so that measurement may be helpful in classification of diabetes in an already diagnosed patient when drawn either fasting, postprandially (especially if concomitant with elevated blood glucose levels), or after glucagon or Sustacal stimulation testing. C-peptide is thought to be secreted by the beta cell in equimolar concentrations so that higher levels would seem to reflect ongoing insulin secretion, be helpful in better biochemical definition of endogenous insulin production/availability p. 714p. 715and be helpful in defining the honeymoon period or a period of resumption of insulin production when it was previously absent or minimal.

B. Diabetic ketoacidosis (see Chapter 54)

C. Hyperglycemia without dehydration. If dehydration is not present at diagnosis and there is no vomiting, insulin can be started on an outpatient basis.

D. Insulin treatment. Intensive (“aggressive”) insulin treatment using basal-bolus concepts (multidose insulin [MDI]) can be started as soon as possible in an attempt to “rest” the damaged islet cells and help to “induce” a remission (“honeymoon,” see Section II.F.3). Any insulin that is affordable and available can be used to help lower initial

hyperglycemia/ketonemia, but analogs such as glargine (Lantus or Basaglar) or detemir (Levemir) insulins can provide basal insulin coupled with bolus doses of fast acting analogs (lispro [Humalog], aspart [Novolog], or glulisine [Apidra]) around meals and snacks. Hypoglycemia is decreased compared to older regular and NPH animal-based or synthetic human types of insulin. Insulin degludec (Tresiba) is also a newer basal insulin alternative to glargine and detemir with a somewhat flatter and more predictable basal pattern shown to be useful in several studies. The newer analogs provide quicker more physiologic action to counter initial hyperglycemia at the same time they decrease faster than older insulins and therefore produce less hypoglycemia hours afterwards. **Detemir is almost always given twice-a-day whereas** glargine is sometimes needed only once-a-day at bedtime especially in early days after diagnosis of type 1 diabetes. **Many youngsters will nevertheless need glargine also on a twice-a-day regimen** presumably because of smaller total dose requirements and less mass-action that ends up decreasing duration effects. Other advantages of analog-based MDI regimens include the following:

1. Hypoglycemic reactions may be decreased.
2. Because 80% to 90% of children will have “total diabetes” within 2 to 5 years of diagnosis, it seems prudent to initiate two, three, or even four or five times a day shot (MDI) schedules using very small and minimally painful pen tip needles attached.

E. Other considerations regarding insulin therapy

1. Insulin analogs (lispro, aspart, and glulisine) are the most physiologic rapid-acting insulin preparations and can be given immediately before or after eating to mimic previous endogenous insulin delivery. However, administering insulin about 15 minutes prior to eating seems to allow optimal matching of food absorption, prandial glycemia, and absorption of insulin given subcutaneously thus minimizing both hypoglycemia and hyperglycemia. Regular (human or animal based) insulin takes longer to be absorbed, reaches a peak after injection later than such rapid-acting insulin analogs, and often has a more prolonged “tail effect” causing delayed hypoglycemia hours after use. Analogs can also be used in combination with intermediate-acting insulins in any patient with diabetes who demonstrates postprandial hyperglycemia after meals and/or snacks, with overlapping NPH

providing basal insulin function. Better still, they can be used with the longer sustained analogs like glargine and detemir.

2. In a three shot-per-day regimen, prebreakfast, presupper, and bedtime insulin are given. This most commonly involves a combination of analog or regular insulins plus an intermediate-acting insulin prebreakfast, analog or regular insulin alone presupper, and intermediate-acting insulin alone at bedtime. This has a major benefit of decreasing peak early nocturnal insulin effects between 2 A.M. and 4 A.M. from suppertime NPH. Sometimes combinations of two types of insulin are used at two or three of these injection times based on actual blood glucose readings.
3. Prandial analog insulin doses with a prebedtime intermediate or long-acting insulin work best for some patients with type 1 diabetes (four- or five-shot regimen). This regimen tends to provide greater flexibility with changing patterns or inconsistent food provision; changing activity may also respond better under such circumstances offering improved dosing flexibility. Overlapping doses of intermediate-acting insulins can be combined with any or all of these four injection times based on blood glucose data, but with the expectation that these older less expensive NPH insulins would still have significant peak effects and more variability than the newer basal analogs.

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4. Glargine and detemir insulins as well as degludec insulin help decrease hyperglycemia and in many parts of the world have become the preferred basal insulins. Usually glargine as a basal insulin can be started alone at bedtime. In very young children, glargine is sometimes given only at breakfast. Most youngsters, however, need glargine insulin twice-a-day to prevent a waning effect at the 16th to 24th hours. Detemir insulin as a basal insulin is almost always used via a twice-a-day regimen, but as with all insulin regimens, it is often started alone at bedtime and a morning dosage added based on actual blood glucose results in an individual patient rather than with preconceived rules. Degludec with a somewhat flatter and longer duration effect usually is administered just once-a-day for basal insulin effect.
5. In general, insulin doses with analog insulin should be given about

15 minutes before meals to best match food absorption and insulin absorption characteristics. If regular insulin is used, it should be given 30 to 60 minutes before food but this is rarely sustained because of its inconvenience. For very young children where food intake is unpredictable, the newest fast acting analogs (lispro, aspart, and glulisine) can be given immediately **after** food is consumed, so that less guessing and food–battling occur.

6. Insulin absorption may be different in different parts of the body. Different manufacturers use different buffers in their insulin preparations, and this may contribute to insulin–food mismatches if brands change frequently. Ideally, the same brand of insulin should be used unless a specific reason exists to change from one manufacturer to another or availability of insulin is problematic. **Insulin absorption is most consistent in the abdominal and buttocks regions**. Exercise-related changes in extremity absorption of insulin can contribute to poor glucose control because of **changing absorption when there is changing activity of the arms and legs during the day**.
7. **Insulin lipohypertrophy**, while much less common and less intense than years past, occurs when the same site is overused. Individual sensitivity to hypertrophy predisposes some patients more than others even when sites are varied. Any insulin **lipohypertrophy interferes with insulin absorption** consistency and contributes to erratic hyperglycemia as well as hypoglycemia. Improved purity of insulin has likely helped decrease hypertrophy problems.
8. Insulin lipoatrophy now is rarely seen with current highly purified animal or human insulin preparations.
9. Lente and ultralente insulins have generally been discontinued, although they are still available in some parts of the world.

F. How much insulin is needed

1. Most youngsters at diagnosis need approximately 1.0 U/kg/day. With MDI regimens, about 50% of total dose is given as basal insulin. Usually this would entail about 80% to 90% as bedtime glargine and 10% to 20% as breakfast glargine (but with varying amounts and individualized proportioning if detemir is used instead of glargine). About 10% of patients, particularly younger patients, need a “reverse” distribution with more in the morning dose of glargine and less at bedtime (sometimes none at all at

bedtime in toddlers). The prandial analogs would constitute the other 50% distribution with about 20% prebreakfast, 10% prelunch, and 10% predinner plus the remaining 5% to 10% presnacks.

2. Because of overnight cortisol and growth hormone effects, the morning "**dawn phenomenon**" may also be seen and this **requires relatively larger boluses** than would be needed at other times of the day. Reverse dawn phenomena, however, also occurs not infrequently.
3. The remission stage (**honeymoon phase**) results from a **partial recovery** of islet cell function (as documented by C-peptide as well as relative ease of control and stability of treatment seen in blood glucose results from day-to-day). It occurs within 1 to 3 months after diagnosis and can last from weeks to a few months, during which time insulin requirements fall drastically to less than 0.3 U/kg/day and, in some (rarely), to no requirement for insulin at all. However, insulin administration usually is not discontinued during this time because of potential p. 716p. 717development of insulin allergy (see Section II.G), as well as the need to reinforce the concept that type 1 IDDM is a lifelong illness. Remission phases last longest in older teenagers and young adults.
4. Eventually, most prepubertal youngsters require between 0.6 and 0.8 U/kg/day. Using an intensified MDI regimen which frequently has replaced a twice-a-day regular plus NPH overlap, small bursts of insulin analogs (i.e., lispro, aspart, or glulisine insulin) are used about 15 minutes prior to meals (and often before snacks too), with some type of basal insulin provided either at bedtime alone, bedtime plus breakfast or in overlapping doses (if using NPH) throughout the day and night. Ratios are usually 50% basal plus 50% prandial boluses.
5. Teenagers may need as much as **1.0 to 1.5 U/kg/day** during the rapid growth spurt at or around puberty; in subsequent years they return to lower insulin requirements.
6. If there is concomitant or subsequent **obesity**, such dose–weight ratios increase because there is also usually significant **insulin**

resistance with a need for higher doses to accomplish the same glucose lowering effect.

7. **NPH, lente, and ultralente** insulins are **absorbed somewhat more inconsistently** on a day-to-day basis, and thus **produce more peak effects** in a much more variable manner than faster acting, lower-peak, and longer-lasting analog insulins such as detemir, glargine, and degludec. Glargine and detemir as well as the newest basal insulins such as degludec produce somewhat more predictable insulin effects from day-to-day and also do so with lower peaks to explain improved glycemic variability, efficacy, and lowered hypoglycemia. This is especially well documented with reductions in nocturnal hypoglycemia. While supposed to be peakless, glargine and detemir sometimes will have a (small) peak effect at 12 to 16 hours.
8. Insulin doses at lunchtime and mid-afternoon, and the number of insulin injections, vary depending on activity intensity and consistency as well as food ingestion, glycemic effect and which type of basal insulin is utilized. Some with large afternoon snacks and relatively little afternoon activity also need presnack analog insulin to keep predinner blood glucose levels in target range.

G. Types of insulin. Human analog insulin is preferred at the time of diagnosis to reduce the likelihood of future allergic problems such as itching, burning, redness, and hives. Because purity of insulin seems to be related to lipoatrophy at injection sites, such atrophic sites may be completely avoided with the use of either pure pork or human insulins. Lipoatrophy was very commonly seen up to the late 1970s but is extremely rare due to the availability of purer insulin preparations and quality-controlled preparations.

H. Insulin allergy

1. Local allergy to insulin is now quite rare. It may occur minutes to hours after injection and may manifest with redness, pruritus, swelling, and heat as well as urticaria. It usually occurs within the first few weeks of therapy and can be self-limiting.
2. Rarely, **systemic allergy** to insulin occurs with manifestations of total body urticaria, angioneurotic edema, and frank anaphylaxis especially in an allergy-prone individual. This type of insulin allergy may be related to prior intermittent use of insulin as may occur during the honeymoon phase or when gestational diabetes needs change after delivery, so that insulin is discontinued but then

later, insulin is resumed. The immediate systemic reaction is more likely IgE mediated (local allergy tends to be IgG mediated). Insulin **desensitization** is the required preventive measure. Insulin allergy desensitization kits can be obtained from most insulin manufacturers.

I. Administration of shots

1. Some problems may occur when overemphasis is placed on children younger than 10 to 12 years measuring insulin doses and administering their own shots. In general, adults should retain the major responsibility for diabetes care during this time and often even directly supervising teenagers.
2. Automatic injection or pen delivery systems may be preferred for children on MDI regimens especially if school-time doses are needed.

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3. Lack of comprehension of the importance of glucose control, eating disorders, depression and anger in patients, and patients feeling overwhelmed by the difficulties of modern diabetes treatment, all contribute to **insulin omission**.
4. A form of anorexia nervosa which we coined as “diabulimia” exists where insulin is surreptitiously omitted causing chronic hyperglycemia, and recurring DKA. Often there is significant psychological distress played out through diabetes.
5. Fear of hypoglycemic reactions is another reason for insulin omission. Ketoacidosis and death may result when cases are extreme.

III. HOME MONITORING

A. Self blood glucose monitoring (SMBG) or self blood glucose monitoring (SBGM)

1. Automatic lancet injectors (e.g., Monojector Penlet, Autolance, and Autolet) are available for skin puncture to minimize trauma and discomfort using short and very fine disposable lancets.
2. Reflectance meters and electronic meters (LifeScan’s Ultra, Profile and Verio, Abbott’s Precision Xtra, and Free Style series; Roche’s AccuChek series meters; Bayer’s glucometer, Dex as well as Contour; Nipro meter, etc.) are widely used because of increased accuracy and ease of administration. Many diabetologists and

patients as well as parents prefer memory meters, which can also be downloaded into computers and cell phones. All of this facilitates ongoing data analysis and graphic displays to help analyze patterns of glucose control. The newest meters use minute amounts of capillary blood (1 to 5 μL) to decrease pain and discomfort. The newer meters also auto-calibrate. Some meters can be programmed to automatically send results to insulin pumps. The newest will use bluetooth technology to send data for storage and analysis automatically. Meters, of course, are also used to assist in calibrating continuous glucose monitoring systems (CGMSs) such as those that are manufactured by Medtronic Minimed, DexCom Abbott's Navigator series.

3. Blood sugar monitoring should ideally be done every 2 to 3 hours around the clock and this includes preprandial as well as postprandial assessments. Newer but expensive CGMS capabilities can provide up to 288 daily glucose values (i.e., automatically every 5 minutes). Attaching such CGMS to insulin pumps to provide semiautomated feedback will effectively help "close the loop" and move toward a hybrid or truly artificial pancreas. Low glucose suspend (LGS) features of CGMS connected to insulin pumps have documented better control and less frequent hypoglycemia. Automatic basal pump adjustments based on CGMS also has more recently been shown to move toward the "hybrid" artificial pancreas systems, predicting rising as well as falling glycemia and thus avoiding more sustained glycemic aberrations. Daily monitoring for type 1 diabetes is usually recommended before and after breakfast, before and after lunch, before and after dinner, and at bedtime. Occasional middle-of-the-night BGs are also needed to identify asymptomatic hyperglycemia as well as nocturnal hypoglycemia (see Table 52-1 for an example of an SMBG protocol).
4. On sick days assessing hyperglycemia or for specific problem solving, blood glucose monitoring every 1 to 2 hours has been used to identify subtle hypoglycemia (see Section VII.F) as well as fine-tuning basal-bolus MDI regimens. CGMS facilitates such data collection (Table 52-2).
5. There have been no significant problems with local cellulitis, abscess, or excess callus formation using this protocol in patients as young as neonates.

Routine alcohol swabbing is no longer recommended, although obvious handwashing to keep food particles and obvious dirt out of the path of the sterile lancet remain appropriate.

B. Urine testing

1. Glucose testing

a. Double-voided urine testing allows assessment of both sugar and acetone in a semiquantitative fashion. Urine glucose testing is less accurate than blood glucose testing because of changes in renal threshold, fluid intake and output.

b. Combination systems such as Chemstrip uGK and Keto-Diastix allow identification of glucose and ketone spillage. These are the standard urine testing p. 718p. 719systems for use on sick days and on days when blood sugars are either running high (>250 mg/dL) or are not being otherwise checked.

TABLE 52-1 Home Blood Glucose Monitoring Protocol

	Check prior to							
Interval	Breakfast	Mid-morning	Lunch	Mid-afternoon	Dinner	Bedtime	11 P.M.–MN	3 A.M.–5 A.M.
"Profile" 3 days each month[a]	bG	bG	bG	bG	bG	bG	bG	bG
Daily	bG		bG	bG	bG			
Every 8 days (awake profile)	bG	bG	bG	bG	bG	bG		

A problem-solving profile should be obtained whenever there is a question of dosage needing adjustment or change. Keeping written records is important, so that patterns can be identified.
[a]On sick days, follow this profile for testing, sometimes more often, and remember to **check for acetone** whenever blood glucose level is more than 240 mg/dL.
bG, blood glucose; MN, midnight.

2. Ketone testing

a. Urine testing for ketones remains extremely valuable during sick days or whenever ketoacidosis may occur. Combination systems, such as Chemstrip uGK or Keto-Diastix, can be used, or, alternatively, simple ketone testing urine systems, such as Chemstrip uK or Ketostix, can be used. If these are unavailable, older nitroprusside powder can also be used. All such systems test for acetone and acetoacetate, but not for β-hydroxybutyric acid, and provide guidance regarding the

need for extra insulin and fluids.

b. Ketone capillary blood systems (Precision Extra meters) are available that will test specifically for blood β-hydroxybutyric acid and may eliminate the need for nonspecific urinary acetone and acetoacetate testing while also providing earlier data about ketonemia.

IV. SBGM WITH INSULIN AND CARBOHYDRATE ALGORITHMS.

Better decisions regarding insulin, food amounts, and food choices, as well as exercise, may result from using insulin algorithms (Table 52-1).

A. Tight blood sugar goals include the following:

1. To achieve near-normal blood sugar levels (about 100 mg/dL) **without frequent episodes of (severe) hypoglycemia** throughout the day and night and concomitantly to sustain A_{1c} levels below 7.5% (some would say below 7.0%), thus mitigating or avoiding short- and long-term diabetes-related complications.
2. An overall target is 70 to 140 mg/dL preprandially and lower than 160 to 180 mg/dL postprandially.

B. Considerations in achieving blood sugar goals

1. Usually 0.5 to 1.0 U of fast-acting analog or regular insulin decreases blood sugar levels by 40 to 50 mg/dL for patients taking 20 to 40 U/day if blood sugar levels are below 240. Above 240, the patient may need proportionately more insulin to accomplish the same goal (1 to 2 U to decrease 40 to 50 mg/dL).
2. This produces what is called an insulin correction factor (CF; or insulin sensitivity factor) with those needing very small total amounts of insulin each day (youngest p. 719p. 720p. 720p. 721infants and children) often having an insulin CF of 1:100 whereas those with somewhat higher doses needing the more typical CF of 1:50. Those with insulin resistance and needing proportionately higher insulin doses because of obesity or other factors would need a CF of 1:25–30.

TABLE 52-2 New England Diabetes and Endocrinology Center (NEDEC) Algorithms, Sick-Day Advice, and Hypoglycemia Information

INSULIN ALGORITHM—(how to adjust or **VARY INSULIN** for high and low BGs)—this intensified insulin system only works if you know BG level and then allows adjustments for food, activity, stress, etc.

FOR_____DATE_____

BLOOD GLUCOSE	BREAKFAST BOLUS	LUNCH BOLUS	AFTERNOON BOLUS	DINNER BOLUS	BEDTIME SNACK BOLUS
<69 (JUICE)					
70–100					
101–150					
151–200					
201–250					
251–300*					
301–350*					
351–400*					
401–450*					
451–500*					
>501*					
BASAL INSULIN					

*=check ketones even if not sick

DAY–DAY GLYCEMIC INDEX ADJUSTMENTS: approximately 1:15 insulin:carbohydrate coverage ratio (DIFFERENT FOOD EFFECTS ON BG LEVELS: USE_____MORE HUMALOG OR NOVOLOG INSULIN FOR HIGH GLYCEMIC INDEX FOODS SUCH AS: CORN PRODUCTS, POTATO PRODUCTS, ROLLS, CHINESE FOOD, PASTA, PIZZA, AND MOST "FAST" FOOD. IF MERELY OVEREATING, DECIDE IF YOU NEED MORE HUMALOG OR NOVOLOG TO "COVER" BG EFFECTS.

BUT **DECREASE** HUMALOG OR NOVOLOG INSULIN BY_____UNITS OR ADD EXTRA SNACK FOR PLANNED **ACTIVITY**

NEDEC SICK DAY ADJUSTMENTS: *CHECK BG EVERY 2–3 HOURS INCLUDING OVERNIGHT BGS*

1. GET WEIGHED AT LEAST THREE TIMES EACH DAY. WEIGHT LOSS MEANS POSSIBLE DEHYDRATION. DRINK MORE SALTY FLUIDS LIKE SOUP.
2. CHECK KETONES AT LEAST EVERY 3–4 HOURS. IF +, MORE INSULIN NEEDED IF BG LEVELS ARE ALSO HIGH.
3. EXTRA INSULIN **(SICK DAY BOOSTER)** IS BASED ON 10%–20% OF TOTAL DAY'S INSULIN DOSE () IF YOUR BLOOD GLUCOSE WAS 100. THIS 10%–20% SICK DAY BOOSTER IS GIVEN EVERY 3–4 HOURS DAY & NIGHT. THIS IS MUCH MORE THAN USUAL ALGORITHM CHANGES

   →10% SICK DAY BOOSTER IF BG >240 & KETONES NEGATIVE: ☐ **EXTRA HUMALOG OR NOVOLOG**

   →20% SICK DAY BOOSTER IF BG >240 & KETONES POSITIVE: ☐ **EXTRA HUMALOG OR NOVOLOG**
4. CALL IF NOT BETTER, SYMPTOMS DO NOT GO AWAY, SEVERE HEADACHE OR ACTING STRANGE, VOMITING DOES NOT STOP OR WEIGHT LOSS CONTINUES OR IF NOT SURE WHAT TO DO
5. RARELY, WITH ILLNESS, INSULIN NEEDS TO BE DECREASED—WHEN BG <100.
6. ***USUALLY, EVEN IF NOT EATING WELL, ILLNESS BLOCKS INSULIN SO THAT EXTRA INSULIN IS NEEDED.***

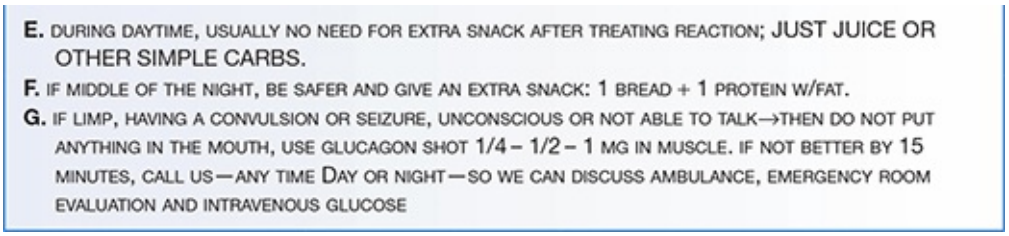
NEDEC HYPOGLYCEMIA RECOGNITION & TREATMENT: *IF POSSIBLE, CHECK GLUCOSE*

A. DECIDE IF EXTRA FOOD NEEDED AT BEDTIME SNACK FOLLOWING INCREASED AFTERNOON OR EVENING ACTIVITY TO PREVENT OVERNIGHT (NOCTURNAL) HYPOGLYCEMIA!!!

B. NEVER GO TO BED WITHOUT KNOWING YOUR BLOOD GLUCOSE LEVEL.

C. REMEMBER THAT MANY EPISODES OF HYPOGLYCEMIA DO NOT PRODUCE SYMPTOMS. CHECK YOUR BLOOD GLUCOSE LEVEL BEFORE A NAP.

D. IF ABLE TO TALK AND RESPOND, GIVE 4–6 OZ OF JUICE OR SUGAR-CONTAINING SODA OR 2–3 GLUCOSE TABLETS OR 7 LIFESAVERS OR GLUCOSE GEL OR HONEY OR REGULAR TABLE SUGAR. RARELY THIS NEEDS REPEATING (NOT CHOCOLATE **or other high fat foods**: TOO SLOW ACTING AND ALSO EXCESSIVE CALORIES).



3. In very young children and in those who are extremely sensitive to insulin, u100 preparations can be diluted (make u10 or u20 insulin with diluent supplied by manufacturer or with normal saline). Then algorithms can be created using 0.1- to 0.2-U increments.
4. SMBG pre and post prandially (or CGMS) is used to double-check and adjust the algorithms being applied to avoid over-corrections and excessive hypoglycemia as well as under-correcting.
5. Improvement (or lack of) is confirmed by hemoglobin A_{1c} (HbA_{1c}) measurements every 4 to 6 weeks.
6. Dietary compliance should focus on carbohydrate counting and glycemic excursions. Virtually free telephone applications such as "Lose-It" are excellent for teaching and confirming carbohydrate counts.

C. Problems with SBGM include the following:

1. Nonacceptance of need for ongoing, frequent blood glucose surveillance.
2. SBGM results will be misleading when done improperly.
3. Financial constraints.
4. Unavailable testing supplies.
5. Falsified results.
6. Lack of analysis or record keeping.

V. MEAL PLANNING.

Dietary prescriptions must take into account the individual and ethnic preferences as well as the family habits of the child, teenager, or adult with type 1 diabetes mellitus. Types and timing of food intake are probably more important with type 1 IDDM patients than total calories as long as obesity is not an associated problem. If weight excess coexists, then more activity and/or fewer calories also need to be considered. Mobile phones or tablets with free or very inexpensive applications (i.e., Lose It) are increasingly prolific and useful.

A. Carbohydrates

1. The total carbohydrate content of the diabetic meal plan is usually about 50% to 60% of total calories.

2. If there is significant obesity in an adolescent or young adult, Atkins-style low or no carbohydrate meal plans can also be considered.
3. Concentrated sugars generally are avoided or minimized except for management of short-activity bursts or actual hypoglycemia treatment. Ten to 15 g of fast-acting sucrose or glucose (i.e., 4 to 6 oz of orange or apple juice or regular carbonated soda, seven small hard candies such as Lifesavers), or 10 to 15 g of a variety of prepackaged dextrose preparations (Monogel, BD Tablets, Instant Glucose, Glutose) is generally adequate treatment. The author of this chapter p. 721p. 722suggests that simple carbohydrates be used for most episodes of hypoglycemia except overnight when more caution should be exercised. Simple carbohydrates can be used for most episodes of hypoglycemia except overnight when extreme caution should be exercised. High-fat chocolate or peanut butter products are not optimal to treat acute episodes of hypoglycemia because the fat tends to slow down the absorption of the simple sugars thus delaying hypoglycemic correction.
4. Complex high-fiber carbohydrates (bran, whole-grain cereals and breads, legumes, vegetables, and whole fruit) generally are encouraged.
5. A small minority of diabetologists and nutritionists recommend a low-carbohydrate/high-protein approach to meal planning. This Atkins-like approach requires less insulin, and therefore it may be easier to counterbalance food and insulin needs under such circumstances.
6. Carbohydrate counting concepts provide added flexibility and decrease the previous restriction on individual carbohydrates by allowing exchanges among all sources of carbohydrates.
7. Paying individual attention to glycemic index variabilities allows for more appropriate adjustment of insulin according to different types of foods and snacks.
8. In those with concomitant celiac disease (gluten sensitivity), occurring in the range of 5% to 10% of type 1 diabetes patients in many parts of the world, wheat and gluten restrictions demand changes to more rapid-acting types of carbohydrates with concomitant need for relatively higher doses of prandial insulin to

cover these expected and earlier peak hyperglycemic surges.

B. Protein

1. The total protein content of the diabetes meal plan is usually about 15% to 20%.
2. Protein and fat may be very helpful in the bedtime snack to help prevent overnight hypoglycemia because they slow absorption of carbohydrates.
3. Sugar-containing high-fat ice cream may be an ideal bedtime snack because the protein and fat content in such ice cream preparations allows for slower glycemic availability throughout the night-time hours and thus decreases the chances of overnight hypoglycemia. Uncooked cornstarch mixed with liquids or solid foods may also provide a source of long-acting carbohydrates to prevent overnight hypoglycemia. In some, but not all patients, the fat in peanut butter can also produce similar effects.

C. Fats

1. Total fat content usually should be no more than 25% to 30% of total calories. Saturated animal fat intake should be reduced for improved cardiovascular health.
2. In youngsters with type 1 diabetes, lipid values may be increased particularly in the subset of patients whose glucose remains out of control. Most reflect higher triglyceride values postprandially but, more importantly, higher low-density lipoprotein (LDL) and total cholesterol values.
3. The following guidelines should be used: skim or low-fat milk; margarine may not be any different than butter in terms of saturated fat content, so both should be decreased; decrease red and brown meats; increase poultry, tofu, fish, and vegetable-based oils; encourage skim milk–based cheeses.
4. With documented hypercholesterolemia and/or hypertriglyceridemia, more restrictions in dietary saturated fat and trans-fatty acids will be important—perhaps also supplemented by lipid lowering medications.

D. General dietary considerations

1. Total calories are guided by body habitus and general appetite.
2. General rule of thumb: Start with 1 000 kcal/day for a 1-year-old and increase by about 100 kcal/year thereafter.
3. For boys, keep increasing calories to about 2 600 to 2 800 kcal for a base diet, but 3 000- to 3 500-kcal daily may be needed for

coverage of prolonged and regular athletic sports activity or several weeks at camp. Late adolescent males and young adult males usually require <2 500 kcal/day except if increased physical activity continues.

4. Girls usually need to start calorie restriction at about age 10 to 12 years (usually associated with earlier puberty than for boys), so that meal plans are increased to about 1 800 to 2 000 kcal/day until this stage and then decreased to 1 100 to p. 722p. 7231 700 kcal/day according to metabolic needs, activity patterns, and desired weight, with 1 200 to 1 400 kcal being the mean.
5. If overweight or frankly obese, caloric restriction plus increasing activity will be needed.
6. Attempts should be made to identify early signals of hypoglycemia with SMBG, so that appropriate quick-acting carbohydrate may be used.
7. For special religious fast days (e.g., Yom Kippur or Ramadan), education should be used to minimize hypoglycemia with appropriate monitoring and reduction of insulin and activity during such periods when less food is provided.

VI. EXERCISE. The goal of modern diabetes treatment includes consistent daily activity. Some who exercise will have an accentuated, early adrenaline-like hyperglycemic effect, whereas others will show hypoglycemia mid-activity compared to more prolonged and delayed hypoglycemia hours after the activity has been completed.

A. Burst activity

1. Short burst activity generally requires extra short-acting carbohydrate intake just before or just after such activity, whereas prolonged exercise requires a reduction in insulin as well as an increase in carbohydrates, proteins, and fats.
2. Some patients need extra food at the start of bursts of activity, whereas others need extra food only after the activity is completed. With increased intensity and/or duration of activity, more delayed hypoglycemic effects can be expected, that is, several hours after the activity.

B. Prolonged, planned activity

1. The longer the activity (and the more aerobic), the more likely it is to cause a delayed hypoglycemic effect. Recognizing this phenomenon allows for additional food to be provided several hours after the activity is completed or for appropriate reductions in insulin. Foods generally higher in protein and fat (e.g., peanut butter) may be used to counterbalance such prolonged activity. With planned activity, one may decrease the amount of insulin.

C. General considerations

1. In theory, it should not matter whether a patient reduces insulin in anticipation of activity or compensates with extra food in an attempt to balance energy expenditure.
2. Sports should be encouraged for all. Supervisory personnel at school or at a park or camp must be made aware of the presence of a person with diabetes and be provided with a source of quick-acting carbohydrate to manage hypoglycemia should it occur; guidelines must be given, so that hypoglycemia can be recognized and avoided. Glucagon use and availability should be openly discussed and individual advice provided.
3. Medic-alert tags must be worn.

VII. SPECIAL CONSIDERATIONS

A. Hemoglobin A_{1c} (glycohemoglobin [GHb], HbA_{1c}). This test is an indicator of blood sugar control during the previous 4- to 12-week period.

1. Glucose attaches to hemoglobin in a mostly irreversible fashion throughout the life span (120 days) of the red cell. At any given moment, a sample of **blood will represent a collection of newly "born," middle-aged, and "dying" cells such that the GHb level obtained represents an integrated glucose value that is reflective of the glucose environment confronting the red cell over the previous 1- to 3-month period.** (Especially representing the most recent 2- to 4-week period.)
2. Values less than 7.5% for HbA_{1c} are acceptable, whereas values less than 7% are more optimal as long as excessive or severe episodes of hypoglycemia do not occur. According to the DCCT, the higher the HbA_{1c} value and the longer duration the HbA_{1c} stays out of ideal range, the more likely will be the long-term eye,

kidney, and neurologic complications of diabetes as well as the more likely cardiovascular problems.

3. In patients with anemias or other hemoglobinopathies, alternatives such as fructosamine assays can serve similar purposes (see Chapter 67).
4. At a minimum of every 3 months, A_{1c} results should be available for all patients with type 1 diabetes mellitus.

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B. Limited joint mobility (LJM, joint contractures, diabetic hand syndrome). LJM is present in as many as 15% to 30% of adolescents with type 1 diabetes and may be the harbinger of a subset of (young) people who are at 400% to 600% greater risk for developing the complications associated with hyperglycemia such as retinopathy, nephropathy, hypertension, and neuropathy. LJM probably reflects collagen glycosylation based on long-standing ambient glucose concentrations in the body.

1. As originally described by Rosenbloom, the patient places the hands together in prayer position with the forearm parallel to the floor. Normal placement allows for juxtaposition of all fingers as well as the palm.
2. The earliest abnormality appears to be a sclerodermatous, tight, waxy skin consistency.
3. The fifth finger is most often the initial finger to become less than fully extendable, although all fingers and joints potentially can be involved.
4. The **Brink–Starkman classification** is as follows:
   a. Stage 0: no abnormality;
   b. Stage I: skin thickening without contractures;
   c. Stage II: bilateral fifth finger contractures;
   d. Stage III: other fingers involved bilaterally;
   e. Stage IV: fingers plus wrist involvement bilaterally;
   f. Stage V: fingers, wrist, and other joint involvement.

   The higher the stage, the worse the LJM and the higher the risk of complications.

C. Sick-day guidelines and ketoacidosis. Special attention because of potential acute insulin resistance and associated dehydration is required during illnesses with more blood glucose monitoring, blood

or urine ketone monitoring as well as weight checks several times each day to assess acute changes in hydration status.

1. Unless there is a major vomiting component to the illness, more rapid acting analog or regular insulin is given every 2 to 4 hours (calculated by adding up the total daily insulin requirement and using a sick-day booster dose of 10% to 20%) with each dose. This is either added to the usual insulin dose or given as a supplemental dose until the added stress of such infection subsides. With insulin pump treatment, basal doses can temporarily also be increased quite easily.
2. Prochlorperazine (Compazine) or trimethobenzamide (Tigan) suppositories, bismuth-salicylic acid (PeptoBismol) liquid preparations, and Ondansetron (Zofran) can be used to reduce nausea and vomiting.
3. The provision of large amounts of salty fluids (soups and broths or electrolyte solutions such as Gatorade or Lytren) is perhaps more important than extra insulin in preventing hospitalization from dehydration caused by the osmotic effects of excessive glycosuria.
4. Blood sugar levels greater than 180 to 240 mg/dL associated with ketonuria or increasing levels of β-hydroxybutyric acid demand 10% to 20% more insulin given every few hours throughout the day as well as throughout the night to prevent hyperglycemia and dehydration from progressing to decompensated ketoacidosis, coma, and death. CGMS can provide similar glycemic evaluation.
5. Ketonuria can be present because of relative lack of food (starvation ketosis) as well as insulin deficiency. Blood sugar levels lower than 180 mg/dL with ketonuria do not automatically call for additional insulin; instead, liquids containing carbohydrates should be added to the treatment program at home (i.e., Gatorade, sweetened juices, and sugar-containing carbonated soda) and alternated with salty fluids. This more typically occurs with gastrointestinal illnesses whereas hyperglycemia and DKA more typically occurs with respiratory or other infections.

D. Uncontrolled diabetes mellitus and recurrent DKA. Omission of insulin is a frequent cause of recurrent ketoacidosis in adults and some adolescents.

E. Hypoglycemia

1. Very young children may be at higher risk for severe hypoglycemic reactions (unconsciousness or seizures) because of their inability to

recognize and/or communicate subtle symptoms of hypoglycemia.

2. Both MDI and continuous subcutaneous insulin infusion (CSII) have documented decreased A_{1c} values and decreased episodes of hypoglycemia. CGMS added to MDI as well as CSII has shown similar decreases in hypoglycemia in many studies p. 724p. 725around the world as pumps and sensors have continued to improve in sensitivity and specificity/accuracy parameters.
3. The combination of alcoholic beverages with insulin (usually in teenagers or adults) can produce long-lasting and very severe (e.g., 2 A.M. to 6 A.M.) **hypoglycemia hours after alcoholic intake. Alcohol, however, does not specifically cause hypoglycemia** directly, but if hypoglycemia occurs when there is already significant alcohol in the system, the **liver is "too busy" metabolizing the alcohol to be able to respond** with glycogenolysis and glucose production—so that whatever hypoglycemia occurs, the body cannot receive a corrective response either from the muscles or the liver.
4. Recent studies suggest a frequent and early abnormality of counterregulatory response in many patients with diabetes which may account for prolonged and unpredictable hypoglycemia.
5. **Hypoglycemia unawareness** (see Chapter 53) is associated with recurrent and severe episodes of hypoglycemia with little recognition of symptoms by the patient. Frequent blood glucose monitoring, sometimes including nocturnal monitoring, is often required to prevent periods of unconsciousness or convulsions induced by such hypoglycemia. Research documenting very promising CGMS with predictive alarms as well as automatic LGS systems help decrease and prevent severe episodes of hypoglycemia have been successful without concomitant increases in overall glycemic levels or A_{1c} results. Efforts to minimize hypoglycemia under such circumstances focus on retraining (called hypoglycemia awareness training [HGAT] or blood glucose awareness training [BGAT]). HGAT and BGAT utilize frequent monitoring and focus on relearning early warning signals that presage additional, more severe episodes. If severe episodes of

hypoglycemia occur, evaluation for celiac disease, adrenal insufficiency, thyroid disorders, and growth hormone deficiency should be considered even though fairly uncommon (see also CGMS section and Insulin pump section)

6. Approximately 30% of daytime hypoglycemia remains asymptomatic, although it may be recognized by family members or close friends. Even more worrisome, similar data analysis from CGMS suggest that overnight hypoglycemia may be asymptomatic in about 50% of patients with type 1 diabetes and both these examples of hypoglycemia unawareness may be the earliest diabetes complication from autonomic neuropathy.

F. Somogyi phenomenon (rebound effect)

1. The Somogyi phenomenon is a series of events caused by **overinsulinization** and its attendant episodes of hypoglycemia—with or without symptoms. It probably occurs less commonly with increased MDI and CSII and perhaps also with CGMS offering predictive alarms, low threshold suspend and now also automatic basal dose responses. As the insulin dose is increased beyond the amount required for any given portion of the day, the effect of the excessive insulin is to cause either overeating or frank hypoglycemia.
2. This excessive insulin effect elicits an excessive counterregulatory hormone response followed by "rebound" hyperglycemia from adrenaline, cortisol, and/or growth hormone among other factors.
3. Some cases of uncontrolled diabetes may actually be caused by this counterregulatory response, so that wide glucose excursions are seen and this may also represent an early form of autonomic neuropathy.
4. In its most common form, relatively minor hypoglycemia from any cause or combination of causes (inadequate meals or snacks, excess activity, unopposed insulin, alcohol) contributes directly to subsequent hyperglycemia which may last for 8 to 24 hours (although Somogyi's original description commented on rebound hyperglycemia lasting as long as 72 hours after hypoglycemia).
5. In rare instances, this counterregulatory response is so excessive as to produce not only ketonuria but also full-fledged DKA.
6. Recognition of the possibility that some episodes of high blood sugar levels might be caused by too much rather than too little insulin, especially in the middle of the night, leads to the correct

conclusion that reduction of insulin can correct some causes of fasting hyperglycemia. Somogyi problems, however, are not as p. 725p. 726commonly seen as previously thought, and most morning hyperglycemia is caused by a waning effect of free insulin availability (the **Dawn effect**, compounded by increased overnight cortisol and/or growth hormone) rather than overnight "Somogyi-ing". Blood glucose testing should be used to diagnose, confirm, or refute such patterns. CGMS helps automatically identify such overnight hypoglycemia and rebound hyperglycemia.

G. Dawn phenomenon

1. Many patients with type 1 diabetes mellitus demonstrate an **early-morning (4 A.M. to 8 A.M.) rise in glucose levels** that is aggravated by intake of food at breakfast (but not due to it) and that tends to peak in mid-morning. It often occurs because of **waning insulin availability** plus concomitant **increase in growth hormone and cortisol** overnight effects.
2. It appears to be unrelated to food intake or activity, and whether it represents an increase in hepatic glucose production or decreased peripheral utilization (or both) is not known. It does indicate a further requirement for basal insulin levels that may be ideally treated with continuous subcutaneous infusions such as those provided by insulin pumps. With CSII, basal insulins can be automatically raised, that is, from 4 A.M. to 8 A.M. without having to concomitantly provide extra basal insulin at midnight or 2 A.M. or throughout the remainder of the day.
3. The dawn phenomenon may be confused with the Somogyi phenomenon because both show up as hyperglycemia otherwise unexplained by food or too little insulin. Sampling of glucose levels throughout the night should help differentiate the two conditions.
4. Some have recommended an earlier injection in the morning (5 A.M. to 6 A.M.), and most suggest a late-evening (before bedtime) injection of intermediate-acting NPH insulin if an insulin pump is not being used or basal analogs are not being used or available. With an insulin pump, increasing the basal insulin in an effort to counterbalance the dawn phenomenon is usually successful, just as

the new, long-lasting insulin analogs (glargine, detemir, or degludec insulins)—all provide smoother (relatively peakless) insulinization without concomitant overnight peaks.

H. Idiosyncratic insulin needs

1. Reverse dawn phenomenon where supper or evening insulin needs exceed those of the predawn breakfast hours occurs in up to 10% to 20% of youngsters.
2. Other patients exist who have no dawn or reverse dawn phenomenon but relatively "flat" basal needs; some with a small dinnertime insulin need and others with an early afternoon peak requirement.

I. Growth

1. Decreased growth velocity appears to be more common in males than in females with type 1 diabetes mellitus, and may be as common as 5% to 10% in large pediatric and adolescent cohorts.
2. Extreme growth failure can be associated with pubertal delay and hepatomegaly (**Mauriac syndrome**) caused by severe and chronic diabetes mellitus out of control. This is still seen in parts of the world, where insulin is not consistently available. With such chronic diabetes mellitus out of control, **reintroduction of control demands close attention to the retina** so that unexpected severe retinopathy does not develop unchecked.
3. With reasonable glucose control, growth and pubertal progression should be very close to that of the control population cohort.

J. Teenage and adult pregnancy

1. The teenager who has diabetes and becomes pregnant has many added burdens affecting both herself and the child. The first trimester is often associated with increasing episodes or severity of hypoglycemia, whereas the second and third trimesters are usually associated with rapidly increasing insulin resistance, and therefore insulin doses rise dramatically.
2. Discussions about contraception and birth control options must become part of the repertoire of professionals responsible for diabetes care.
3. Patients ready to conceive must be made aware that improving blood sugar control at—or ideally *before* conception—reduces the risks of congenital anomalies, as well as prematurity and its associated complications.

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K. Thyroid dysfunction and other autoimmune endocrinopathies

1. Thyroid problems often coexist with type 1 autoimmune diabetes mellitus (see Chapters 38 and 42). In the type 1 diabetes population, 5% to 10% have a variety of thyroid dysfunction including euthyroid goiters, hyperthyroidism, and hypothyroidism. Hypothyroidism (low T4, low free T4, and elevated TSH) or compensated hypothyroidism (normal T4, normal free T4 but elevated TSH) should be treated as should hyperthyroidism.
2. The vast majority of thyroid problems seen in association with type 1 diabetes are secondary to chronic Hashimoto thyroiditis consistent with the concept that type 1 diabetes mellitus, to a large extent, is an autoimmune disorder. Thyroid antibodies may be positive in 20% to 40% of young type 1 patients. Therefore, **thyroid antibodies should be checked yearly** along with thyroid function tests, but euthyroid Hashimoto thyroiditis does not automatically require immediate hormone treatment.
3. Similarly, exactly how often should TSH, total or free T4 levels be checked? This author checks total T4 and TSH annually until about 10 years after diagnosis; if the levels remain absolutely normal and if antibody levels are persistently negative, then less frequent checking would be reasonable.
4. Achlorhydria and mild iron deficiency related to possible iron malabsorption may occur (associated with positive gastroparietal antibodies). Folic acid and vitamin B_{12} deficiency is also more common with positive gastroparietal antibodies and often with minimal or no symptoms. If thyroid antibodies are positive, it is prudent to then also **check gastroparietal antibodies** as well as obtain baseline **folic acid, vitamin B_{12}, iron and ferritin levels.**
5. Adrenal insufficiency (adrenalitis) may coexist with type 1 diabetes associated with autoimmune (positive adrenal antibodies) dysfunction that may be life-threatening and occurring more commonly in the subset of type 1 diabetes patients who also have other evidence of autoimmunity, that is, celiac or thyroid related antibodies, or overt thyroid or bowel dysfunction. However,

routine adrenal antibody determination in the subset with positive transglutaminase and/or thyroid antibodies produces a higher yield and seems to be worthwhile, so that this author recommends such testing where available and affordable followed by more definitive testing (cortisol and ACTH levels or stimulation testing) if positive results occur.

6. Celiac disease with positive transglutaminase, endomysial, and/or other gluten-related (gliadin) antibodies is also significantly more common in many cohorts of patients with type 1 diabetes, particularly in those populations with ancestry in or around the Mediterranean Sea. Estimates suggest positivity in about 6% to 10% of a type 1 diabetes population (particularly Caucasians). Calcium, iron, and trace mineral deficiencies can occur under such circumstances.
7. Gonadal (testicular or ovarian) antibodies are also less commonly seen than celiac or adrenal antibodies.

L. Vitamin D, osteopenia, or osteoporosis

1. There are some research reports suggesting increases in this population.
2. There is an increased prevalence and incidence of osteopenia if celiac disease coexists. Bone density DXA scanning may be important to follow sequentially.
3. Vitamin D insufficiency (hypovitaminosis D) in mild, moderate, or severe degrees is often very common and likely somewhat worsened in a type 1 diabetes cohort in this author's experience. Because vitamin D has important effects on some of the same tissues that are affected by chronic hyperglycemia, correcting (asymptomatic) hypovitaminosis D is likely to help reduce long-term microvascular and macrovascular complications of diabetes and even has been reported to help reduce respiratory infections, cancer incidence, and help with attention deficit disorders and learning problems.
4. Measurement of blood total vitamin D is recommended by this author approximately twice-a-year to help with decisions about supplement dosage aimed to correct low levels and especially to correct documented osteopenia and/or osteoporosis.

M. Hypertension and nephropathy

1. **Blood pressure should be obtained at least every 6 months in all patients from diagnosis onwards and**

documented in the medical record.

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2. Hypertension should be treated aggressively in an effort to reduce morbidity and mortality associated with diabetic complications.
3. Essential hypertension can occur in any youngster or young adult with type 1 diabetes. Most cases of hypertension are associated with diabetic nephropathy.
4. Thiazide diuretics can be safely used in most cases to control hypertension. β-Blockade can also be used, but with some caution because of the potential to mask symptoms of hypoglycemia. Angiotensin-converting enzyme (ACE) inhibitors play a role not only in normalizing mild hypertension but also in reducing glomerular hyperfiltration and microalbuminuria. Therefore, **ACE inhibitors may be the medication of choice.** Other antihypertensive agents all have a place particularly in the patient who appears to be resistant to one or more antihypertensive agents and additional options should be considered. All such medications seem safe to use without any special precautions in a diabetes population.
5. Sequential evaluation of renal function with blood urea nitrogen, creatinine, overnight or 24-hour urine protein, and creatinine clearance is helpful in early detection of **nephropathy**. Microalbuminuria (>7 to 20 mg being used as cutoff points in various research studies over the years for children and adolescents) obtained in overnight or 24-hour collections as well with random screening sampling utilizing microalbumin: creatinine ratios may identify subpopulations at risk for diabetic nephropathy. If abnormal, protein intake may need to be restricted (to as low as 12%). **ACE inhibitors** have also been helpful under circumstances when microalbuminuria or proteinuria occurs even when hypertension is not present. Controlling hyperglycemia is most important, and smoking cessation is also helpful.
6. Onset of proteinuria and hypertension during the first 10 years of type 1 diabetes mellitus should not be automatically considered as indicative of diabetic nephropathy (uncommon in the first 10 years of diabetes mellitus), and its etiology should be vigorously pursued.

N. Lipids. Fasting blood levels should be obtained for total cholesterol,

triglyceride, and high-density lipoprotein (HDL) cholesterol, as well as direct or calculated LDL cholesterol values at least every 6 to 12 months to identify which patients require further dietary lipid control as well as more intensified insulin therapy. Calculated non-HDL cholesterol levels can also be helpful.

1. If fasting triglycerides are normal, then nonfasting direct LDL measurements plus HDL and total cholesterols can be done nonfasting to make timing of testing easier.
2. Antilipid medications such as sterols, stanols, resins such as cholestyramine and colestipol, as well as gemfibrozil and statin medications can be used in conjunction with insulin treatment.
3. Plant sterols and stanols can also be safely prescribed especially if there is documented chemical myositis or liver dysfunction with statins.

O. Ophthalmologic evaluation. Baseline ophthalmology evaluation, including fundus photographs, is recommended within the first 2 to 3 years of developing diabetes and might be repeated at 1- to 2-year intervals after 5 years duration of type 1 diabetes mellitus (or age 10 years) to pick up early vascular changes in the retina and to assess cataract risk or presence.

1. Fluorescein angiograms may show the earliest abnormalities of diabetic retinopathy years before dilated-eye examinations or fundus photography.
2. Poor glycemic control is clearly associated with earlier and more severe types of retinopathy.
3. Rapid improvement of chronic very poor control is also associated with retinopathy and sometimes rather fast and dangerous changes in vision.
4. Laser treatment of retinopathy saves vision.

P. Neuropathy. Significant neuropathy is often not seen in the child or adolescent unless there has been prolonged lack of insulin. Alcohol, substance abuse, or nicotine abuse may exacerbate neuropathy.

1. Symptomatic diabetic neuritis is fairly rare but may show up after 5 to 10 years of high A_{1c} levels and especially if exacerbated by alcohol, drug use, smoking, untreated hyperlipidemia, or combinations of such risks.

2. Symptomatic diabetes neuritis can include autonomic neuropathy with abnormal counterregulation and abnormal hormone responses to hypoglycemia, burning pain, absent reflexes, and other autonomic dysfunction such as gastroparesis with severe gut motility problems.
3. **Gastroparesis** can be relatively asymptomatic or can cause diarrhea or constipation.
4. Neuropathic pain treatment is especially problematic, if diabetic neuritis occurs affecting peripheral nerves; narcotics do not often provide ideal relief.
5. It is rare for significant diabetic neuropathy to occur without significant glycemic elevations and concomitant prolonged periods of time of A_{1c} abnormalities. Often there is also significant LJM.
6. Optimizing glucose control at any point in time either helps prevent and/or treat diabetic neuropathy.

Q. Cardiovascular and macrovascular complications

These are extremely rare in those under 21 years of age and are often linked in type 1 diabetes patients with much longer duration as well as other concomitant risk factors such as obesity, hyperlipidemia, and/or smoking history.

VIII. CONTINUOUS GLUCOSE MONITORING SYSTEMS

A. CGMS is now available with results usually produced at 5-minute intervals by most sensors (i.e., Enlite, DexCom, Navigator, and Guardian).

B. Newer models have a reduced error rate to the 5% to 10% range compared with capillary blood glucose readings and continue to be most helpful to identify decreasing as well as increasing glycemic trends. This allows potentially earlier corrections of both high and low glucose readings whether treated by MDI or CSII and may be especially helpful for those with hypoglycemia unawareness or recurrent seizures as well as those with recurring nocturnal problems.

C. Several research studies of CGMS have documented lowered A_{1c} levels, decreased glycemic variability, and most importantly less severe and fewer episodes of hypoglycemia, especially loss of consciousness and coma episodes. Newer systems download directly to mobile telephones as well as Internet servers and can be accessible via tablets and computers. CGMSs, which provide 288 blood glucose

equivalent values each day, identify information that would otherwise escape detection.

IX. INSULIN PUMPS, INTENSIFIED MDI THERAPY, AND NEW DEVICES LEADING UP TO THE ARTIFICIAL PANCREAS PROJECTS

A. General considerations

1. Although totally implantable artificial endocrine pancreases and pancreas transplants (partial and β-cell) continue to be investigated, insulin pumps (CSII systems) coupled with extensive SMBG and now CGMS are being used in adults and children more frequently than ever.
2. CSII and MDI therapy has been applied successfully in research settings and in clinical practice.
3. Development of improved implantable and noninvasive glucose sensors is on the horizon and likely will continue to revolutionize current diabetes care. Sensors are coupled to internally or externally situated programmable insulin delivery systems that potentially can feed appropriate amounts of insulin adjusted frequently according to glucose fluctuations in the blood or interstitium.
4. Automatic LGS systems are available and such systems not only provide predictive alarms for rate of glucose decline and rise as well as absolute hypoglycemia and hyperglycemia limits, but also automatically suspend insulin delivery at set values (i.e., <60 mg/dL).
5. Pumps that provide insulin alone or insulin and glucagon are now available.

B. Continuous subcutaneous insulin infusion

1. Insulin pumps are being prescribed with improved success for appropriate candidates. CSII may be the preferred treatment modality for infants and toddlers because of an ability to immediately turn off delivery and for fine-tuning adjustments.

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2. Hypoglycemia may be decreased with successful use of insulin pumps, particularly when insulin analogs are used in conjunction with automatic sensors.
3. Newer and smaller pump models have dose calculators and

carbohydrate counting wizards as well as built-in meters to facilitate dosing decisions.

4. Wireless devices and catheter-less "pods" improve acceptance and ease-of-use of CSII for patients who do not like the ideas of long tubes for insulin delivery.
5. Insulin basal and bolus distributions are similar to MDI algorithms with subsequent individualized adjustments based upon pre- and postprandial SMBG or CGMS profiles.
6. Automatic downloading to network data centers has been developed with significant improvement.

C. Intensive MDI therapy

1. Where CSII uses analog (or regular) insulin delivered in small boluses over 24 hours with larger prefood boluses given as needed, MDI uses basal-bolus algorithms of subcutaneous insulin in a variety of programs. Some examples are the following:
   a. Glargine or detemir insulin before breakfast and again at bedtime with additional analog (or regular) insulin before meals and snacks as needed (BID long-acting insulin with premeal boluses).
   b. Analog (or regular insulin) given before breakfast, before lunch, and before supper with glargine or detemir insulin at suppertime. (Bedtime long-acting insulin with premeal boluses.)
   c. Glargine insulin prebreakfast with prandial analogs often used in preschoolers who do not need any bedtime insulin.
   d. Analog or regular insulin plus NPH before breakfast; analog or regular alone before supper; and NPH alone at bedtime (BID NPH with premeal boluses).
   e. Analog or regular insulin plus NPH before all three meals, plus NPH alone at bedtime. (Overlapping NPH with premeal bolus mixtures.)
   f. Same as example e, and also with analog insulin before afternoon snack (when there is no afternoon activity).
   g. Analog or regular insulin given before breakfast, before lunch, and before supper with ultralente insulin at suppertime or bedtime in circumstances where ultralente remains available. (Ultralente basal insulin plus prandial boluses.)
   h. Same as example a or b but with degludec instead of other basal insulins in association with prandial fast-acting insulins.

D. Inhaled insulin

may replace injected bolus insulin in MDI, but still

must be coupled with injected basal insulin analogs or overlapping intermediate-acting insulins. Inhaled insulin is presently not-approved for pediatric use.

X. RESOURCES

There are many diabetes organizations and resources available for support such as:
International Diabetes Federation (IDF)
American Diabetes Association (ADA)
Juvenile Diabetes Research Foundation (JDRF)
International Society for Pediatric and Adolescent Diabetes (ISPAD) www.ispad.org
Changing Diabetes in Children (CDIC)
Life for a Child (LFAC)
Diabetes Forecast
Countdown
www.chidrenwithdiabetes.com
myglu.com

XI. SUMMARY. Efforts to provide ongoing education and support for the patient with type 1 diabetes should be aimed at obtaining blood sugar levels as close to normal as possible without causing excessive hypoglycemia. With attention to the psychological needs of the child, teenager, and family members, and with a positive, nonpunitive empowering attitude on the part of the health care team, more patients should be able to live better, happier, and longer lives free of the complications of IDDM.

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53 Hypoglycemia-Associated Autonomic Failure (HAAF) in Diabetes Mellitus

Norman Lavin

Hypoglycemia in the diabetic is the result of relative or absolute therapeutic insulin excess and compromised physiologic (defective glucose counterregulation) and behavioral (hypoglycemia unawareness) defenses against falling plasma glucose concentrations. Hypoglycemia-associated autonomic failure (HAAF) implies that recent antecedent iatrogenic hypoglycemia causes defective glucose counterregulation. It does this by reducing epinephrine responses to a given level of subsequent hypoglycemia in the setting of absent decrements in insulin and absent increments in glucagon. HAAF also causes hypoglycemia unawareness by reducing sympathoadrenal and the resulting neurogenic symptom responses to a given level of subsequent hypoglycemia, followed by a vicious cycle of recurrent hypoglycemia. The clinical impact of HAAF is well-established in type I diabetes and may affect those with advanced type II diabetes. Usually, HAAF is reversible within 2 or 3 weeks, if there is significant avoidance of hypoglycemia.

The specific mechanisms of HAAF are not well defined. The loss of the glucagon secretory response, which is a key feature of defective glucose counterregulation, is plausibly explained by insulin deficiency, specifically loss of the decrement in intraislet insulin that normally signals glucagon secretion as glucose levels fall. Reduced neurogenic symptoms, a key feature of hypoglycemia unawareness, are largely the result of reduced sympathetic neural responses to falling glucose levels. The mechanism by which hypoglycemia shifts the glycemic thresholds for sympathoadrenal activation to lower plasma glucose concentrations, the key feature of both components of HAAF, is not known. It does not appear to be the result of the release of a systemic mediator, such as cortisol or epinephrine, during antecedent hypoglycemia or of increased blood-to-brain glucose transport. It is likely the result of alterations of brain metabolism. Although there are several possibilities, the specific alteration remains to be identified.

There appears to be diverse triggers of HAAF. In addition to recent antecedent hypoglycemia, these include exercise- and sleep-related HAAF, and I believe the overcorrection of modest hyperglycemia with excessive amounts of insulin, thereby resulting in frequent relative hypoglycemic episodes. These patients are often directed by their physician to receive six to eight bolus injections daily.

Is HAAF adaptive or maladaptive? Clearly, the vicious cycle of severe iatrogenic hypoglycemia triggered by HAAF is maladaptive. However, HAAF appears to protect against brain damage and fatal cardiac arrhythmias from subsequent severe hypoglycemia in rats, findings that raise the possibility of an adaptive response, somewhat akin to ischemic preconditioning.

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54 Diabetic Ketoacidosis

Benjamin Fass

I. DIABETIC KETOACIDOSIS

A. General principles

A diagnosis of diabetic ketoacidosis (DKA) is made when hyperglycemia: blood glucose >200 mg%, and metabolic acidosis: blood bicarbonate <15 mEq/L, or venous pH <7.3, exist in the presence of ketonemia and ketonuria. DKA is more common at presentation of type 1 diabetes, though also reported in 5% to 25% of patients of all ages at diagnosis of type 2 diabetes. Mortality rates range from about 1% in children and adults to 10% in the elderly. The abnormalities associated with DKA can be traced to an absolute or relative lack of insulin that develops over several hours or days. In the newly diagnosed diabetic, insulin lack results from failure of endogenous insulin secretion. In the known insulin-dependent diabetic, insulin deficiency can result from insulin omission (commonly seen in the noncompliant adolescent), insulin pump failure, or from increased requirements for insulin caused by an underlying stressful condition such as, intercurrent infection (pneumonia, urinary tract infection, upper respiratory tract infection, meningitis, cholecystitis, pancreatitis), a vascular disorder (myocardial infarction, stroke), an endocrine disorder (hyperthyroidism, Cushing syndrome, acromegaly, pheochromocytoma), trauma, pregnancy, or emotional stress. The concomitant increased secretion of counterregulatory hormones or stress hormones (hormones antagonistic to the action of insulin—glucagon, epinephrine, cortisol, and growth hormone) explains the additional insulin requirements in such disorders. From 10% to 20% of patients presenting in DKA have no identifiable precipitating cause.

B. Pathophysiology of DKA

1. Role of insulin

a. The sequence of events in DKA (Fig. 54-1) is one of insulin deficiency leading to hyperglycemia and a resulting osmotic diuresis that leads in turn to dehydration and electrolyte depletion.

b. The insulin deficiency activates glycogenolysis (glycogen

breakdown to glucose) and gluconeogenesis (protein breakdown that leads to nitrogen loss and production of amino acids that serve as precursors in formation of new glucose). In addition, lipolysis results in production of free fatty acids (FFAs) as well as glycerol, which further helps fuel new glucose production.

c. Contributing further to the hyperglycemia are the decreased peripheral glucose utilization (secondary to both insulin lack and resistance) and the volume depletion (secondary to the osmotic diuresis), which reduce renal blood flow and consequently the amount of glucose filtered and excreted by the kidneys.

d. FFAs are delivered to the liver, where ketone bodies are produced (ketogenesis) with resultant ketonemia, which is intensified by decreased peripheral utilization. This leads to ketonuria, which further depletes electrolytes by an associated obligatory loss of cations.

e. Acidosis occurs as body bases are exhausted in the process of buffering the ketone anions that accumulate, accounting for the elevated plasma anion gap.

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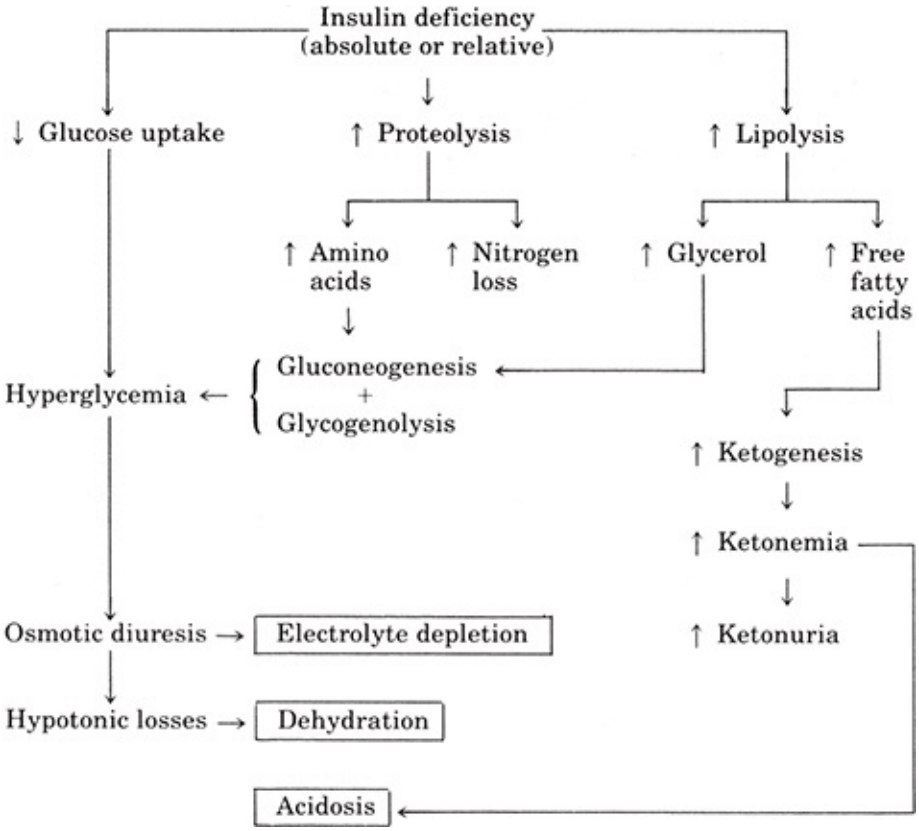

Figure 54-1. Pathophysiology of diabetic ketoacidosis. (From Davidson MD. Diabetes mellitus and hypoglycemia. In: Hershman JM, ed. *Endocrine Pathophysiology: A Patient-Oriented Approach.* Philadelphia, PA: Lea & Febiger; 1982.)

2. **Role of counterregulatory hormones.** The hypersecretion of epinephrine, glucagon, cortisol, and growth hormone contributes to ketoacidosis by:
   - **a.** Inhibiting insulin-mediated glucose uptake by muscle, that is, peripheral utilization (epinephrine, cortisol, and growth hormone)
   - **b.** Activating glycogenolysis and gluconeogenesis (epinephrine, glucagon, and cortisol)
   - **c.** Activating lipolysis (epinephrine and growth hormone)
   - **d.** Inhibiting residual insulin secretion (epinephrine and growth hormone)

C. Clinical presentation

1. Signs and symptoms

- **a. Polydipsia, polyuria,** and **weakness** are the most common presenting complaints; the severity depends on the degree of hyperglycemia as well as the duration of illness.

b. **Anorexia, nausea, vomiting,** and **abdominal pain** (more common in children) may be present and may mimic an abdominal emergency. Ketonemia is thought to be responsible for most of these symptoms. Young children may present with dehydration, abdominal pain, or fatigue, and the presence of oral and perineal candidiasis.

c. **Ileus** (secondary to potassium depletion from the ongoing osmotic diuresis) and **gastric dilatation** may occur and predispose to aspiration.

d. **Kussmaul breathing** (deep, sighing respiration) is present as respiratory compensation for the metabolic acidosis and is usually apparent when the pH is <7.2.

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e. **Neurologically**, 20% of patients are without any sensorial changes at all, whereas 10% are actually comatose. Some patients experience headache, altered level of consciousness, agitation, lethargy and, more ominously, inappropriate incontinence, sustained heart deceleration, and/or elevated BP. All these signs and symptoms may be harbingers of more serious central nervous system (CNS) involvement (see Section G.e.ii and iii, p. 748).

2. **Physical examination**

a. Presence of dehydration. Estimation of degree of dehydration is generally imprecise. An assumption that most DKA patients presenting to the ED are 10% dehydrated may be excessive. Some have suggested that 5% to 7% is a truer estimation (Olivieri). Prolonged capillary refill time (≥2 second), abnormal respiration (hyperpnea), and abnormal skin turgor (tenting) are the most useful signs for estimating 5% dehydration in children 1 month to 5 years. Other useful signs include sunken eyes, absent tears, dry mucus membranes, weak pulses, and cool extremities, and when taken together indicate more severe dehydration. Hypotension, weak or impalpable pulses, and oliguria may indicate ≥10% dehydration.

b. State of mentation. Initial evaluation of mental status and level of consciousness should be recorded. Glasgow Coma Scale may be used to track neurologic changes, but it does not record other suggestive signs of cerebral edema, such as headache, vomiting,

irritability, age-inappropriate incontinence, and vital signs.

c. Hypothermia is common in DKA. A fever should be taken as strong evidence of infection and vigorously pursued.

d. Hyperpnea or Kussmaul respirations (depth and not rate of respirations is important) are present and are related to the degree of acidosis.

e. Tachycardia is often present, but blood pressure is usually normal except in the presence of profound dehydration.

f. Musty (fruity) breath odor can often be detected.

g. Poor skin turgor may be prominent, depending on the degree of hydration.

h. Hyporeflexia (associated with low serum potassium) can be elicited.

i. Signs consistent with a "surgical abdomen" can follow severe ketonemia and can obscure the clinical picture.

j. In extreme cases of DKA, one can see hypotonia, stupor, coma, incoordination of ocular movements, fixed dilated pupils, and, finally, death.

k. Other signs from a precipitating illness can be present.

D. Laboratory data

1. Glucose

a. Serum glucose is usually elevated above 300 mg/dL, although levels range from almost normal to very high levels (≥600 mg/dL) which occasionally overlap with characteristics of hyperosmolar hyperglycemic state (HHS).

b. One important determinant of the glucose level is the degree of extracellular fluid depletion. Severe depletion results in decreased renal blood flow, decreased glucose excretion, and further hyperglycemia. The osmotic diuresis that results from the hyperglycemia causes additional fluid and electrolyte loss, dehydration, and hyperosmolality. At normal levels, the contribution of blood glucose to osmolality is slight. In DKA, the degree of hyperglycemia commonly seen can contribute significantly to the raised serum osmolality (generally up to 330 mOsm/kg), but generally not to the levels seen in HHS.

c. The amount of high-carbohydrate fluids consumed prior to seeking medical attention may further elevate the hyperglycemia.

2. Ketones. The three principal ketone bodies are ***β-***

hydroxybutyrate (BOHB), acetoacetate, and **acetone**. If measured, the total ketone concentration is usually >3 mmol/L and can go as high as 30 mmol/L (normal values are up to 0.15 mmol/L).

a. Serum acetone concentration (formed by nonenzymatic decarboxylation of acetoacetate) is high on admission. It is usually three or four times the concentration of acetoacetate. In contrast to other ketones, it does not contribute to the acidosis.

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b. BOHB and acetoacetate (1:1 ratio in normal individuals) accumulate in the serum at a ratio of 3:1 (mild DKA) to as high as 15:1 (severe DKA).

c. Standard nitroprusside reagents react with acetoacetate and not BOHB. They react only weakly with acetone. Therefore, a small ketone reading does not imply absence of ketoacidosis.

d. As the DKA state is corrected, BOHB is converted into acetoacetate, giving a stronger or more positive reading when tested with nitroprusside. However, it does not indicate worsening of the DKA state.

e. To more precisely measure ketone burden, a quantitative serum BOHB is recommended, if available, to help guide DKA management and its resolution. A level >3 mmol/L is indicative of DKA. If not available, the anion gap, pH, or serum bicarbonate is used to direct DKA treatment.

3. Acidosis

a. The metabolic acidosis is characterized by a serum bicarbonate of <15 mEq/L and a venous pH of <7.3.

b. It is due mainly to accumulation of BOHB and acetoacetate in the serum.

c. The ketone bodies are strong acids that dissociate completely under physiologic conditions and thereby produce the acidemia.

d. Some degree of lactic acidosis exists from hypoperfusion.

e. Hyperchloremic acidosis can exist as a “nongap acidosis” after prolonged intravenous (IV) therapy with normal saline (NS) and manifest during the recovery phase of DKA. If unclear as to resolution of ketoacidosis, BOHB is precise and should be obtained.

f. Stratification of acidosis is based on laboratory results and

clinical assessment:

i. Mild: pH >7.25, or CO_2 >12, and no alteration of mental status
ii. Moderate: pH 7.10 to 7.25, or CO_2 7 to 12, patient may be lethargic
iii. Severe: pH <7.10, or CO_2 <7, patient may have altered mental status (owing to dehydration, acidosis, hyperosmolality, hypernatremia, hyponatremia, cerebral edema, or a combination of these serious metabolic perturbations).

4. **Electrolytes**
   a. The serum sodium level may be low, normal, or high. The presence of the elevated serum glucose results in the obligatory movement of water from the intracellular to the extracellular space. This redistribution of body water can contribute to apparent hyponatremia despite dehydration and hyperosmolality. The presence of hypertriglyceridemia can also contribute to an artifactually lowered serum sodium.
   b. Serum potassium levels can be low, normal, or high. Potassium levels reflect both egress of potassium from cells secondary to the existing acidosis and the degree of intravascular contraction. Because of this and other circumstances, a normal or high serum potassium level does not reflect the actual total-body deficits of potassium that uniformly exist secondary to the ongoing osmotic diuresis. An initial low potassium concentration attests to severe depletion and should be managed aggressively.
   c. The serum phosphate level can be normal on admission but, like serum potassium, does not reflect the actual body deficits that uniformly exist while shifts of intracellular phosphate to the extracellular space occur as part of the catabolic state. This phosphate is subsequently lost in the urine as a result of osmotic diuresis (Table 54-1).
5. **Other laboratory tests**
   a. **Blood urea nitrogen (BUN)** levels are usually in the range of 20 to 30 mg/dL, reflecting moderate volume depletion.
   b. **Leukocytosis** in the range of 15 000 to 20 000/μL occurs frequently in DKA and therefore cannot be used as a sole

indication of an infectious process.

c. **Serum amylase** levels can be elevated. The reason is unknown, but the elevation might be of pancreatic (but not indicating pancreatitis) or salivary gland origin.

d. **Transaminases** can be elevated, but their significance is unknown.

e. **Thyroid function studies** in the presence of DKA tend to be unreliable. This might be another example of the "euthyroid sick syndrome" (see Chapter 30).

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TABLE 54-1 Average Fluid and Electrolyte Losses in Diabetic Ketoacidosis

	Maintenance requirements	Losses
Water	1 500–2 000 mL/m^2	100 mL/kg (range 60–100 mL/kg)
Sodium	45 mEq/m^2	6 mEq/kg (range 5–13 mEq/kg)
Potassium	35 mEq/m^2	5 mEq/kg (range 4–6 mEq/kg)
Chloride	30 mEq/m^2	4 mEq/kg (range 3–9 mEq/kg)
Phosphate[a]	10 mEq/m^2	3 mEq/kg (range 2–5 mEq/kg)
Magnesium[b]		0.5–1.5 mEq/kg

[a]1 mM/L = 1.8 mEq/L = 3.1 mg/dL.
[b]1 mM/L = 2 mEq/L = 2.4 mg/dL.
Adapted from Sperling MA. Diabetic ketoacidosis. *Pediatr Clin North Am* 1984;31:596.

f. **A_{1C} level.** Although it does not change initial management, it can provide valuable information regarding the chronicity and severity of hyperglycemia in all patients and overall glycemic control in established diabetics. Results usually obtained in <24 hours.

g. **Antibody studies.** Although not contributory to early management of DKA, in the newly presenting diabetic patient, especially if obese, antibody titers (anti-insulin, anti-islet, and GAD-65) may be obtained at the initial blood draw and will subsequently help differentiate between type 1 and type 2 diabetes. Turnaround time, 2 to 5 days.

E. Treatment

The goals of therapy include rehydration, reduction of hyperglycemia, correction of acid–base and electrolyte imbalances, and investigation of precipitating factors. Corollary treatment goals include avoidance of hypoglycemia, hypokalemia, and, in children, avoidance of therapeutic maneuvers that may increase the risk of cerebral edema. Most protocols outline somewhat similar approaches based on current literature and extensive clinical experience. The most important factor to emphasize is the frequent monitoring of the patient both clinically and biochemically (as opposed to an "automatic pilot" approach) as the best way to minimize morbidity and mortality.

1. **General management techniques**
   - **a.** A flow sheet that includes weight (admission weight should be used for all calculations), height (if possible), and laboratory data to include: glucose, serum ketones, electrolytes, BUN, creatinine, serum osmolality, albumin, calcium, phosphorus, venous gases, urine glucose and ketones, and urine pregnancy test (females of childbearing age). In addition, intake and output should be carefully recorded, as well as the type of hydrating solution used and the mode, timing, and amount of insulin administered. Initially, laboratory data should be obtained every 1 to 3 hours, and then less frequently once clinical improvement is noted. Patients with DKA should, in general, be admitted to an intensive care facility, where close monitoring is more easily assured.
   - **b.** If the patient is in shock, stupor, or coma, use of a nasogastric tube, especially if vomiting is present, and a urinary catheter is recommended.
   - **c.** Frequent assessment of potassium status is vital. A lead II electrocardiogram (EKG) can provide a rapid assessment of hyperkalemia (peaked T waves and short QT interval) and hypokalemia (prolonged PR interval, flat T waves, and presence of U waves). Hyporeflexia and ileus are clinical indications of potassium deficiency.
   - **d.** At least hourly checks of neurologic status are vital to detect signs of cerebral edema.

   - **e.** Bedside glucose determinations can be obtained every 30 to 60 minutes at the onset of therapy to help determine the rate of

serum glucose fall and to determine the point at which dextrose should be added to the IV solution.

f. Point-of-care BOHB bedside meters, if available, can be done every 2 hours.

g. A "two-bag" IV fluid method is an effective and rapid way of administering concentrations of glucose to children who have DKA. This system consists of two bags of IV fluids that contain identical electrolyte concentrations, but with one bag containing 10% dextrose and the other 0% dextrose. They are administered simultaneously in a piggyback manner. The rates of administration of each bag are adjusted to give the desired concentration of dextrose while maintaining a constant overall rate of administration of fluid and electrolytes.

2. Fluid and electrolyte therapy

a. General principles. IV fluids are administered for initial volume re-expansion and for subsequent correction of dehydration. The re-expansion phase will restore renal perfusion, which helps filter and clear glucose and ketones. Adults present with large volume losses requiring more aggressive fluid replacement, whereas children, owing to the feared complication of cerebral edema, are corrected more gradually.

b. Fluid replacement. With hyperglycemia, water is drawn from the intracellular to the extracellular space, thus depleting the former. Simultaneous extracellular water depletion (specifically, the intravascular compartment) occurs as a result of the obligatory osmotic diuresis. Electrolytes (sodium, potassium, chloride, phosphate, and magnesium) are considerably depleted as well, but the osmotic diuresis represents a hypotonic loss, as more water than electrolytes is excreted. This fluid loss can be aggravated further by other ongoing fluid loss, such as occurs with vomiting. The goal of fluid management is to replete both the extracellular and the intracellular compartments.

c. Re-expansion solution**.** The initial hydrating fluid should be 0.9% NS for the following reasons:

i. As serum glucose levels decrease and tonicity falls, water shifts back into the intracellular space. This redistribution can unmask the degree of dehydration actually present in the intravascular space, which was previously "hidden" by the degree of water that shifted into this compartment in

response to the elevated serum osmolality. This unmasking may further aggravate the circulatory losses and, in severe cases, may contribute to circulatory collapse. Therefore, the use of NS rather than a hypotonic solution is recommended to minimize this effect.

ii. Because patients with DKA universally demonstrate hyperosmolality, even NS may be hypotonic in relation to serum osmolality (NS = 308 mOsm/L; ½ NS = 154, 5% dextrose + NS = 560, 5% dextrose + ½ NS = 406, 5% dextrose in water = 250 mOsm/L, lactated Ringer's = 275). Some studies state that a rapid fall in serum osmolality is an important contributor to cerebral edema; therefore, a gradual lowering of tonicity is desirable; this is best obtained by avoiding the use of hypotonic IV solutions during the initial stages of therapy. (Some use lactated Ringer solution, which has less chloride, 109 mEq/L, than NS, and therefore can reduce the degree of hyperchloremic acidosis that may be associated with ongoing therapy. It has 130 mEq/L of Na^+, 4 mEq/L of potassium, and 28 mEq/L of lactate, which is slowly metabolized to bicarbonate).

a) Severe hypovolemic shock. The following is recommended.

1) Adults. NS at about 20 mL/kg bolus over 30 to 60 minutes is given and repeated if necessary, to maintain the intravascular space and restore blood pressure and renal perfusion. Once restored, the fluid rate is reevaluated.

2) Children. Shock is rare in children in DKA, but if it is present, NS at 10 to 20 mL/kg bolus may be given over 30 to 60 minutes, and repeated until blood pressure is normalized, capillary refill time improved (<3 seconds), and peripheral pulses are palpable. Usually, no more than two to three such infusions are needed to reverse the hypotensive crisis.

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b) Nonshock presentation

1) Adults. NS is infused at a rate of 15 to 20

mL/kg/hour over the first hour (usually 1 to 1.5 L in an average adult) until hypotension is corrected, blood volume and blood pressure are stabilized, and urine flow is normalized (50 to 100 mL/hour).

2) **Children.** NS is infused at a rate of 10 mL/kg over the first hour. Severe fluid depletion results in decreased renal blood flow and worsening hyperglycemia. The fluid given in this first hour will begin to correct this by substantially increasing renal perfusion and enabling glucose to be cleared, thus lowering blood glucose levels. *Euvolemia is not the goal*. NS should be continued after this first hour if subsequent hydration solutions have not yet been prepared, but at the rehydration rate noted below. Once electrolyte values are known, the addition of potassium to these solutions (see Table 54-2 and Section B.3, p. 625) depends on the serum K^+ levels and the absence or presence of oliguria. (Note: insulin infusion is only started after this first hour of hydration and bolus insulin is never used.)

TABLE 54-2 Outline for Treatment of DKA and HHS in Adults

Laboratory evaluation

- Admission labs: CBC, BG, electrolytes, BUN, creatinine, serum ketones, osmolality, calcium, phosphorous, arterial blood gases, and UA.
- Additional labs if clinically indicated: EKG, CXR, and cultures of blood, urine, and sputum.
- Ongoing therapy: Bedside BG q1h; electrolytes, BG, BUN, creatinine, phosphorus, and venous pH q24, or as needed.

Fluids

- First hour: 15–20 mL/kg/hr (usually 1–1.5 L) NS, until hypotension corrected, urine flow normalized (50–100 mL/hr).
- Ensuing hours: ½ NS, if [Na^+] normal or high, to NS if [Na^+] low; run IV at 250–500 mL/hr.
- When BG is <200 mg/dL, change to D5 ½ NS to allow continued insulin administration to resolve ketonemia and avoid hypoglycemia.

Insulin

- Give 0.1 U/kg IV bolus, followed by 0.1 U/kg/hr as a continuous infusion. Alternatively, start insulin infusion at 0.14 U/kg/hr without a bolus unless BG does not fall by 10% in the first hour, in which case, may give 0.14 U/kg as a bolus.
- Rate of decline of BG ideally between 50 and 70 mg/hr.
- When BG is 200 mg/dL, change IV to D5 ½ NS and reduce insulin rate to 0.02–0.05

U/kg/hr.
- Adjust insulin rate to maintain BG levels between 150 and 200 mg/dL until serum bicarbonate is ≥18 mEq/L and pH is >7.30.
- With mild to moderate DKA, SC rapid-acting analogs may be an alternative to IV insulin (see caveats discussed later).

Potassium

- If initial serum K^+ is >5.3 mEq/L, no supplementation is required and K^+ rechecked hourly.
- If initial serum K^+ is 4–5 mEq/L, add 20–30 mEq K^+ to each liter of replacement fluid after adequate renal function is established (urine flow at least 50 mL/hr). If serum K^+ is 3–4 mEq/L, add 40 mEq to each liter of replacement fluid.
- If initial serum K^+ is <3.3 mEq/L, depletion is severe. Hold insulin and give 20–30 mEq K^+ per hour until K^+ is >3.3, then add 40 mEq to each liter of replacement fluid. Additional supplementation may be needed based upon hourly K^+ measurements.

Bicarbonate

- If pH is <6.9, may give 100 mEq of bicarbonate with 20 mEq of KCl in 400 mL of H_2O to run at 200 mL/hr for 2 hr until venous pH > 7.0.
- Do not give bicarbonate if pH is >7.0.

Phosphate

- If indicated (serum levels <1 mg/dL), administer 20 to 30 mmol potassium phosphate over 24 hr. Monitor serum calcium level.

Transition to subcutaneous insulin

- Insulin infusion should be continued until resolution of ketoacidosis (glucose <200 mg/dL, bicarbonate >18 mEq/L, and pH >7.30).
- When DKA resolves, start subcutaneous insulin regimen.
- To prevent recurrence of DKA during transition period to SC insulin, continue IV insulin for 1–2 hr after SC insulin is given.

HHS: A similar protocol should be used for HHS except that no bicarbonate is needed for HHS, and switching to glucose-containing fluid is done when BG reaches 300 mg/dL. HHS is resolved when glucose is ≤300 mg/dL, osmolality is <320, and patient is alert.

BG, blood glucose; BUN, blood urea nitrogen; CBC, complete blood count; DKA, diabetic ketoacidosis; EKG, electrocardiogram; HHS, hyperosmolar hyperglycemic state; NS, normal saline; SC, subcutaneous; UA, urinalysis; CXR, chest XR.

Data from (1) Kitabchi AE. Medical guidelines for clinical practice. Hyperglycemic crises in diabetes mellitus. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Diabetes Care* 2006;24(12):2739–2748; (2) Kitabchi AE, Murphy MB. Consequences of insulin deficiency. In: Skyler JS, ed. *Atlas of Diabetes.* 3rd ed. Philadelphia, PA: Current Medicine; 2005, with permission; (3) Nyenwe EA, Kitabchi AE. Evidence-based management of hyperglycemia emergencies in diabetes mellitus, Review. *Diabetes Res Clin Pract* 2011;94(3):340–351.

3. Rehydration phase

a. **Adults.** After the initial hour of re-expansion, the subsequent choice of fluid replacement depends on the hemodynamic status, state of hydration, urinary output, and serum electrolytes. In general, ½ NS infused at 4 to 14 mL/kg/hour (250 to 500 mL/hour) is appropriate if serum Na^+ is normal or elevated, and NS—at a similar rate—if corrected serum Na^+ is low. Adequate urine output of 0.5 to 1 mL/kg/hour is a goal of hypovolemic correction to avoid oliguric renal failure. Rate is decreased to 150 to 200 mL/hour when blood glucose (BG) reaches 200 mg% at which point 5% dextrose is added to IV solution. The IV insulin infusion (either regular insulin or an insulin analog can be used at the same concentration; they are equally effective in treating DKA) is decreased to 0.02 to 0.05 U/kg/hour or 2 to 3 U/hour at this time. In general, fluid replacement in adults is estimated to correct deficits within the first 24 hours.

b. **Children. Type of solution:** Because of a higher risk of cerebral edema in children that may occur during therapy for DKA, as well as a lack of an obvious cause, it is recommended that near-isotonic fluids (>½ NS, e.g., 2⁄3 NS, ¾ NS) should be used in the first 12 hours to help prevent the rapid fall in osmolality that occurs when BG concentrations drop with ongoing therapy. We routinely use ¾ NS for this phase of rehydration beginning at the second hour of replacement. Others recommend use of an isotonic solution (NS, Ringer lactate, or Plasmalyte) for the first 4 to 6 hours of initial fluid therapy.

c. **Rate of infusion.** Because the severity of dehydration may be difficult to determine, total amount of fluid, as well as rate, may be overestimated. This is particularly true on admission to the ED, where a child in DKA may be overzealously hydrated. At times, adult protocols for assessing dehydration and fluid replacement are used with children (including use of insulin in first hour of therapy). Because of the risk for cerebral edema, consensus statements as to rehydration rate in children after the initial hour of expansion, uniformly recommend that rate should rarely exceed 1.5 to 2 times daily maintenance p. 740p. 741requirements based on age, weight, or body surface area.

This recommendation takes into account not only the avoidance of rapid reduction of plasma osmolality, but also the overly cautious fluid resuscitation that may prolong the cytotoxic effects of dehydration and acidosis (Tables 54-2 and 54-3). We, as others, using body surface area, recommend fluid replacement rates of 3 000 mL/m^2/day (subtracting from this the total amount of fluid given in the first hour of re-expansion and dividing result by 24 hours for an hourly rate). Others distinguish deficit losses (which are necessarily proportional to weight) from maintenance requirements (which are proportional to energy expenditure, i.e., surface area). They calculate maintenance at 1 500 mL/m^2/day and add p. 741p. 742p. 742p. 743to that estimated fluid deficits that are corrected evenly over 48 hours. When fluid deficits are not reliably known (which is often the case), an estimated deficit of 5% to 7% can be safely assumed (10% may be an overestimation unless clinical examination clearly suggests otherwise). Urinary losses are not replaced unless clearly excessive. As a guide: fluid volumes should not exceed 40 to 50 mL/kg during the first 4 hours of treatment, or exceed 4 000 mL/m^2 over the first 24 hours of therapy, and, if calculating deficit losses, then replacement of losses should be over 48 hours.

TABLE 54-3 Emergency Department Management of Pediatric Patients in DKA and HHS

The acute management of DKA in pediatric patients (<18 yr old) is different from that of adults, because children are at risk for acute cerebral edema with accompanying high morbidity and mortality.

Initial approach

- Obtain and monitor vital signs, including blood pressure, on all patients.
- Assess the degree of hydration and mental status.
- Do a bedside glucose determination. Note: Many meters do not read above 600 mg% and will indicate only “HI.”
- Obtain a urine sample for ketone determination. Note: Patients in ketoacidosis will have moderate to high ketones.
- Draw blood for serum glucose, ketones, electrolytes, BUN, creatinine (which may be artifactually elevated because of elevated ketones), and complete blood count. Obtain a venous pH.

- Start an IV and give **10 mL/kg** of NS or Ringer's lactate over 30–60 min. Note: *Shock rarely occurs in pediatric DKA.* However, if shock is present, give 20 mL/kg of NS, which may be repeated until the patient is hemodynamically stable.
- Order to bedside:
  - **A. Insulin drip**: Usually a concentration of regular insulin to NS of 100 U/100 mL (1 U/mL).
  - **B. IV solutions**:
  - **1.** ¾ NS + 20 mEq Kphos/L + 20 mEq Kacetate/L (total: 40 mEq/L) *as well as*
  - **2.** D10, ¾ NS + same electrolytes This is done now to avoid any delay in obtaining appropriate IV solutions later. One may vary the concentration of glucose infused by piggybacking these IVs and running each at different rates, but with both rates combined equaling the desired total hourly infusion rate.
- Consult with a pediatric endocrinologist as soon as possible.

Based on lab results and clinical assessment, patients can be stratified by the degree of acidosis:

Mild: pH > 7.25, or CO_2 > 12, and no alteration of mental status. Consider admission unless patient improves sufficiently.

Moderate: pH 7.10–7.25, or CO_2 7–12, and patient lethargic. Arrange for admission.

Severe: pH < 7.10, or CO_2 < 7, and patient c altered mental status. Arrange for admission.

Initial management for all three stratifications is essentially the same, with some caveats for each:

- After the initial hour of isotonic volume expansion, and if bedside BG is >300 mg%, run ¾ NS plus above electrolyte solution (b) at a maximum rate of 1.5–2 times maintenance, not to exceed 200 mL/hr.[a] Note: Unless patient is hyperkalemic (>5.5 mEq/L), start K^+ within 2 hr of admission to the emergency department, or when insulin has been started. If patient is hypokalemic (<3.5 mEq/1 L), increase IV K^+ replacement to 60–80 mEq/L added as KCl with close K^+ monitoring. If IV solution not ready, continue with NS. If bedside BG <300 mg%, run the D10, ¾ NS + same electrolytes.
- Begin an insulin drip at 0.1 U/kg/hr of regular insulin. In *mild* DKA, may give 0.2 U/kg of rapid-acting (lispro, asparte) SC if it is decided that IV insulin is unnecessary and continue with other monitoring guidelines.
- Follow electrolytes every 2 hr until bicarbonate trends upward and then every 4 hr. However, this schedule may be different (q1–2h) if hypokalemia (<3.5 mEq/L) or hyperkalemia (>5.5 mEq/L) is of concern.
- Do bedside glucose hourly. If BG falls to <300 mg% and patient is being given IV insulin, change IV solution to D10, ¾ NS + electrolyte solution. Maintain BG between 200 and 300 mg% while the acidosis is resolving.
- In moderate to severe DKA, monitor VS continuously with neuro checks. Arrange for a PICU bed ASAP.
- In severe DKA, if patient is in shock or obtunded, consider nasogastric tube, especially if vomiting, and urinary catheter.

Do nots (see text for further discussion):

- Do not give more than 20 mL/kg as a single fluid bolus.
- Do not give bolus insulin.
- Do not give boluses of sodium bicarbonate.
- Do not start insulin until a fluid bolus has been given and maintenance fluids begun. This may wait until admission to the hospital if this occurs within no more than 2 hr of admission to the emergency department.

HHS: Plasma glucose >600 mg%; venous pH > 7.25, arterial pH > 7.30; serum bicarbonate
- > 15 mEq/L; small ketonuria, absent or mild ketonemia; effective serum osmolality >320 mOsm/kg; altered state of consciousness (obtundation, combativeness) or seizures.
- Fluids: Deficit ~12%–15% of body weight, replaced over 24–48 hr. Initially, NS ≥20 mL/kg. Give additional NS fluid boluses, as needed, to restore peripheral perfusion. Replace urinary losses. Note: >40 mL/kg fluids in first 6 hr usually needed to avoid shock. Give ½ to ¾ NS after NS infusion to replace deficit in fully resuscitated patient. Hydration alone should lower BG by 75–100 mg%/hr. If BG fall is greater, add 2.5%–5% glucose. Corrected serum [Na^+] should decline with treatment. If not, may require hemodialysis.
- Insulin: Early administration not necessary. Start infusion when fall of BG is <50 mg%/hr on fluids alone. Insulin infusion: 0.025–0.05 U/kg/hr.
- Electrolytes: K^+, phosphate, magnesium deficits greater than in DKA; 40 mEq K^+ in each liter; monitor 1–3 hr; replace phosphate as in DKA (50:50 mixture); follow calcium. Bicarbonate contraindicated.
- Magnesium: may have large deficits. Replacement dose: 25–50 mg/kg/dose for 3–4 doses given every 4–6 hr; maximum infusion rate: 150 mg/min and 2 g/hr.

BG, blood glucose; BUN, blood urea nitrogen; DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; HI, high; PICU, pediatric ICU.

[a]Calculation of maintenance fluids per 24 hours: 100 mL/kg for first 10 kg of body weight; 50 mL/kg for the next 10 kg of body weight; 20 mL/kg for each additional 1 kg of body weight. Example: A 25-kg child would receive 1 000 mL + 500 mL + 100 mL = 1 600 mL/24 hours, or 67 mL/hour of maintenance fluids.

If calculating maintenance as 1 500 mL/m^2 per 24 hours: 10 kg = 0.5 m^2, 30 kg = 1 m^2, 50 kg = 1.5 m^2, 70 kg = 1.7 m^2.

Effective serum osmolality: 2 × serum [Na^+] + blood glucose/18. Normal values 290 mmol/kg water. BUN not included because it is freely permeable in and out of cells.

Anion gap = Na − (Cl + HCO_3); normal: 8–16 mEq/L.

Calculated/corrected serum Na = Na measured + (BG − 100)/100 × 1.6 mEq/L.

Source: The Southern California Kaiser Permanente Regional Pediatric Endocrinologists offer these guidelines, based on a document by the late Dr. James Seidel of Harbor–UCLA, for the acute management of pediatric DKA in the emergency department and the 2014 consensus statement of *ISPAD (International Society for Pediatric and Adolescent Diabetes) for HHS.

d. In the later stages of therapy, ½ NS can be used as replacement fluid because free-water deficits are reversed after the extracellular fluid volume has been restored.

e. If initial serum Na^+ exceeds 150 mEq/L, instead of NS, a solution of lesser tonicity can be used (½ NS, 2⁄3 NS, and ¾ NS). It is helpful to consider that each 100 mg/dL elevation in BG depresses serum Na^+ by 1.6 mEq/L, thus obtaining a "calculated" serum Na^+.

4. Potassium

a. As correction of acidosis proceeds (by hydration and

administration of insulin), potassium is shifted back to the cells and serum levels fall, with risk of hypokalemia. Hypokalemia, rather than hyperkalemia, is more common and associated with more serious complications (i.e., life-threatening arrhythmias). Adjustments of potassium supplementation should be based on clinical, electrocardiographic, and chemical parameters of K^+ deficiency.

b. K^+ addition should be accomplished within 2 hours of admission to the ED and/or concurrent with the start of insulin therapy.

c. In adults, if K^+ levels are normal on admission (3.3 to 5.3 mEq/L), then adding 20 to 30 mEq of K^+ to each liter of IV fluid will keep serum K^+ at the 4 to 5 mEq/L range. In children, this is usually accomplished by adding 40 mEq of K^+ to each liter of hydrating solution. Potassium can be added as a combination of K^+ acetate, K^+ phosphate, or K^+ chloride (½ KPhos and ½ Kacetate; 2⁄3 KCl and 1⁄3 KPhos).

d. In adults, if K^+ levels fall during therapy, add 40 mEq K^+ to each liter, and in children, increasing IV potassium concentration to 60 to 80 mEq/L (the additional K^+ added as KCl), may be required to maintain K^+ concentration ≥3.5 mEq/L. Note: Potassium chloride raises the serum potassium concentration at a *faster rate* than potassium bicarbonate (whose precursor is K^+ acetate). There are two goals here: one is to counter the acidosis and the other is to treat worsening hypokalemia. If hypokalemia does not seem to be the biochemical problem, then the choice of K^+ acetate and K^+ phosphate is very appropriate. When hypokalemia is added to the mix, that is, with acidosis, then KCl will increase the $[K^+]$ at a faster rate and therefore is added as well and, depending on the degree of hypokalemia, may be the preferred choice over the other two. So, K^+ acetate is added for its alkaline benefits; KPhos for the theoretical benefit of avoiding effects of hypophosphatemia, and KCl for its ability to raise $[K^+]$ faster than the other two in combination, especially in severe hypokalemia.

e. If potassium levels are elevated on admission (≥5.0 mEq in

adults and ≥5.5 mEq/L in children), potassium supplementation is withheld and serum K^+ concentration is checked hourly. If hyperkalemia is life-threatening with concomitant EKG changes, then, in addition to insulin, bicarbonate therapy may be beneficial.

f. If initial K^+ levels are low, then depletion is severe and K^+ replacement is started at the time of initial volume expansion and before starting insulin therapy. In adults, if K^+ is ≤3.0 mEq, give 20 to 30 mEq of K^+ per hour until [K^+] increases to 3.3 mEq/L. It may be given as (2⁄3 KCl and 1⁄3 KPhos), and when K^+ ≥ 3.3 mEq/L, then 40 mEq K^+ is added to each liter of replacement fluid and insulin may be started. Higher amounts of K^+ may be needed if depletion is more severe. In children, if serum K^+ concentration is ≤3.5, then a total of 60 to 80 mEq of K^+ is added to the IV solution (the additional K^+ as KCl) until K^+ is p. 743p. 744≥3.5 mEq. The maximum recommended rate of K^+ replacement in children is usually 0.5 mEq/kg/hour. If hypokalemia persists despite a maximum rate of K^+ replacement, then the rate of insulin infusion can be reduced.

g. Be aware of dose adjustments for oliguria, anuria, or azotemia: Extreme caution is recommended because of a high risk of hyperkalemia. It should be noted that high variability exists in dosing/infusion rate recommendations—this should be carefully reviewed prior to infusion.

5. Bicarbonate

a. The use of bicarbonate remains controversial. The cornerstone for correction of ketoacidosis is insulin administration, which inhibits lipolysis. The resolution of ketoacidosis should not require bicarbonate. Yet, others argue, severe acidosis is associated with impaired myocardial contractility, predisposes to arrhythmias, and decreases cardiac and peripheral vasculature response to catecholamine stimulation, among other concerns. Prospective randomized controlled studies, however, have not demonstrated any benefits of bicarbonate therapy in DKA patients with pH ≥6.9 (see Section 6.C.3 following) and, indeed,

have demonstrated its potential for harm. Several factors should be considered before utilizing alkali therapy.

i. In DKA, 2,3-diphosphoglycerate levels are decreased (mostly secondary to phosphorus depletion) with a resultant shift of the oxygen dissociation curve to the left (oxygen is held more tightly by hemoglobin). This effect is compensated for by the existing acidosis, such that the curve remains essentially unchanged (Bohr Effect) and oxygen is released to the tissues normally. If bicarbonate therapy is initiated, the curve again shifts to the left, with theoretically less oxygen being delivered to the tissues.
ii. With alkali therapy, potassium shifts back into the cell and may potentiate hypokalemia.
iii. Ketone bodies are themselves metabolized to bicarbonate once proper therapy is begun (fluids, electrolytes, insulin), and exogenous administration of bicarbonate can overcorrect, leading to alkalosis.
iv. Commercially available bicarbonate solutions are hyperosmolar and can aggravate the already-existing high serum osmolality.
v. Alkali therapy can contribute to CNS symptoms (from clouding of consciousness to frank coma), and specifically, to cerebral edema. Bicarbonate combines with hydrogen ion and dissociates to water and carbon dioxide. This carbon dioxide easily crosses the blood–brain barrier, whereas bicarbonate does so with difficulty. Therefore, despite improved peripheral pH values, a paradoxical CNS acidosis may be created or aggravated and may affect cerebral consciousness.
vi. There is no evidence that bicarbonate therapy accelerates metabolic recovery. Therefore, at present there seems to be no evidence to support the use of bicarbonate and in children, it is not recommended. However, having said that, some have indicated situations where its use may be considered:
    a) In the presence of life-threatening hyperkalemia (some consider this the *only* situation in which it may be beneficial).
    b) Recent literature suggests that the decision to administer

bicarbonate to adult patients whose pH falls to <6.9 should be individualized and not based solely on an arbitrary blood pH value as many complex considerations need to be taken into account. However, in those adults with arterial pH <6.9, a decision to administer bicarbonate may be considered when clinical condition is complicated by shock that is refractory to appropriate fluid resuscitation measures (NS, plasma, albumin, whole blood), in an attempt to improve cardiac output and slow ongoing metabolic deterioration. If bicarbonate is used in this situation, give 100 mEq of sodium bicarbonate in 400 mL of sterile water with 20 mEq KCl given at a rate of 200 mL/hour for 2 hours until venous pH >7.0. Bicarbonate therapy is stopped when pH >7.0.

c) In children, if pH remains <6.9, and plasma bicarbonate is <5 mEq/L, and there is no response to standard therapeutic maneuvers (restoration p. 744p. 745of hemodynamic stability), then use of bicarbonate has been considered at a dose of 1 to 2 mEq/kg of sodium bicarbonate given over an hour. The sodium bicarbonate can be added to ½ NS, with any required K^+, and this solution can be used as the rehydration solution for that hour. No bicarbonate therapy is necessary if pH is >7.0. If one uses different hydrating solutions, the combination of the Na in sodium bicarbonate and the Na in the IV solution should not exceed the concentration of NS.

6. Phosphate

a. Phosphate therapy is also a somewhat controversial issue in the treatment of DKA. Total-body phosphate stores can be markedly depleted in DKA. However, serum phosphate concentration is usually slightly elevated or in the high-normal range on admission because of the vascular contraction. In severe depletion (serum levels <0.5 mg/dL), serious organ dysfunction can ensue (rhabdomyolysis, altered consciousness,

muscle weakness, impaired cardiac function, and respiratory failure). However, in reality, the deficiency is usually clinically silent and only detected chemically. It should also be remembered that vigorous phosphate replacement can precipitate both hypocalcemia and hypomagnesemia. It may be argued that to avoid cardiac and skeletal muscle weakness and respiratory depression as a result of hypophosphatemia, in patients with cardiac dysfunction, anemia, and respiratory depression, and in those with phosphate levels <1.0 mg/dL, replacement may be beneficial. Currently, some degree of phosphate replacement is routinely accepted.

b. If the phosphate is replaced, it is given as potassium phosphate, subtracting this amount of potassium from that given as potassium chloride. A minimum requirement of 90 mEq (50 mM) of phosphate in the first 24 hours can be anticipated in the adult. In children, phosphate replacement can be safely calculated at 1 mEq/kg/day. Generally, one may simply give one half of the total potassium requirement (Tables 54-1 and 54-2) as the phosphate salt. This can usually be done by adding 20 mEq/L potassium phosphate to replacement fluids. Phosphate therapy should not to be used in patients with renal insufficiency.

7. Magnesium. The normal magnesium concentration is 1.5 to 2.5 mEq/L. Although depleted (usually in prolonged ketoacidosis), it is usually not a problem in most cases of DKA. If the magnesium level is low (usually <1 mEq/L), replacement can be given as a 50% magnesium sulfate solution. See Pediatric DKA Table at end of chapter.

F. Insulin therapy

1. Initially, severe fluid depletion results in decreased renal blood flow and further BG elevations. The first hour of volume re-expansion will increase glomerular filtration and thus begin to lower BG levels and reverse acidosis by enabling glucose and ketoanion excretion. It will also begin to reduce the burden of counterregulatory hormones, and decrease peripheral insulin resistance. But the bottom line: Insulin administration is necessarily required to suppress the ongoing lipolysis and ketogenesis. In adults, a standard, low-dose insulin infusion is started at the *beginning* of therapy. In children, the insulin infusion

is started only *after* the first hour of hydration to avoid a too rapid drop in glucose and serum osmolality which may lead to cerebral complications, in addition to predisposing the child to hypokalemia. As a guide: Do not start insulin until serum K^+ levels are known, a fluid bolus has been given and maintenance fluids begun. This may wait until admission to the hospital if this occurs within no more than 2 hours of admission to the emergency department.

2. Standard, low-dose insulin infusion at 0.1 unit regular insulin/kg/hour, is the mode of insulin administration that is generally accepted for both children and adults. In adults, if this infusion is used then an insulin bolus of 0.1 U/kg is given before the start of the infusion. Alternatively, studies show that if an insulin infusion of 0.14 U/kg/hour is used, then a bolus dose is not required. If BG does not fall by 10% in the first hour of therapy, then a 0.14 U/kg bolus is given, and the infusion continued at the previous rate. In children, a lower dose insulin-infusion of 0.05 U/kg/hour has been found to be noninferior to the standard, low-dose infusion p. 745p. 746with respect to rate of BG decrease and resolution of acidosis, with somewhat lower incidence of hypokalemia and hypoglycemia. This has been used routinely in some institutions, and limited to specific situations in others (e.g., children <5 years of age with new onset type 1 in DKA). Note: For the same reasons that an insulin infusion is started only *after* the first hour of hydration, a bolus dose of insulin is *never* appropriate in children before or during that first hour of hydration.

3. The benefits derived from continuous low-dose insulin infusion are as follows:

- **a.** It avoids the potential hazards of rapid and erratic serum glucose and osmolar fluctuations.
- **b.** It avoids, to a greater extent, episodes of late hypoglycemia and hypokalemia.
- **c.** With a constant amount of insulin infused, a steady linear fall in glucose can be expected (usually 50 to 90 mg/dL/hour, although this varies from patient to patient) and appropriate changes in IV solution anticipated (i.e., addition of 5% to 10% dextrose to

initial hydration solution when serum glucose concentration fall in the range of 200 to 300 mg%—see Section 4b below).

d. One has the advantage of instantaneously adjusting the insulin infused in response to sudden clinical and chemical changes.

4. Management of insulin infusion and IV glucose concentrations

a. Regular insulin (insulin analogs can be used at the same concentration because they are equally effective in treating DKA; kinetics are identical and the data show no advantage of one versus the other, but owing to higher cost of analogs, they may not be used as frequently as regular) is mixed with NS to give the desired concentration, usually 100 U in 100 mL, to give a 1:1 solution. In children, a more dilute concentration may be desired (125 U/250 mL, to give a 1:2 concentration) to give smaller doses of insulin, but the final volume of dilution should not be excessive. IV tubing should be flushed with the infusate and insulin delivered via a rate-control pump piggybacked onto the regular IV line.

b. Hyperglycemia usually resolves before the acidemia, but the insulin infusion must be continued to achieve full resolution of the ketoacidosis (pH > 7.3, bicarbonate > 15 mEq/mL, BOHB < 1 mmol/L, and/or closure of the anion gap). In order to allow for this and to avoid hypoglycemia, target BG should be between 200 and 250 mg% in the first 12 to 24 hours of therapy. In adults, when BG is ≤200 mg%, 5% dextrose is added to IV fluids and insulin infusion decreased to 0.02 to 0.05 U/kg/hour (or 2 to 3 U/hour) to maintain glucose at that level until ketoacidosis is resolved or serum osmolality is ≤320 mEq/kg, and patient is normally alert. In children, 10% dextrose is added to the IV solution when BG lowers to 250 to 300 mg% allowing for uninterrupted continuation of the insulin infusion and for resolution of the ketoacidosis while avoiding hypoglycemia. Please refer to the “two-bag” IV administration system described in Section E.1.g, p. 738.

c. When glucose levels continue to fall despite IV 10% dextrose, to avoid impending hypoglycemia, the rate of the IV hydrating solution can be increased if calculations of fluid requirements allow, or the addition of more glucose substrate (12.5%) to the IV solution is recommended. If, despite this, the BG drops further, then, in children, the insulin infusion can be decreased

to 0.08 to 0.05 U/kg/hour, but generally no less than 0.03 U/kg/hour.

d. Half-hourly to hourly bedside finger punctures for glucose determinations are recommended in the initial hours of therapy.

e. If the glucose level does not improve after an hour of infusion, the rate of insulin infusion is doubled until a response is noted. If, after an additional hour, there is still no response, the infusion of insulin is again doubled, with the crucial proviso that the IV insulin access line and infusion pump are checked for correct functioning before each increase.

f. If within 3 to 4 hours of onset of therapy, there is no metabolic improvement (no fall in serum glucose, and no change in or worsening of pH), then, after checking that the IV is functioning properly and has not infiltrated, under-hydration, occult infection, or other coexisting medical problems might be complicating the medical response. If these last conditions are unlikely, p. 746p. 747then the increasing doses of insulin can indicate the more rare type of insulin resistance that requires very high doses.

g. Once started, the insulin infusion can be run until the acidosis is fully corrected and the serum bicarbonate is back to normal (usually 12 to 24 hours) before switching to subcutaneous (SC) insulin. In this regard, it has been shown that normalization of BOHB (<3 mmol/L) is the best marker of ketoacidosis resolution. However, if for any reason, it is desired to discontinue the infusion and to start SC insulin, a serum bicarbonate of 18 mEq/L may be used as a suitable switching point. One should give the first SC insulin dose about 60 to 90 minutes (regular) to, 30 to 60 minutes (rapid-acting analogs), to 2 hours (Lantus) before discontinuing the IV infusion.

5. If IV access is difficult in a *mild* DKA patient (pH > 7.25, CO_2 > 12), or if IV hydration is deemed unnecessary (tissue perfusion is good), SC rapid-acting insulin analogs (lispro or aspart) have been shown to be effective. Patients receive 0.2 U/kg initially, followed by 0.1 U/kg every hour or an initial dose of 0.3 U/kg followed by 0.2 U/kg every 2 hours until BG is ≤250 mg%, then the insulin dose is decreased by half to 0.05 or 0.1 U/kg, respectively, and

administered every 1 or 2 hours until resolution of DKA.

6. After discontinuing the insulin infusion, it is not necessary to switch to sliding-scale regular insulin coverage q4h. Instead, one may proceed to either of the following methods of insulin coverage, though other combinations exist:
   a. Regular/NPH regimen—used less frequently today:
      i. A total daily insulin dose of about 0.7 U/kg should be administered, with a range of 0.5 to 1 U/kg/day depending on age and weight of child or adult.
      ii. Give two thirds of this total amount before breakfast and one third before supper.
      iii. Give one fourth to one half of the AM and PM dose as regular or rapid-acting insulin and the rest as NPH. Short-acting insulin (regular) is given 30 to 45 minutes before the meals, or rapid-acting insulin, 15 to 30 minutes before the meals.
      iv. Younger children may demonstrate a greater sensitivity to both rapid-acting and short-acting insulin. Therefore, it may be prudent to start with a lower dose of either.
   b. Basal/Bolus regimen
      i. Basal insulin: 24-hour acting peakless insulin (e.g., glargine) may be well used in association with rapid-acting insulin in the management of children with diabetes and can be used after the DKA has resolved. Usually, 40% to 50% of the total calculated daily insulin dose is given initially as the basal insulin in the evening, around 9 P.M., which is a good switching point from IV to SC insulin.
      ii. Bolus insulin: Rapid-acting insulin is given before meals according to defined ratios that are adjusted to fine-tune control. For older children and teenagers, a starting ratio of 1 U for each 15 g of carbohydrates (insulin to carbohydrate ratio: I/C) combined with a serum glucose correction ratio (correction factor ratio: CF) of 1 U for each 50 mg% serum glucose above 150 mg% is the total rapid-acting insulin dose given prior to meals. Snacks are covered according to these ratios as, in general, are random BG readings above 150 mg%. For younger children, I/C ratios may be 0.5 U or less, for each 20 or more grams of carbohydrates, and CF ratios may be 0.5 U or less, for every 100 mg% BG > 200

mg%, or other appropriate ratio.

c. Insulin pumps/continuous glucose monitors (CGMs)

i. In many infants and younger children, insulin pumps and/or CGMs have been used at the outset of SC treatment as a way to help parents better manage the child's BG excursions and, more urgently, to warn of impending hypoglycemia or extreme hyperglycemia. Pumps and CGMs may be used by all diabetics.

ii. For those on a pump at time of admission to ED that was necessarily discontinued at beginning of DKA therapy, it may be resumed at this time.

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d. In all methods, the amount of insulin administered or delivered is adjusted accordingly in subsequent days, based on finger-stick readings obtained before meals and 2 hours postprandially, in addition to obtaining bedtime, and 3 A.M. readings.

G. Complications

1. **Metabolic abnormalities** must be watched for and quickly corrected (severe acidosis, hypokalemia, hypoglycemia, and hypocalcemia).
2. **Nonmetabolic complications** can also be devastating, and therefore must be considered during patient evaluation.
   - **a. Infection.** Although infection occasionally accompanies ketoacidosis, it is rarely a cause of death. Elevated temperature should lead to a serious search for the focus of infection.
   - **b. Shock.** The severity of shock depends on the degree of volume depletion and acidosis. If the patient does not respond to the usual resuscitative techniques, then one should consider etiologic factors such as cardiogenic shock (secondary to myocardial infarction) or gram-negative sepsis.
   - **c. Vascular thrombosis.** This is usually secondary to severe dehydration, high serum viscosity, and low cardiac output. Cerebral vessels seem to be most susceptible. It occurs hours to days after onset of therapy.
   - **d. Pulmonary edema** can exist on a noncardiogenic basis. It is thought to be caused by aggressive crystalloid fluid therapy.
   - **e. Cerebral edema in children**
     - **i.** Cerebral edema varies in occurrence from 0.5% to 1% of

children with DKA, and its outcome is poor. In national population studies, mortality rates from 21% to 24% have been reported, with a 10% to 25% rate of permanent neurologic morbidity. Only 7% to 14% of patients have been reported to recover completely without permanent neurologic deficits.

ii. Either at time of presentation to the ED or, more typically, within 4 to 16 hours of initiation of therapy, cerebral edema may present without warning or is heralded by headache, lethargy, recurrence of vomiting, and age-inappropriate incontinence. Impending cerebral edema should be suspected with declining or fluctuating mental status; sudden development of hypertension not detected at presentation; an unexpected decline in urine output without clinical improvement or tapering of IV fluids; corrected Na^+ falling to hyponatremic levels; or a drop of effective osmolality to ≤275 mOsm/kg. More ominous signs of increased intracranial pressure include, papilledema, ophthalmoplegia, dilated, unresponsive, sluggish, or unequal pupils, and hypotension and bradycardia. Diabetes insipidus (a sign of cerebral herniation interrupting blood flow to the pituitary gland) and hyperpyrexia have been described and may coincide or precede mental stupor, and finally, coma, in the previously conscious patient.

iii. Multiple factors have been associated with increased risk of cerebral edema. Factors associated prior to treatment: New onset type 1 diabetes; age <5 years; long duration of DKA symptoms (greater dehydration, more profound acidosis); CNS hypoxia; degree of hyperglycemia and hyperosmolality; higher initial BUN (greater dehydration); and lower initial partial pressure of arterial carbon dioxide: <18 mmHg. Factors associated with treatment: Rapid fall in glucose levels with rapid changes in osmolality with excessive rate of rehydration; insulin use (bolus insulin and continuous insulin infusion) in the first hour of therapy; failure of Na^+ to rise as BG falls (marker of excessive administration of free water); and use of bicarbonate treatment (altered cerebral pH with paradoxical

cerebrospinal fluid acidosis). Newer data suggest that pathogenesis of cerebral edema may be intrinsic to DKA and the result of decreased cerebral perfusion due to dehydration; an activation of the brain cell membrane Na^+/H^+ exchanger that allows more Na^+ into brain cells, increasing intracellular osmols, and thereby water into cells; and a possible direct role of ketone bodies that affect vascular integrity and permeability, thus contributing to cerebral edema, all factors that may be aggravated by DKA therapy.

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iv. Of all these associations, it has been reasonably shown that: (a) unexpectedly elevated BUN at presentation, (b) low partial pressure of arterial CO_2, (c) serum Na^+ that fails to rise as serum glucose decreases, and (d) treatment with bicarbonate, pose the greater risk. Add to this, those children who present already neurologically compromised and with an altered mental status. However, it appears that at present no one factor can clearly be implicated as *causative* of cerebral edema, and it may ultimately be an interplay of all the above-indicated factors plus others that have not yet been identified. (The reader is advised to review the references for comprehensive viewpoints.)

v. Treatment: If cerebral edema is suspected, immediately give IV mannitol (0.5 or 1 g/kg over 20 minutes; this may be repeated hourly as necessary), or a 3% hypertonic saline solution (2.5 to 5 mL/kg over 30 minutes). Some have suggested furosemide (1 mg/kg) and dexamethasone (0.25 to 0.5 mg/kg per dose—anecdotal report by this author of successful use with one patient, though no evidence exists for its efficacy or for that of furosemide). Other measures include raising the head of the bed by 30°, reducing the rate of IV infusion by 30%, and possible mechanical hyperventilation to help reduce brain swelling, but clearly avoiding lowering the partial pressure of CO_2 to critical levels (≤20 mmHg). Note: As symptoms present, an inclination to obtain a noncontrast CT in the emergency

department may become uppermost. *However*, if cerebral edema is suspected, it should be treated promptly before sending the child for imaging.

II. HYPEROSMOLAR HYPERGLYCEMIC STATE (HHS). **HHS** was previously termed hyperosmolar hyperglycemic nonketotic coma. The change in term reflects that altered mental status can occur without coma, and that HHS may exist with variable degrees of ketosis, albeit not severe. It occurs in middle-aged and elderly patients, although it has been described in children. Most patients have type 2 diabetes or no prior history of diabetes, but it has been described in type 1 diabetes associated with DKA. When seen in the pediatric population, case series have suggested that obese African-American children with type 2 diabetes are at greater risk for HHS. As in DKA, it is characterized by an absolute or relative lack of insulin. When there is lack of ketosis in this syndrome, it has been traditionally explained by the presence of insulin in sufficient levels to prevent lipolysis and ketogenesis but not sufficiently high to prevent hyperglycemia. However, other mechanisms must be at play, because it has been noted that in some cases of HHS, insulin levels are not markedly different from those observed in DKA. The extreme hyperglycemia might be explained by the coexistence of decreased renal function in a great majority of these patients, limited access to fluids, and, in general, an osmotic diuresis that may exist for a prolonged period before presentation to the emergency department. Thus, DKA and HHS may represent points along a continuum of clinical presentations of poorly controlled diabetes, differing only in the severity of dehydration, ketosis, and metabolic acidosis. Possible complications of HHS include venous thrombosis, rhabdomyolysis, and malignant hyperthermia, in addition to altered mental status (associated with osmolality >330 mOsm/kg) (see Tables 54-2 and 54-3). See Chapter 58 for a full discussion of HHS.

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55 Type 2 Diabetes Mellitus

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I. INTRODUCTION

Type 2 diabetes mellitus (T2DM) accounts for >90% of all cases of diabetes in the United States. The prevalence of diabetes is increasing, with the disease affecting 29.1 million Americans or 9.3% of the U.S. population. More than 200 000 people die each year because of complications of diabetes, making it the seventh leading cause of death. Diabetes is also a leading cause of renal failure, new blindness in adults, and nontraumatic limb amputations. Heart disease and stroke are the leading causes of death in individuals with diabetes. All evidence suggests that the prevalence of type 2 diabetes will continue to increase both in the United States and in the rest of the world.

II. ETIOLOGY

The origin of T2DM is multifactorial, including genetic and environmental factors. Studies of identical twins document the genetics of T2DM, in whom concordance rates are nearly 100%. The strong environmental and genetic contribution to diabetes may be best seen in the Pima Indians of the Gila River Valley in Arizona. As they turned to a more Western European lifestyle, not only did the tribe members become more obese, the incidence of diabetes increased from a negligible number to nearly 50%. Another portion of the tribe returned to a more physically active lifestyle, in Mexico. They performed >40 hours of physical labor per week, compared to <3 hours among those living a Western European lifestyle. In the Mexican Pimas, the prevalence of diabetes in males decreased to 6.3%, compared to 54% in the Arizona Pimas. This example demonstrates that even though the genetics of the tribe did not change, their environment did, and this in turn had a significant impact on the development of diabetes. Although these genes are helpful for peoples living a traditional lifestyle, those same genes put us at risk for diabetes, obesity, and their associated complications when living a Western European lifestyle.

III. PATHOPHYSIOLOGY

T2DM is a complex, progressive disease. Current understanding suggests that type 2 diabetes results from the combination of pancreatic β-cell deficiency, insulin resistance in the adipose tissues and skeletal muscles, and excessive hepatic glucose production.

A. Insulin resistance. The earliest defect in patients with type 2 diabetes is insulin resistance. This concept has now been broadened as the **metabolic syndrome**, although other names are also used. Although the role of insulin resistance in the pathogenesis of diabetes has been recognized since the first radioimmunoassays for insulin, Gerald Reaven showed that the combination of hyperinsulinemia, hypertension, high triglycerides, and low high-density lipoprotein (HDL) cholesterol predicted the development of atherosclerosis even in people who were not yet diabetic and not obese. These individuals also had a high incidence of developing diabetes and eventually becoming obese. Reaven called this **syndrome X**. Current thinking has attributed some etiologic component of the metabolic syndrome to visceral adiposity. Waist circumference has become a key element in the signs used to make the diagnosis.

Current U.S. criteria as outlined in the NCEP ATP III guidelines are given in Table 55-1.

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TABLE 55-1 Metabolic Syndrome

Risk Factor	Defining Level	
Abdominal obesity (waist, in)	Men > 40	Women > 35
Triglycerides (mg/dL)	≥150	
HDL-C (mg/dL)	Men < 40	Women < 50
Blood pressure (mmHg)	≥130/85	
Fasting glucose (mg/dL)	(ADA ≥ 100)	

ADA, American Diabetes Association; HDL-C, high-density lipoprotein cholesterol

B. Controversy and the metabolic syndrome. The body initially compensates by increasing insulin production to maintain normal glucose levels. However, a subset of patients with decreased β-cell secretory capacity is unable to sustain the necessary level of insulin

production and develops diabetes. Early on in the course of the disease, these patients may have higher-than-normal circulating insulin levels, but these levels remain below those needed to maintain euglycemia, and hence, these patients are **still relatively insulin-deficient**.

C. Progression to diabetes mellitus. Insulin secretion continues to increase, but it continues to be less than is needed, and by an increasing margin. This is the result of decreased pancreatic β-cell function. The results from the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that affected individuals may have lost 50% of their β-cell function by the time of diagnosis, and that this level decreases in a linear fashion over time. The clinical correlate is elevated postprandial blood glucose values. As a result, patients may have normal or near-normal fasting blood sugars, but their blood sugars are not controlled after eating.

Further decline in insulin release leads to inadequate suppression of hepatic gluconeogenesis, resulting in further fasting and postprandial hyperglycemia. Thus, the combination of insulin resistance and diminished insulin secretion creates the setting for profound hyperglycemia.

Despite extensive investigation, the molecular mechanisms of diminished insulin secretion and insulin resistance have not been fully clarified. **Chronic elevation of free fatty acids**, a characteristic of T2DM, as well as structural changes in the islets of Langerhans as a result of **amyloid accumulation** may contribute to reduced insulin secretion and apoptosis. Weight loss has been demonstrated to improve insulin sensitivity. Many therapies are now targeted at the reduction of insulin resistance in hopes of improving insulin secretion and reducing hyperglycemia.

D. Other hormones and pathogenesis. These include **amylin** and incretin hormones (glucagon-like peptide 1 [**GLP-1**], glucose-dependent insulinotropic polypeptide, etc.). New therapies for T2DM are now targeting these hormonal pathways as well.

IV. DIAGNOSIS

A. Hyperglycemia. Individuals at risk of developing diabetes may be identified before the clinical onset of disease. It is important to remember that mild to moderate hyperglycemia while asymptomatic contributes to the development of the complications of diabetes. In the

UKPDS, a significant proportion of the patients presented at diagnosis with both macrovascular disease and, more surprisingly, microvascular disease, including retinopathy. Although we often think of polyuria and polydipsia as presenting symptoms of diabetes, these symptoms do not develop until the renal threshold for glucose has been exceeded. Depending on the patient's age, this may occur with blood glucose values in excess of 180 mg/dL.

Given the significant number of Americans with undiagnosed diabetes and prediabetes, early detection and treatment is essential to prevent complications of T2DM. The American Association of Clinical Endocrinologists (AACE), in the 2015 p. 752p. 753position paper, recommends annual screening of all individuals who are at risk for having or developing T2DM.

B. Risk factors are defined as follows:

1. Family history of diabetes
2. Cardiovascular disease
3. Overweight or obese status
4. Sedentary lifestyle
5. Latino/Hispanic, non-Hispanic black, Asian American, Native American, or Pacific Islander ethnicity
6. Previously identified impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)
7. Hypertension
8. Increased triglycerides, low concentrations of HDL cholesterol, or both
9. History of gestational diabetes
10. History of delivery of an infant with a birth weight >9 lb
11. Polycystic ovary syndrome
12. Psychiatric illness
13. Chronic steroid use
14. Sleep disorder including obstructive sleep apnea, chronic sleep deprivation, and night-shift workers with previously identified Hemoglobin (Hg) A_{1c} >5.7%, IGT, or IFG

C. Definitions. Based on the 2016 American Diabetes Association (ADA) guidelines, **normal** is defined as fasting glucose concentration <100 mg/dL; IFG or **prediabetes** as 100 to 125 mg/dL; and **overt**

diabetes mellitus as ≥126 mg/dL.

National Health and Nutrition Examination Survey data indicate that normal is defined as HbA_{1c} < 5.6%; prediabetes as 5.7% to 6.4%; and overt diabetes mellitus as ≥6.5%.

The oral glucose tolerance test (OGTT) is the centerpiece of the WHO guidelines. The WHO criteria reflect a fasting glucose of <115 mg/dL as potentially normal and that between 115 and 140 mg/dL as tentative for IGT or diabetes; thus, a 2-hour OGTT is required. A 2-hour OGTT value of <140 mg/dL is normal, whereas one between 140 and 200 mg/dL is diagnostic for IGT, and >200 mg/dL is diagnostic for diabetes.

IGT patients have an increase in cardiovascular risk of up to 60%. Therefore, recognition of these patients is imperative in the prevention of disease-associated risk. As a result, patients who have repeated fasting plasma glucose levels >90 mg/dL may benefit from further diagnostic testing using the OGTT.

Of note, patients with IFG and IGT are considered to have "prediabetes."

D. Interpretation of plasma glucose values. See Table 55-2.

E. Diagnostic criteria for diabetes mellitus. See Table 55-3.

Based on the 2016 ADA guidelines, diabetes may be diagnosed based on the plasma glucose criteria (fasting glucose or the 2 hours plasma glucose value after a 75 g OGTT) or the HbA_{1c} criteria.

F. Diagnosis of gestational diabetes mellitus (GDM) (see Chapters 63 and 75). The criteria used for the diagnosis of GDM are endorsed by the ADA. Patients at increased risk for GDM include age >25 years, overweight or obese state, family history of diabetes mellitus, history of abnormal glucose metabolism, history of poor obstetric outcome, history of delivery of an infant weighing >9 lb, history of polycystic ovary syndrome, ethnicities including Latino/Hispanic, non-Hispanic black, Asian Americans, Native American, or Pacific Islander, fasting plasma glucose >85 mg/dL, or 2-hour postprandial glucose concentration >140 mg/dL. Patients with these risk factors should be **screened at their initial obstetric visit** with glucose testing. If they are not found to have diabetes mellitus at that time, they should be retested **between 24 and 28 weeks of gestation**. Women with a history of gestational diabetes should also be tested at initial presentation to exclude the possibility of

previously undiagnosed type 2 diabetes, which is associated with the possible consequence of congenital anomalies in the fetus. These congenital anomalies occur during embryogenesis (early in the first trimester).

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TABLE 55-2 Diagnosis of Diabetes Mellitus Type 2

Glucose Concentration (mg/dL)	Interpretation
Fasting	
<100	Within normal reference range
100–125	IFG/prediabetes
≥126	Diabetes mellitus
2-hour OGTT (75 g)	
<140	Within normal reference range
140–199	IFG/prediabetes
≥200	Diabetes mellitus
Hemoglobin A_{1c}	
<5.6%	Within normal reference range
5.7%–6.4%	IFG/prediabetes
≥6.5	Diabetes mellitus

IFG, impaired fasting glucose; OGTT, oral glucose tolerance test.

TABLE 55-3 Diagnostic Criteria

Two or more of the following criteria should be met for diagnosis:

- Symptoms of diabetes (polyuria, polydipsia, unexplained weight loss) and random plasma glucose concentration ≥200 mg/dL
  or
- Fasting plasma glucose concentration ≥126 mg/dL (fasting is defined as no caloric intake for at least 8 hr)
  or
- Two-hr postchallenge glucose concentration ≥200 mg/dL during a 75-g oral glucose tolerance test
  or
- Hemoglobin A_{1c} ≥ 6.5%

Patients with average risk require screening only between 24 and 28 weeks of gestation. Practitioners should perform an initial screening by measuring plasma or serum glucose 1 hour after a 50-g oral glucose load (glucose challenge test or GCT). OGTT should be performed on women who exceed the glucose threshold on the GCT (1-hour postchallenge glucose concentration >140 mg/dL). OGTT can be performed using either a 75-g or a 100-g glucose load. The 100-g OGTT is better validated in the literature. The two-step diagnostic approach, using a glucose threshold value of >140 mg/dL, identifies approximately 80% of women with GDM. This yield may be increased to 90% by using a glucose threshold value >130 mg/dL. It is important to note that patients should be instructed to carbohydrate-load prior to the OGTT.

G. Diagnostic criteria for GDM using OGTT. See Table 55-4.

V. PREVALENCE

In 2015, epidemiologic studies of individuals in the United States 20 years of age or older, it was reported that 29.1 million people or 9.3% of people have diabetes. This includes 8.1 million people who are not aware of their disease. Diabetes affects 25.9% p. 754p. 755of people over the age of 65. Even more alarming is that another 86 million people (37%) in the United States aged 20 years or older have prediabetes. About 1.4 million new cases of diabetes are diagnosed annually. If current trends continue, as many as 1 in 3 American adults will have diabetes by 2050.

TABLE 55-4 Diagnosis of Gestational Diabetes

Time	Plasma Glucose Concentration (mg/dL)
75-g challenge	
Fasting	>92
1 hr post-glucose administration	>180
2-hr post-glucose administration	>153
100-g challenge	
Fasting	>95
1 hr post-glucose administration	>180
2 hr post-glucose administration	>155
3 hr post-glucose administration	>140

VI. CLINICAL EVALUATION

The clinical evaluation of a patient with diabetes should include documentation of the onset and progression of diabetes, medication history, and history of glycemic control. Notation should also be made of cardiovascular risk factors, history of retinopathy, date of most recent retinal examination, presence of microalbuminuria, and any history of neuropathy or lower-extremity ulcers. Given the correlation between diabetes and obesity, patients should also be evaluated for nonalcoholic steatohepatitis with measurement of liver function tests. In *Journal of Clinical Endocrinology and Metabolism*, June 2015, p. 2231, it says that ultrasound is superior to liver enzymes to detect nonalcoholic fatty liver disease (15% to 20% enzyme; 20% to 46% ultrasound).

Patients should also be questioned for symptoms of polyuria, polydipsia, blurry vision, and weight loss. Patients with these complaints are likely to have significant blood glucose elevation. Additionally, history of extremity pain, numbness or tingling, sexual dysfunction, or visual changes because of retinopathy should be documented.

Although we are seeing more adolescents with type 2 diabetes or **mature-onset diabetes of youth**, we are also encountering more adults with **latent autoimmune diabetes in adults**. This is an important distinction to make because these patients require a very different treatment strategy.

VII. POTENTIAL COMPLICATIONS ASSOCIATED WITH T2DM

The management of diabetes should be directed at the control of hyperglycemia as well as the prevention of the long-term complications of diabetes. The long-term complications of diabetes may be classified as microvascular diseases (affecting the eyes, kidneys, and nerves) or macrovascular diseases (affecting the heart, brain, and peripheral vascular system).

A. Prevention. The Diabetes Control and Complications Trial (DCCT), completed in 1993, was a long-term, randomized, prospective study involving 1 441 patients with T1DM, which demonstrated that near-normalization of blood glucose with intensive therapy was able to prevent or delay the development of diabetic retinopathy, nephropathy, and neuropathy.

B. Pathophysiology of complications. Several molecular mechanisms of glucose-induced damage have been proposed. These

include: **(a)** increased polyol pathway flux; p. 755p. 756**(b)** increased intracellular advanced glycation end product (AGE) formation; **(c)** activation of protein kinase C; and **(d)** increased hexosamine pathway flux.

1. **Glycation end-product mechanism.** One of the central pathogenic processes of chronic diabetic complications is mediated by AGEs. These glycation end products are a direct result of glucose attaching to protein through nonenzymatic reactions. Damage of target tissues occurs through modification of intra- and extracellular proteins and matrix components. The **glycation of proteins results in protein dysfunction** because of structural changes occurring at sites that are important for protein action, or by an alteration of protein half-lives brought about by a decrease in the enzymatic cleavage and disposal of proteins. When proteins are glycated, the glucose moiety that glycates the protein becomes unusually chemically reactive, **forming free radicals**. These activated glucose derivatives, as free radicals, polymerize and induce the **"browning reaction,"** which is why diabetic patients' scars are dark brown when their glucose levels are poorly controlled. The free radicals can also induce cross-linking, thereby decreasing the effectiveness of normal degradative enzymes. Glycation reactions also occur with smaller molecules, leading to the formation of soluble AGEs. The relative importance of soluble versus insoluble AGEs is not currently known.
2. **Smoking.** Smoking can drive AGEs because it results in the inhalation of particulate matter composed of glycated proteins from the tobacco plant. **During smoking, AGEs are elevated** in the plasma.
3. **Hypertension.** Glycated end products can also affect arteriolar muscle cells, resulting in hypertension. Normally, the synthesis of nitric oxide induces relaxation of smooth muscles of arterioles, preventing hypertension. However, in the setting of glycation, nitric oxide levels are diminished because of impaired synthesis, and there is a higher likelihood of **vasoconstriction** and associated hypertension. From a systemic point of view, the vasoconstriction causes microvascular damage in the eye, kidney,

and nerve.

4. **Kidneys.** Finally, **AGEs can affect renal glomerular function**, through disturbances of the structural integrity of the glomerular filter. Such filtration abnormalities result in increased hydrostatic pressure in the glomerulus and the excretion of albumin into the urine, which, if >20 mg/dL, is known as microalbuminuria.

VIII. HYPEROSMOLAR NONKETOTIC COMA OR HYPEROSMOLAR HYPERGLYCEMIC STATE

Hyperosmolar nonketotic coma (HONC) is one of the more devastating complications of T2DM. Mortality may be as high as 20% and increases with increasing age.

A. Definition. The physiologic response to hyperglycemia is primarily regulated by insulin and glucagon. Insulin acts to restore euglycemia by decreasing hepatic glucose production, via reduction in glycogenolysis and gluconeogenesis, and by increasing glucose uptake by skeletal muscle and adipose tissue. Insulin-induced inhibition of glucagon secretion then further inhibits hepatic glucose production. Therefore, in uncontrolled hyperglycemia, several major abnormalities are largely responsible for the decompensation of euglycemia, including insulin deficiency and/or resistance, and glucagon excess. The development of ketoacidosis then occurs when ketones are needed to provide an alternate source of energy because of impaired glucose utilization.

B. Clinical manipulations. These disorders in glucose metabolism and catabolism may be manifested as either diabetic ketoacidosis (DKA) (see Chapter 54) or HONC. These are related disorders that differ according to the presence of ketoacidosis and the degree of hyperglycemia. In **HONC, circulating insulin levels are likely adequate to control ketogenesis but are insufficient to maintain euglycemia**. Therefore, in HONC, there is little to no ketoacid accumulation and plasma glucose concentrations may exceed 600 to 1 000 mg/dL. To accumulate this degree of hyperglycemia, it is necessary for the patient to have limited access to water. A typical patient exhibits polydipsia to a sufficient degree to prevent blood sugar from being sustained at these levels. For that reason, HONC usually occurs in elderly or p. 756p. 757neurologically impaired

individuals, partially explaining the high mortality. Other differences between DKA and HONC include the degree of hyperosmolality, which may reach as high as 380 mOsmol/kg in HONC. In addition, neurologic abnormalities are frequently present in HONC, with coma occurring in 25% to 50% of affected patients. Finally, HONC may develop over the course of a week or longer, whereas DKA develops over 1 to 2 days.

C. Underlying causes. Similar to DKA, HONC may be triggered by infections (including pneumonia, which is present in 40% to 60% of cases, and urinary tract infections), alcohol and drug abuse, myocardial infarction, stroke, pancreatitis, trauma, medications that impair insulin secretion or action (e.g., corticosteroids, phenytoin, diuretics, immunosuppressants), hot weather or dehydration, and nonadherence to insulin therapy.

D. Signs and symptoms. The presenting signs and symptoms include polyuria, polydipsia, fatigue, weakness, lethargy, drowsiness, anorexia, mental status changes, seizures, aphasia, or even hemiplegia. Diagnosis of this condition is based on serum **glucose >600 to 800 mg/dL, serum osmolality >320 mOsmol/kg**, mental status changes, absent to low ketones, and absence of acidosis. Of note, neurologic symptoms usually develop when the serum osmolality exceeds 350 mOsmol/kg.

This condition should be suspected in patients who exhibit evidence of volume contraction, altered mental status/coma, sensory deficits, and an absence of Kussmaul respirations. The initial evaluation should include a complete blood count, chemistry panel, glucose, serum and urine ketones, urinalysis, arterial blood gas, chest radiograph, electrocardiogram, and blood cultures.

E. Treatment. Once a diagnosis of HONC is made, treatment should be as follows:

1. **Intravenous fluid.** Rapid repletion of 2 to 3 L of normal saline (NS); the usual fluid deficit is about 10 L. Replete one half of estimated fluid deficit (5 L) within the first 6 hours at a rate of 250 to 500 mL/hour. NS is then changed to ½ NS with close monitoring of the electrolytes. Continue to monitor fluid status carefully to avoid volume overload, especially in patients with underlying cardiac disease. The goal is to replace the estimated deficits within the first 24 hours. Once adequate rehydration has be achieved the rate of ½ NS can be reduced to the maintenance rate.

2. **Insulin.** Start an insulin infusion with the goal of decreasing blood glucose by 100 mg/dL/hour, but only after fluid repletion has been initiated, usually after the first 2 or 3 L of NS (Table 55-5).

TABLE 55-5 Differentiating between Diabetic Ketoacidosis (DKA) and Hyperosmolar Nonketotic Coma (HONC)

	DKA			
	Mild	Moderate	Severe	HONC
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–7.24	<7.0	>7.30
Serum bicarbonate (mEq/L)	15–18	10–15	<10	>15
Urine ketones	Positive	Positive	Positive	Small
Serum ketones	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)[a]	Variable	Variable	Variable	>320
Anion gap	>10	>12	>12	Variable
Alteration in sensorium	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

[a]Effective osmolality = 2Na + (glucose/18).

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IX. GOALS OF TREATMENT

Chronic complication rates are directly proportional to the prolongation of hyperglycemia (as defined by elevated levels of glycated Hg).

A. Prevention of complications. Macrovascular events require lower glycated Hg levels when compared with microvascular complications. Studies clearly indicate that decreased epidemiologic risk for macrovascular disease is associated with blood glucose levels in or near the normal range (UKPDS, $HbA_{1c} < 6.2\%$) when compared with higher blood glucose levels. The UKPDS data further indicate that in patients with type 2 diabetes, intensive or aggressive glucose control reduces mortality and cardiovascular event rates. Thus, for every 1% reduction in A_{1c}, there is about a 10% to 15% cardiovascular event rate reduction.

B. HbA_{1c} goals. Recent recommendations from the ADA propose a

goal HbA_{1c} of <7.0%, while the AACE recommends tighter control, with goal HbA_{1c} of <6.5%. Additionally, the AACE, in its 2015 practice guidelines, recommends fasting plasma glucose concentration <110 mg/dL and 2-hour postprandial glucose concentration <140 mg/dL.

In a study by Monnier et al., investigators concluded that, in patients with HbA_{1c} >10.2%, fasting blood glucose levels contribute 70% to overall glycemia. In patients with HbA_{1c} <7.3%, the overall contribution of fasting glucose is only 30%. The contribution of fasting and postprandial blood glucose values to overall glycemia is approximately equal in patients with HbA_{1c} levels between 7.3% and 8.4%. Based on these findings, therapies for diabetes may be targeted at different types of blood glucose impairment depending on HbA_{1c}. In 2008, however, the ACCORD Trial (Action to Control Cardiovascular Disease in Diabetes) showed that too **aggressive attempts at control in patients with existing cardiovascular disease led to increased mortality**. In these patients then, a higher A_{1c} goal of 7.5% or higher is appropriate.

X. BLOOD GLUCOSE MONITORING

Home blood glucose monitoring permits adjustments of drugs and dosages; glycated Hg levels indicate whether the adjustments did or did not result in achieving the goal.

A. Home blood glucose monitoring. It is important that *all* diabetic patients have access to home blood glucose monitoring. Of course, it is also recommended that insulin-treated patients check their glucose level before administering insulin.

Patients whose blood glucose levels continue to be above target range on oral agents and/or once-daily insulin should be encouraged to check their blood glucose more frequently. Patients should also be encouraged to check their blood glucose if they suspect hypo- or hyperglycemia based on physical symptoms.

Blood glucose goals are as follows: morning fasting blood glucose 85 to 110 mg/dL; preprandial blood glucose <110 mg/dL; 1-hour postprandial <180 mg/dL; 2-hour postprandial <140 mg/dL. Home blood glucose monitoring at various times should assist the provider to determine **(a)** which medications should be used, **(b)** when patients should be taking their medicines, and **(c)** what the doses

should be, regardless of whether treatment is an oral agent or insulin.

B. Glycated Hg testing

1. **Gestational diabetes.** The higher the glycated Hg level, the higher was the congenital malformation rate. With >12% glycated Hg levels, offspring from diabetic mothers had a 15% malformation rate, and with a glycated Hg level <8% or normal for the assay used, the malformation rate was the same as for offspring from nondiabetic mothers, at 1.5%. The glycated Hg level was a good measure of the potential for chronic diabetic complications.
2. **Complications.** Chronic diabetes complications are a manifestation of increased blood glucose levels, measured most effectively as elevated glycated Hg levels. Furthermore, it has been shown that complication rates increase very sharply after the glycated Hg exceeds 8% for eye disease and 9% for microalbuminuria.
3. **Frequency of testing.** HbA_{1c} should be checked every 3 months as a measure of the patient's longer term blood glucose control. As mentioned earlier, if a discrepancy is noted between the patient's fasting blood glucose and A_{1c} values, p. 758p. 759postprandial blood glucoses should be measured. For example, if the HbA_{1c} is 6.4%, the average blood glucose is 110 mg/dL; an HbA_{1c} of 7.2% correlates with a blood glucose of 150 mg/dL; an HbA_{1c} of 9.2% correlates with a blood glucose of 230 mg/dL, and so on.
4. **Errors.** The glycated Hg test can be **altered by significant anemia, hemoglobinopathies** (including hemoglobins C, D, and S), and in any condition that reduces the lifespan of erythrocytes. Other substances may cause falsely high HbA_{1c} values. These include prehemoglobin A_{1c} (reversible aldimine intermediate), carbamylated Hg (uremia), or Hg F.
5. **Fructosamine test.** If a measure of blood glucose values over a shorter period of time is desired or abnormal Hg or hemoglobinopathies exist, a serum fructosamine may be measured. Fructosamine is formed by nonenzymatic glycosylation of serum proteins (predominantly albumin), which have **a much shorter**

half-life than erythrocytes, 14 to 21 days. This test may be affected by low albumin states. It is important to note that fructosamine has not been standardized to the degree that HbA_{1c} has and is not accepted as useful by all investigators.

XI. THERAPY

Therapy should be tailored to each individual patient. Multiple algorithms have been proposed for the stepped-care treatment of patients with type 2 diabetes. Specific protocols can be found through the ADA or AACE.

A. Diet and exercise. Lifestyle modifications are the initial therapy for the prevention and treatment of newly diagnosed T2DM. Weight loss and reduction in adipose tissue, especially abdominal obesity, decreases insulin resistance. Weight loss has been proven to reduce the amount and dosage of medications needed to control hyperglycemia and potential complication of T2DM.

B. Medications. Although the initial treatment for diabetes is often monotherapy, most patients eventually require combination therapy. Based on the mechanism of action, medications may be split into three categories: (a) medications to help overcome insulin resistance or insulin sensitizers (e.g., biguanides, thiazolidinediones [TZDs]); (b) medications to help with the β-cell defect (e.g., sulfonylureas, meglitinides/amylin analogs, incretin mimetics, dipeptidyl-peptidase 4 [DPP-4] inhibitors); and (c) medications that target the reabsorption of glucose (e.g., sodium-glucose cotransporter-2 [SGLT-2] inhibitor). I would include insulin in category 2, but others may describe it as category 4.

1. **Biguanides (metformin).** Metformin is often the **initial choice** of medication for patients with newly diagnosed diabetes characterized by insulin resistance. However, it is important to remember that this may not be the right choice for all patients, especially if the patient appears to have more β-cell dysfunction than insulin resistance.
   a. **Mechanism of action.** Metformin acts primarily by **reducing hepatic gluconeogenesis** in the presence of insulin. It takes 1 to 2 weeks for the effects of the medication to begin. Therefore, biguanides will not immediately decrease blood glucose values. Because this medication functions independently of β-cell activity, it **does not produce hypoglycemia**. An additional benefit of metformin is **weight**

loss. Studies have also shown that the use of metformin may decrease HbA_{1c} by 1% to 1.5%.

b. **Adverse reactions.** The potential adverse reactions to metformin include gastrointestinal upset, including nausea, diarrhea, and abdominal pain. For most patients, these side effects abate with long-term use of the medication. Metformin should be avoided in patients with impaired renal function because it may lead to an increased risk of medication-associated lactic acidosis. This medication should also be **avoided in patients of advanced age (>80 years old)** and in those with hepatic dysfunction, metabolic acidosis, dehydration, or alcoholism. It is also advised that metformin be **withheld prior to contrast studies or surgery**, when the patient is at a higher risk of developing renal insufficiency. The medication should be **held for 48 hours following the procedure**, or longer if renal insufficiency develops.

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c. **Indications.** Metformin may be used as monotherapy or in combination with sulfonylureas, TZDs, insulins, incretin mimetics, DPP-4 inhibitors, or SGLT-2 inhibitors.

2. **TZDs**

a. **Controversies.** *The New England Journal of Medicine* in 2007, described an **increased risk of myocardial infarction in patients using rosiglitazone** compared with a control group (OR, 1.43; 95% CI 1.03 to 1.98; $p < 0.03$). However, these findings did not extend to the entire class of medications. Results recently published from IRIS (Insulin Resistance Intervention After Stroke) trial by Kernan et al., in the *New England Journal of Medicine* in 2016, showed that in insulin resistant patients who had recent ischemic strokes or transient ischemic attacks randomized to **pioglitazone** 45 mg daily for 4.8 years, actually had less incidents of stroke or myocardial infarction (9.0% vs. 11.8%).

b. **Mechanisms of action.** TZDs appear to function by **increasing insulin sensitivity in the liver and peripheral tissues**. Currently, two thiazolidinedione medications are commercially available, rosiglitazone and

pioglitazone. The TZDs are pharmacologic ligands that bind to and activate peroxisome proliferator–activated receptors (PPARs), which in turn regulate gene expression in response to ligand binding. Specifically, these drugs interact with PPAR-γ nuclear receptors, which are responsible for the transcription of various genes that regulate carbohydrate and lipid metabolism. It is presumably through this process that TZDs increase insulin-stimulated glucose uptake into skeletal muscles.

Of note, PPAR-γ is found predominantly in adipose tissue, pancreatic β-cells, vascular endothelium, and macrophages. This may explain why, in addition to lowering blood glucose, TZDs have also demonstrated modest **reductions in blood pressure, enhanced fibrinolysis, and improved endothelial function. TZDs may also help preserve pancreatic β-cell function.**

c. Indications. TZDs lower HbA_{1c} comparably to the biguanides and sulfonylureas. They are approved for monotherapy or in combination with metformin, sulfonylureas, DPP-4 inhibitors, or insulin.

d. Adverse effects. Although TZDs are widely considered to be very effective medications, when choosing therapy with these drugs, a myriad of potential adverse effects must be considered. These include **weight gain** (time- and dose-dependent), **fluid retention, heart failure, decreased bone density, increased fracture risk,** and **increased bladder cancer risk**.

3. Secretagogues (sulfonylureas and glinides)

a. Sulfonylureas. This class of medications includes **glipizide, glyburide, and glimepiride**, among others.

i. Mechanisms of action. Sulfonylureas act by **increasing insulin secretion from the pancreatic β cells**. More specifically, these drugs bind to the sulfonylurea receptors on the β cells, leading to the closure of voltage-dependent potassium adenosine triphosphate (ATP) channels. This facilitates cell-membrane depolarization, calcium entry into the cell, and subsequent insulin release. Sulfonylurea therapy may reduce HbA_{1c} by 1% to 2%.

ii. **Adverse effects.** Because of the increase in insulin release, sulfonylurea medications may induce **hypoglycemia**. In addition, because these medications are cleared by the liver and kidneys, they should be used with caution in patients with hepatic or renal insufficiency.

Glyburide is known to cause more weight gain compared with other sulfonylureas. Glyburide is also thought to cause more hypoglycemia, making glimepiride or glipizide a better choice in patients such as the elderly, in whom hypoglycemia can be more dangerous.

iii. **Indications.** These medications are approved for monotherapy and for combination treatment with most other oral medications and insulin.

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4. **Glinides**

a. **Mechanisms of action.** Similar to the sulfonylureas, the glinides **increase insulin secretion from the pancreatic β cells**. These medications differ in that glinides have a much shorter duration of action. When taken at meal times, these medications **improve prandial insulin release, decreasing postprandial hyperglycemia**. Given their short duration of action, they also decrease the risk of hypoglycemia during the late postprandial phase, which may occur with sulfonylureas, because their effect on insulin release has largely diminished by that time. This said, **hypoglycemia** can certainly occur with these medications.

Of the two available glinides, repaglinide and nateglinide, the latter seems to be somewhat less potent.

b. **Adverse effects.** Both repaglinide and nateglinide are metabolized by the liver and excreted by the kidneys and should be used with caution in patients with hepatic insufficiency and dose-adjusted in patients with severe renal insufficiency. Of note, repaglinide is only minimally cleared by the kidneys and may be safe for use in patients with renal impairment.

c. **Indications.** Glinides are often beneficial early on in the care of diabetes, or in patients with HbA_{1c} <7.2% when control of postprandial hyperglycemia is of greater concern. Coupled with

an insulin sensitizer, they can be helpful in curtailing glucose fluctuations associated with eating.

5. **α-Glucosidase inhibitors**
   a. **Mechanisms of action.** α-Glucosidase inhibitors, including acarbose and miglitol, lower blood glucose by **slowing the absorption of carbohydrates** from the gastrointestinal tract. Specifically, they competitively inhibit the enzyme in the small intestine that is responsible for breaking down disaccharides and more complex carbohydrates, delaying their absorption and attenuating postprandial blood glucose elevations. α-Glucosidase inhibitors have been shown to decrease HbA_{1c} by 0.55% to 1%.
   b. **Adverse effects.** Adverse effects include **abdominal discomfort**, flatulence, and diarrhea.
   c. **Indications.** These agents are approved for use as monotherapy or in combination with sulfonylureas.
   These medications are not tremendously effective in controlling blood glucose values and should really be considered only as **adjunctive therapy**.
6. **Amylin analog (pramlintide)**
   a. **Mechanisms of action.** Amylin is a hormone that is **cosecreted with insulin by the pancreatic β cells**. It regulates glucose levels by **suppressing glucagon release**, delaying gastric emptying, and possibly reducing appetite. Pramlintide is a synthetic analog of amylin. In studies, when used as an adjunctive therapy for patients using prandial insulin, it has been shown to reduce postprandial blood glucose excursions, improve weight control, and reduce HbA_{1c} more than in patients taking insulin alone. **When starting pramlintide**, patients should **reduce** their **prandial insulin doses by 50% to prevent hypoglycemia**.
   b. **Adverse effects.** Pramlintide should not be used in patients with gastroparesis or in those who are unable to sense hypoglycemia.
7. **Incretin mimetics/GLP-1 receptor agonists**
   a. **Mechanisms of action.** This new class of medications, including exenatide, liraglutide, albiglutide, and dulaglutide, mimics the effects of human incretin hormone GLP-1. GLP-1 or

incretins are secreted in response to food intake and work via multiple mechanisms, including **enhancing glucose-stimulated insulin release, inhibiting the release of glucagon after meals, delaying absorption of nutrients, and causing the sensation of satiety**.

Incretin mimetics have been shown to decrease HbA_{1c} by 0.78% to 1.9%.

b. **Indications.** Incretin mimetics is indicated for combination therapy with metformin and sulfonylurea, thiazolidinedione, SGLT-2 inhibitor, or insulin. p. 761p. 762Exenatide can be administered via twice-daily (Byetta) or via once-weekly (Bydureon) subcutaneous injections. Liraglutide and lixisenatide are once-daily injectables, whereas albiglutide and dulaglutide are once-weekly. This class of medication has also been shown to produce modest weight loss and decreased appetite. Therefore, in patients who would benefit from additional weight loss, this may be a good choice.

c. **Adverse effects.** Adverse effects include gastrointestinal upset, nausea, vomiting, diarrhea, dizziness, headache, and feeling jittery. Slow titration of the medication dose may help mitigate these side effects. New studies have suggested a possible increased incidence of pancreatitis in patients using incretin mimetics. Thus, although no final conclusion has reached regarding a causal relationship between incretin mimetics and pancreatitis at this time, pancreatitis should be considered in the differential diagnosis when patients on exenatide complain of abdominal pain.

8. **DPP-4**

a. **Mechanisms of action.** DPP-4 inhibitors (DPP4-Is), including sitagliptin, saxagliptin, linagliptin, alogliptin, slow the inactivation of incretin hormones. GLP-1 has a half-life of 1 minute in the circulation. DPP4-I inhibits DPP-4, which is responsible for degrading this hormone and hence allows higher levels to accumulate. The mechanism of the incretin hormones has been described previously. As a result of the aforementioned actions, DPP4-Is help target postprandial glucose elevations but have also been demonstrated to reduce

fasting blood glucose values.

b. Indications. DPP4-I, as a once-daily pill, is the commercially available form. They have been approved for monotherapy as well as in combination with metformin, TZDs, sulfonylureas, incretin mimetics, and SGLT-2 inhibitors. DPP4-Is have been shown to decrease HbA_{1c} by 0.48% to 0.7%. They also have the advantages of **low hypoglycemic** risks and less weight gain. These results make DDP4-I a reasonable alternative to sulfonylurea therapy.

DDP4-I should be considered for patients who need some additional help in reaching blood glucose goals. Their affects are less dramatic than those of incretin mimetics.

c. Adverse effects. There are few side effects associated with DPP4-I. In Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), there were **no significant differences between placebo and sitagliptin group in rates of cardiovascular events, hospitalization for heart failure**, acute pancreatitis, or pancreatic cancer. However, in Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolytic in Myocardial Infarction 53 (SAVOR-TIME 53) trial, type 2 diabetic patients with high cardiovascular risk factors or a history of cardiovascular disease randomly assigned to saxagliptin group experienced **higher risk of hospitalization for heart failure** during the first-year follow-up. Therefore, while on-going studies trying to further investigate this risk, DPP4-I should be used with caution in patients with heart failure.

9. SGLT-2 inhibitor

a. Mechanisms of action. The newest class of diabetic medications includes canagliflozin, empagliflozin, and dapagliflozin. SGLT-2 is a sodium-dependent glucose transporter protein located in the **proximal tubule in the kidneys**. It is responsible for about **90% of glucose reabsorption**. Thus, **inhibition of SGLT-2 leads to an increase in renal glucose excretion**, resulting in lower plasma blood glucose levels. SGLT-2 inhibitors also have been shown to increase insulin sensitivity, decrease gluconeogenesis, and improve insulin secretion from pancreatic β cells.

b. Indications. SGLT-2 inhibitors' mechanism of action is independent of insulin action and, thus, can be used throughout all stages of β-cell loss. SGLT-2 inhibitors have been reported to decrease HbA_{1c} by 0.5% to 1.0% as monotherapy and have additive effects when used in combination with other diabetic medications (metformin, TZDs, sulfonylureas, incretin mimetics, DPP4-I and, p. 762p. 763with caution, insulin). They also have the advantages of modest weight **blood pressure reduction**. The most exciting possible benefits of SGLT-2 inhibitors are the ability to **reduce the risks of cardiovascular mortality**, hospital admission for heart failure, all-cause mortality, and slower progression of kidney disease when empagliflozin is added to standard care in type 2 diabetes at high cardiovascular risk (EMPA-REG OUTCOME trial).

c. Adverse effects. SGLT-2 inhibitors are **not recommended for patients with severe renal impairment** (eGFR < 45). The most common reported side effects are vaginal **yeast infections** and **urinary tract infections**, especially in women. Other adverse effects include mild increase in both low-density lipoprotein and HDL cholesterol, increased risks of bone fracture, and possible risks of liver damage, breast cancer, and bladder cancers (dapagliflozin only). Finally, SGLT-2 inhibitors are contraindicated in type 1 diabetes because of risks of normal euglycemic ketoacidosis (Table 55-6).

10. **Insulin therapy for type 2 diabetes.** Our current understanding of type 2 diabetes, emanating from the UKPDS and other studies suggests that **most diabetics will eventually require insulin therapy** as a consequence of progressive β-cell loss. Some of the newer agents are suggested to reverse or slow this trend, but the data are still very preliminary and often derived from studies of rodent islets, which may not be a good model for human islets. Unlike the situation with type 1 diabetes, about which there is general agreement that basal bolus insulin therapy is the standard, there are still questions as to how to initiate and use insulin in type 2 diabetes. Five different approaches are currently most common:

a. Bedtime NPH insulin
b. Bedtime long-acting basal insulin, either glargine, detemir, or degludec
c. Premixed insulin analog, either Novolog 70/30 or Humalog 75/25 or 50/50
d. Preprandial rapid-acting insulin without basal insulin
e. Full basal bolus therapy

In addition, oral agents are often used in conjunction with many of these approaches. And the same patient may require different approaches at different stages of β-cell loss. Each of these approaches has advantages and disadvantages.

i. **Bedtime NPH therapy.** Human NPH has a **peak action of 5 hours** and a **duration of action of 12 hours**. These time intervals or durations of action, as with all insulins with the exception of the rapidly acting analogs, increase with increasing dosage. The usual **starting dose is 10 U**, which is then titrated up as needed to **produce a normal fasting blood sugar** while avoiding nocturnal hypoglycemia. When given at bedtime, NPH is primarily designed to produce a normal fasting glucose. Following the administration of a nighttime dose of NPH, there is little benefit on the subsequent daytime prandial glucose levels. For this reason, **treatment with an oral secretagogue is also necessary**. This approach is only successful if the patient still has endogenous insulin production. The disadvantages of this approach are twofold: First, the peak effect of NPH occurs at 5 hours with many dosages, increasing the risk of **nocturnal hypoglycemia**. Second, because NPH is a suspension rather than a solution, NPH insulin has greater variability than the basal analogs. This effect may be exaggerated if there is inadequate mixing prior to the insulin being drawn up. An advantage of NPH insulin is lower cost than for the newer basal analogs.

ii. **Bedtime basal insulin analogs**. The three currently available basal insulin analogs, glargine, detemir, or degludec, can also be given at bedtime to control fasting blood sugar. They **differ from NPH in that they produce less of a peak and have a longer duration of action**. Again, the duration of action is dependent on

the dosage. Studies have clearly shown that patient-reported symptomatic hypoglycemia is less with these insulins than with NPH, although few studies have evaluated absolute rates of hypoglycemia. This effect may be explained by the absence of a peak of action, causing less dramatic drops in blood glucose. Therefore, p. 763p. 764 p. 764p. 765the rates of glucose fall will be less severe and thus less likely to produce a catecholamine surge and subsequent adrenergic symptoms even at the same ultimate glucose level.

TABLE 55-6 Medications for Type 2 Diabetes Mellitus

Class/Name	Mechanism of Action	Hypoglycemia?	Caution
Sulfonylureas (tolbutamide, chlorpropamide, tolazamide, acetohexamide, glipizide [Glucotrol], glyburide, glimepiride)	Insulin secretagogue, improves β-cell function	Yes	Weight gain, hypoglycemia, caution if hepatic or renal dysfunction (may prolong duration)
Meglitinides (repaglinide [Prandin], nateglinide [Starlix])	Also insulin secretagogue, but fast onset and short duration of action	Yes	As above, must take before meal
Biguanides (metformin [Glucophage])	Insulin sensitizer, decrease hepatic glucose output and increase peripheral glucose uptake and usage	No	Lactic acidosis (esp. if renal, hepatic, or cardiac dysfunction); hold doses prior to IV contrast, GI disturbances common
α-Glucosidase inhibitors (acarbose, miglitol [Glyset])	Inhibit GI tract enzymes that digest oligosaccharides, thus delaying glucose absorption	No	Flatulence, diarrhea; warn patients they cannot treat hypoglycemia via usual mechanisms
Thiazolidinediones	Bind to nuclear receptors	No	Idiosyncratic

(rosiglitazone [Avandia], pioglitazone [Actos])	(peroxisome proliferator–activated receptors), enhance expression of proteins that enhance cellular insulin action		hepatic failure; ↑LDL levels; weight gain; fluid retention (caution in CHF)
GLP-1 Mimetics (exenatide [Byetta, Bydureon], liraglutide [Victoza], albiglutid [Tanzeum], and dulaglutide [Trulicity])	Main mechanism of action is the stimulation of glucose-dependent insulin release from the pancreatic islet cells; also reduces the secretion of glucagons	No	May slow gastric emptying and cause nausea; Mild to moderate hypoglycemia may occur when given with sulfonylureas
DPP4 inhibitors (sitagliptin [Januvia], saxagliptin [Onglyza], linagliptin [Tradjenta], alogliptin [Nesina])	Function as “incretin enhancers,” inhibiting DPP4, an enzyme that breaks down GLP-1.	No	Hypoglycemia may occur when used with other agents
SGLT-2 inhibitor (canagliflozin [Invokana], empagliflozin [Jardiance], and dapagliflozin [Farxiga])	Inhibition of SGLT-2 transporter in kidney to reduce the reabsorption of glucose	Yes	Hypoglycemia may occur when used with sulfonylureas; initial reduction in renal function; normal euglycemic ketoacidosis

CHF, congestive heart failure; DPP-4, dipeptidyl-peptidase 4; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; IV, intravenous; LDL, low-density lipoprotein; SGLT-2, sodium-glucose cotransporter-2.

What can be either an advantage or a disadvantage is the greater increase in daytime basal rates consequent to the longer duration of action of the basal insulin analogs compared with NPH insulin. In patients with significant β-cell loss, this longer duration of action is an advantage when there is daytime basal insulin deficiency. In the type 2 diabetic who is continuing to gain weight, increased daytime basal insulin may be a disadvantage. Again, when

providing basal insulin levels, these analogs should **not provide prandial coverage and hence a secretagogue and adequate residual insulin-secretory capacity is necessary to maintain euglycemia**. At very high doses, some prandial insulin coverage may be present, but only at the risk of excessive basal insulin coverage with the probability of either weight gain, intermeal hypoglycemia, or both.

iii. **Premixed insulin analogs, including 70/30 (Novo), 75/25 (Lilly), and 50/50 (Lilly).** Premixed insulin analogs are mixtures of a rapid-acting analog and protamine formulated to produce a ratio of 70% protomated analog plus 30% free analog, 75% protamine analog plus 25% free analog, or 50% protamine analog plus 50% free analog. Insulin mixed analogs provide mealtime free analog insulin along with protomated analog for longer duration of action to cover the postpraudial period.

These protomated analogs behave similarly to protomated regular insulin, that is, NPH insulin, with some important differences. They are usually given before breakfast and dinner; in some studies, a third dose was also given before lunch. No data have been released on the action of the protomated rapid-acting analog alone. The advantage is **premeal insulin coverage at breakfast and dinner with some basal coverage** because of the protomated analog. The use of these analogs helps to **avoid the problem of requiring an insulin secretagogue to cover the expected prandial rise** in blood sugar as well as limiting the number of injections a patient must administer on a daily basis.

The major **disadvantages** are similar but more severe compared with those described for bedtime NPH. The protomated analog taken even earlier, that is, at dinner, is even **less likely to provide sufficient insulin to control fasting blood sugar overnight. Nocturnal hypoglycemia** is also a risk based on the kinetics of the protomated analog. A further risk is hypoglycemia before lunch, because use of the protomated analog at breakfast requires a carbohydrate meal 5 hours after administration.

For patients in whom regular PO intake cannot be guaranteed, premixes should be used with caution.

iv. **Preprandial rapid-acting analog only.** Most studies of insulin secretion in type 2 diabetes have shown the loss of prandial insulin occurring before the loss of basal insulin. It therefore seems logical that insulin replacement should start with prandial insulin, with basal insulin added later on, as needed. The risk of hypoglycemia is less with these regimens because the use of insulin is always accompanied by food. To the degree that one believes glucose fluctuations are important factors in the development of complications, these regimens should have the benefit of avoiding postprandial hyperglycemia. Of note, most of these insulin regimens also involve the use of metformin to control fasting blood sugar.

v. **Full basal bolus therapy.** This regimen has the advantage of coming closest to replacing the body's physiologic insulin-secretory pattern. It requires the use of two types of insulin, a basal insulin as described in option **b** and preprandial insulin as described in option **d**. Finally, insulin pump therapy is not commonly used for type 2 diabetes but may become more so in the future.

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vi. **How to choose.** Which of the five options is chosen depends on the patient's and the physician's priorities. If minimizing the number of injections is the major concern, then bedtime NPH, glargine, detemir, degludec, or premixed analogs will be preferred. If avoidance of hypoglycemia is most important or if control of postprandial sugars is the priority, then preprandial or combination basal bolus therapy may be the appropriate method of management.

The success of any regimen depends on choosing the correct dose of insulin. The recommendations described are only starting points and must be individualized for each patient. **The average type 2 diabetic will require between 0.4 and 1.0 U of insulin per kilogram of body weight. Of this, half of the dose should be**

administered as basal and half as bolus. The latter should be divided into three doses and given at mealtimes. The correct basal dose is one that maintains the blood sugar and does not cause it to either rise or fall, in the absence of food. This requires titrating the dose overnight as well as during the day. Only titrating the dose to achieve a normal fasting blood sugar without monitoring the bedtime blood sugar will often result in higher-than-desired basal rates, which are associated with weight gain and hypoglycemia. The rapid-acting analog dose should be titrated by observing the rise in blood sugar from fasting until 1 to 2 hours after the meal.

XII. CONCLUSION

T2DM is rapidly increasing in prevalence. The financial burden of this disease exceeds $245 billion per year. More important, early diagnosis and effective management of this condition can greatly improve the associated complication rates and quality of life of patients.

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56 Glucose Control in Glucocorticoid-Induced Hyperglycemia

Norman Lavin

Hyperglycemia in a patient who is hospitalized can occur for many reasons, including undiagnosed diabetes, physiologic stress, glucocorticoids, withholding of diabetes medications, poor diabetes control, or a combination of these factors. Unfortunately, hyperglycemia is often associated with an increased risk of complications, longer hospital stay, and even mortality. Recently, studies have been implemented on inpatient glucocorticoid-induced hyperglycemia management. In one study by Grommesh et al., a comparison was made between two protocols for achieving glycemic control on patients who experience glucocorticoid-induced hyperglycemia (blood glucose >180 mg/dL) as a result of greater than physiologic doses of glucocorticoids (>10 mg of prednisone or equivalent). The control group received the standard three-part insulin regimen of long-acting basal, rapid-acting bolus, and rapid-acting correction factor, and the experimental group was treated with NPH plus the standard three-part insulin regimen.

In their study group, 31 patients were randomized to the three-part insulin regimen group and 30 patients were randomized to the three-part insulin regimen group plus NPH. The study participants received one or more of four glucocorticoids: methylprednisolone, dexamethasone, prednisone, or hydrocortisone.

Glucocorticoids are commonly prescribed for patients with lung disorders and during cancer treatment, which frequently results in glucocorticoid-induced hyperglycemia. One study at a hospital found that 68 of 200 patients on a general medical ward with blood glucose readings >300 mg/dL were receiving glucocorticoids; but, of course, all patients who receive glucocorticoids do not develop hyperglycemia. Prednisone and prednisolone produce a glucose peak in 4 to 8 hours with a duration of 12 to 16 hours. Because dexamethasone has a longer duration of action, more frequent NPH dosing may be needed. The glucose lowering ability of NPH peaks in 6 to 7 hours and has a duration of 13

hours.

NPH insulin has been used previously for prednisone-induced hyperglycemia when oral diabetes agents were found to be ineffective to treat this problem. NPH was also used in a study for patients with cystic fibrosis who received methylprednisolone, and clinical effectiveness was reported.

Using a regimen of NPH plus the three-part insulin protocol may more effectively treat glucocorticoid-induced hyperglycemia than simply adjusting the three-part insulin protocol. If the long-acting insulin dose is increased too high for the classic patients on the three-part regimen on a once daily glucocorticoid regimen, they are at risk for hypoglycemia because the glucocorticoid's effects on blood glucose diminish after 16 hours, except dexamethasone. When administered at the same time, NPH's action times synchronize with a once daily glucocorticoid dosing regimen with less risk of hypoglycemia later in the day than a long-acting insulin regimen because the duration of action of NPH is shorter than the long-acting insulin (Table 56-1).

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TABLE 56-1 Dosing Recommendations for Glucocorticoid-Induced Hyperglycemia

Steroid Dose	NPH Insulin
2 mg Dexamethasone (Decadron)	3 units NPH SQ at same time as steroid dose
4 mg Dexamethasone (Decadron)	4 units NPH SQ at same time as steroid dose
50 mg Hydrocortisone (Solucortef)	4 units NPH SQ at same time as steroid dose
40 mg Solumedrol	4 units NPH SQ at same time as steroid dose
60 mg Solumedrol	6 units NPH SQ at same time as steroid dose
125 mg Solumedrol	8 units NPH SQ at same time as steroid dose

CONCLUSION

Hyperglycemia in the hospital setting is a serious concern, and standardized evidence-based insulin treatment protocols for glucocorticoid-induced hyperglycemia are needed. Adding NPH to a standard three-part insulin regimen (basal, bolus, and correction factor) may be an effective way to combat glucocorticoid-induced hyperglycemia, although further research is needed in a larger population to confirm these results and evaluate the safety of the protocol.

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57 Bariatric Surgery in Adults with Type 2 Diabetes

Ali Ardestani, Eric G. Sheu, and Ali Tavakkoli

INTRODUCTION

Obesity and its associated comorbidities are a major health concern in the United States, where two-thirds of the adult population is overweight or obese. Obesity is a major risk factor for developing type 2 diabetes (T2D). For instance, a woman with a body mass index (BMI) of 35 or higher is 38.8 times more likely to develop T2D than a woman with a BMI of less than 23. Multiple interventions are available to control T2D, but despite recent advances in patient management and pharmaceutical innovations, less than 60% of diabetic patients reach optimal glycemic control. Bariatric surgery is not only the most effective modality for sustained and significant weight loss, but it also one of the only modalities that brings T2D into remission and lowers the incidence of diabetes in those at risk.

I. BARIATRIC PROCEDURES

There are several bariatric procedures that cause significant weight loss and improvement in diabetes, including the laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), and biliopancreatic diversion (BPD). The most common procedures are SG and RYGB which are briefly described as follows:

A. SG: In this procedure, a major portion of the fundus and body of the stomach is resected. The remaining narrow vertical sleeve creates a significantly smaller stomach, which looks like and is about the size of a banana. SG was originally performed as the first step in the BPD operation to induce weight loss and decrease surgical risk in super obese patients. However, significant weight loss and improvement in comorbidities such as diabetes was observed, leading to the SG being performed as a stand-alone bariatric procedure. Furthermore, the relative technical simplicity and lower risk of longer term complications related to anatomy has led to the SG becoming the **most commonly performed bariatric operation in the United**

States.

B. RYGB: In this procedure, a small gastric pouch is created, and a loop of jejunum (Roux limb) is attached to this pouch. As a result, ingested food bypasses most of the stomach and the proximal part of the small bowel (biliopancreatic limb), which rejoins the Roux limb distally, forming the common limb where food delivered by the Roux limb and gastric, duodenal and pancreatic secretions from the biliopancreatic limb, meet. RYGB was until recently, the most performed bariatric procedure with the longest track-record, and is considered as the gold standard bariatric procedure.

C. Each operation has its own safety profile which tends to inversely correlate with effectiveness. For example, the LAGB is the least complex and least risky, but with the poorest weight loss and rate of diabetes improvement. Conversely, the RYGB is more complex, not only carrying a greater rate of short- and long-term complications, but also conferring excellent weight loss and rates of diabetes remission (Table 57-1). The SG lies in between the RYGB and band in safety and efficacy, and perhaps because of this balance, has been rapidly adopted over the last several years across the United States and worldwide.

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TABLE 57-1 Weight Loss and Diabetes Improvement Profile of the Common Bariatric Operations

	Laparoscopic Adjustable Gastric Banding	Sleeve Gastrectomy	Roux-en-Y Gastric Bypass	Biliopancreatic Diversion
Excess body weight loss[a] (%)	45–50	55–60	60–70	70–75
Diabetes remission in diabetes patients (%)	55	60	80	95
Diabetes remission in I-T2D patients (%)	20	NA	50	NA
Insulin cessation in I-T2D patients (%)	35	NA	60	NA

[a]Excess body weight is calculated based on differences in the actual body weight and ideal body weight.
NA, not available, that is, data from large population studies or meta-analyses were not available.

II. BARIATRIC SURGERY AND DIABETES

There are now multiple sources of scientific information that highlights the superiority of bariatric surgery in controlling diabetes, when compared with medical therapy.

A. Clinical Trials

There are a few principle randomized clinical trials that have directly compared bariatric surgery with intensive medical therapy. All of these studies have shown superior diabetes improvement in the surgical arm, however, due to the use of different definitions for diabetes remission and weight loss, direct comparison of the results is challenging. Here is a summary of these trials:

1. The Dixon et al. clinical trial recruited 60 diabetic obese patients and divided them into LAGB and medical therapy arms. In this trial, they defined diabetes remission as fasting glucose <126 mg/dL and HbA_{1c} <6.2% without antidiabetic medications. At the 2-year follow-up, 73% of the patients in the LAGB arm achieved remission of diabetes in comparison to 22% in the medical therapy arm. Patients with LAGB also experienced 20.0% body weight loss in comparison with 1.4% of the medical arm (equivalent to 62.5% of excess body weight loss in the LAGB arm compared with 4.3% in the medical arm). No serious complication was observed in either arm. It is worth noting that these results, achieved in the trial setting, were better than weight loss and diabetes remission observed in the systemic reviews of LAGB (Table 57-1).
2. The STAMPEDE trial included 150 patients with uncontrolled T2D and randomized them in three arms: medical therapy, SG, and RYGB; with the primary endpoint of diabetes remission as defined as HbA_{1c} ≤6% with or without use of medications. After 3 years of follow-up, 5% of patients in the medical therapy arm met the criteria for the primary endpoint, in comparison with 24% in the SG and 38% in the RYGB arms. The use of antidiabetic medication was also significantly lower in the surgical arms; 35% of the patients in the RYGB group and 20% of patients in the SG

group achieved the HbA_{1c} criteria without taking any antidiabetic medications. Also 65% of the patients in the surgical arms achieved HbA_{1c} ≤7, compared with 40% in the medical arm. In terms of weight loss, patients in the RYGB and SG arms experienced 24.5% and 21.1% body weight loss, respectively, in comparison with 4.2% in the medical therapy arm. When comparing the surgical procedures, the degree of weight loss between the procedures was similar, but the likelihood of stopping antidiabetic medications was higher following an RYGB when compared with SG.

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3. In another clinical trial by Mingrone et al., 60 obese patients with diabetes (with duration of over 5 years) were randomized into three arms: medical therapy, RYGB, and BPD. At 5-year follow-up, 37% in the RYGB and 63% in the BPD arms achieved diabetes remission (defined as HbA_{1c} ≤6.5% without antidiabetic medications). Overall, 42% of patients in the RYGB arm, 68% of patients in the BPD arm, and 37% patients in the medical arm were able to achieve HbA_{1c} ≤6.5% at the 5-year follow-up. Patients in the medical arm experienced 7% body weight loss, in comparison with 28% in the RYGB arm and 31% in the BPD arms. The risk of coronary heart disease was reduced in all groups; however, quality of life improved more dramatically in the surgical arms. Four (27%) patients in the medical arm experienced a major complication of diabetes (including a fatal myocardial infarction). There was no mortality in the surgical group; however, two patients required reoperations for incisional hernia and obstruction. Metabolic events (including iron deficiency anemia and osteopenia) were higher in the surgical arm. The study also noted that some of the patients, who had achieved diabetes remission after 2 years, had a recurrence of their disease by 5 years.
4. In a randomized study comparing RYGB and LAGB to medical therapy, after 3 years, complete (HbA_{1c} ≤5.7% without antidiabetic medications) or partial (HbA_{1c} ≤6.5% without antidiabetic medications) diabetes remission was achieved in 40% of RYGB, 29% of LAGB, and 0% of medical group (n = 18, 20, and 14, respectively; $p < 0.01$).

5. In another randomized study comparing maximal medial therapy to RYGB, SLIMM-T2D investigators showed that after 1 year, the RYGB group had a significantly higher rate of diabetes remission (defined as HbA_{1c} ≤6.5% regardless of use of antidiabetic medications) compared with the medical group (58% vs. 16%; n = 19 each group; $p < 0.05$).

B. Retrospective Studies and Meta-Analyses

Multiple retrospective studies and meta-analysis have confirmed the superiority of bariatric surgery for diabetes treatment. A recent meta-analysis of 4944 diabetic patients undergoing bariatric surgery showed that more than 70% of patients had remission of diabetes in the first few years after bariatric surgery.

Studies have shown that T2D in patients (even those who take insulin) is amenable to remission by bariatric surgery, and many of those who do not achieve remission, experience significant decreases in their antidiabetic medication or no longer require insulin postoperatively. Following RYGB, about a third of patients cease antidiabetic medications as early as 2 days postoperatively suggesting a weight-independent effect on diabetes.

In general, there is a higher rate of insulin cessation and diabetes remission in procedures that change the bowel anatomy (i.e., RYGB and BPD) in the early postoperative period. In contrast, patients who undergo procedures with only gastric restriction (LAGB and SG) mostly benefit from weight dependent improvement in T2D. In our study using the bariatric outcomes longitudinal database (BOLD) national database, more than 30% of T2D patients who undergo RYGB achieved clinical remission at 1 month (with less than 20% excess body weight loss), whereas less than 15% of LAGB patients experienced diabetes remission with a similar degree of weight loss. At 1 year RYGB patients experienced more than 60% excess body weight loss and more than 60% of patients achieved clinical T2D remission (about double the LAGB patients) (Fig. 57-1). Clinical remission of diabetes (cessation of all antidiabetic medications) also occurred in 50% of insulin-treated type-2 diabetic (I-T2D) patients which is considerably higher than 20% in LAGB patients but lower than the 70% to 80% observed in all diabetic patients who undergo bariatric surgery.

III. BARIATRIC SURGERY IN I-T2D PATIENTS

Insulin therapy is a major component of diabetes management, and about 30% of diabetic patients utilize insulin for glycemic control which has been relatively stable since 1988. Whereas in patients with type 1 diabetes (T1D), intensive management with insulin and continuous glucose monitoring is first-line therapy, in patients with T2D, insulin is not the initial recommended treatment. Most T2D patients begin with lifestyle

p. 771p. 772modifications followed by oral pharmacotherapy with Metformin. Insulin therapy is then considered in those with markedly elevated blood glucose levels or A_{1c} and those who fail to achieve or maintain the A_{1c} target on noninsulin therapy. Furthermore, owing to the progressive nature of the T2D, many patients will eventually require insulin therapy as a consequence of gradual β cell loss. Despite recent advances in insulin delivery devices, insulin treatment remains challenging due to complexity of dosing and administration. There are also risks associated with insulin therapy, for example, weight gain and hypoglycemia. It is estimated that insulin therapy cost 6 billion dollars in the United States in 2012 and hypoglycemia contributes to about 30000 hospitalizations and 100000 emergency room visits annually in the United States.

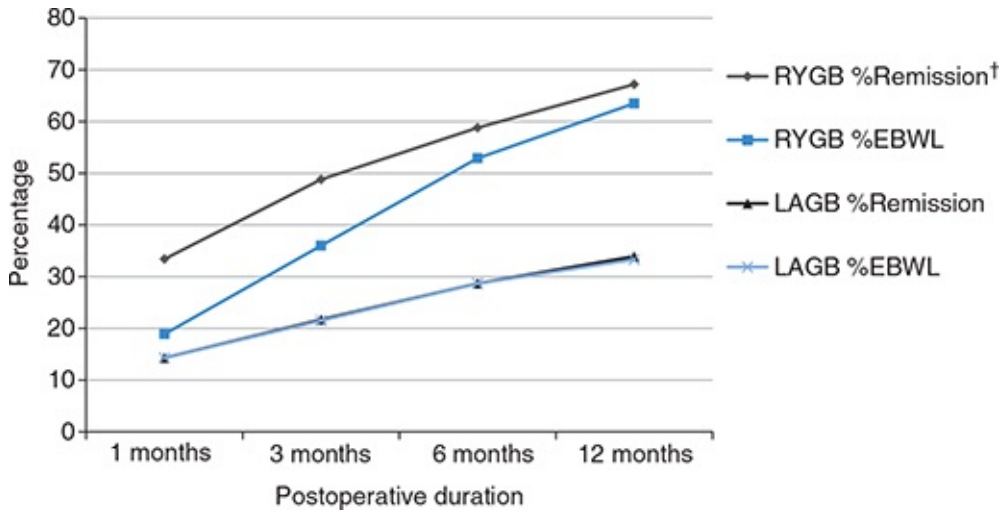

Figure 57-1. Comparison of percentage excess body weight loss (%EBWL) and percentage of patients in clinical remission (no longer require antidiabetic medication) following bariatric procedures ($p < 0.001$ for all comparisons between RYGB and LAGB) in over 30 000 diabetic patients from a national database. LAGB, laparoscopic adjustable gastric banding; RYGB, Roux-en-Y gastric bypass. †Remission defined as cessation of all antidiabetic medications.

Bariatric surgery has been shown to improve diabetes in I-T2D patients, but the benefits of bariatric surgery are attenuated to some degree in these patients. Although it has been shown that patients can successfully discontinue insulin up to 7 years after the operation, the average diabetes remission rate is about 50% in this patient population.

IV. PROGNOSTIC FACTORS

A. Baseline glycemia: Lower baseline glycemia (either blood glucose levels or A_{1c}) is a measure of (at least) partial preserved β cell function, and therefore patients who have lower glucose blood levels have a higher chance of insulin cessation and diabetes remission.

B. Diabetes duration: Similarly, shorter duration of diabetes increases the odds of β cell function restoration and consequently the odds of diabetes remission. This highlights the importance of performing surgery at early stages of diabetes before β cell reserve is completely depleted. Also, the likelihood of diabetes remission after surgery decreases with increased duration of insulin therapy, presumably caused by beta cell burnout. However, it has been shown that insulin dosing might be a better prognostic factor than diabetes duration for diabetes remission in I-T2D patients.

C. Weight loss: As highlighted before, weight loss plays a major role in increasing the odds of diabetes improvement. Several factors impact postoperative weight loss. The major factors include compliance with lifestyle changes (diet and exercise) after the surgery and the type of procedure. Another factor that has been shown to impact postoperative weight loss is preoperative BMI; patients with lower BMIs observe a higher reduction in their BMI. This effect is even more prominent with restrictive p. 772p. 773procedures such as LAGB and SG, and more important because diabetes improvement in these patients is more weight dependent. Overall, achieving and maintaining the optimal weight loss is an important predictor of diabetes improvement in the longer term (i.e., over 2 years after the surgery).

D. Procedure: Even with similar weight loss, there are some differences in insulin cessation and diabetes remission in T2D patients who undergo different procedures. This is summarized in Table 57-1. Some studies have shown diabetes improvement without significant weight loss, especially in diabetic overweight (but not obese) patients (30

kg/m^2 > BMI > 25 kg/m^2).

V. RELAPSE

About a **third of diabetic patients experience a relapse of their diabetes**, which occurs at a **median of 8 years after surgery**. This highlights the need for continuous glucose monitoring in all patients. However, the majority of patients are still capable of maintaining an HbA_{1c} <7 with proper management. The relapse rate is higher (adjusted hazard ratio of 1.9), and the duration of remission is shorter, for I-T2D patients. Greater pancreatic β cell loss and lower endogenous insulin secretion are among the factors that contribute to a reduced chance of diabetes remission, shorter remission duration, and higher rate of relapse in I-T2D patients.

VI. LONG-TERM CONSIDERATIONS

There are a few considerations regarding long-term effects of bariatric surgery. There is an increased risk of vitamin and mineral (mostly calcium and iron) deficiencies after bariatric surgery, particularly in RYGB and BPD. As a result, these patients are more prone to developing iron deficiency anemia and osteoporosis. Therefore, patients who undergo bariatric surgery require lifelong nutritional supplementation and monitoring. Another long-term effect is **hyperinsulinemic hypoglycemia** which has been reported in rare cases and is associated with an inappropriate insulin response. This type of hypoglycemia (in some cases) might be refractory to medical management and requires the reconstruction of gastroduodenal continuity.

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58 Diabetes Mellitus and the Geriatric Patient

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Diabetes mellitus is a common disease in the elderly population, which will continue to be of clinical significance as the aging population increases and thus does the prevalence of diabetes mellitus. According to the American Diabetes Association, the prevalence of diabetes mellitus in **seniors age 65 and older is 25.9%** or 11.8 million. The interaction of many factors, including increased body mass, decreased exercise, medications, coexisting illness, and insulin secretory defects associated with the aging process, all play a role in the development of alteration in glucose tolerance in older people. Elderly people with diabetes experience not only an increase in its associated morbidity and mortality, but also a decline in function and quality of life. Despite the high prevalence of diabetes and its associated morbidity and mortality in the aged, most studies on diabetes have focused on middle-aged subjects. Although there are many similarities between diabetes in middle-aged and elderly subjects, there are unique aspects of diabetes in the elderly.

I. PATHOPHYSIOLOGY OF HYPERGLYCEMIA OF AGING

Spence first described aging in association with increase in fasting and postprandial blood glucose levels. Some potential aspects of pathophysiology involved in the development of this "hyperglycemia of aging" are briefly discussed.

A. Metabolic changes and autoimmune abnormalities. Studies of lean and obese elderly diabetic patients have demonstrated absent first-phase insulin release in both groups in addition to impaired second-phase insulin release in lean elderly type 2 diabetics. Fasting insulin levels were increased in obese diabetic patients and normal in lean diabetic patients. Unlike middle-aged subjects, lean elderly type 2 diabetic patients seldom had resistance to insulin-mediated glucose disposal. However, consistent with the evidence in middle-aged subjects, marked resistance to insulin-mediated glucose disposal was observed in obese elderly type 2 diabetic patients. These data suggest

that an impairment in glucose-induced insulin release is the primary metabolic defect in lean elderly type 2 diabetics, whereas in obese elderly subjects, the primary abnormality is resistance to insulin-mediated glucose disposal, which often occurs in middle-aged persons with type 2 diabetes.

It is well known that autoimmune phenomena play an important role in the pancreatic β-cell failure in type 1 diabetics. Studies have shown that **autoimmune abnormalities** may also be an important contributing factor to the marked impairment in insulin release that occurs in a significant proportion of **elderly type 2 diabetics**. In a study of elderly type 2 diabetic patients age 65 and older, 12% had autoantibodies to glutamic acid decarboxylase 65 and/or islet antigen-2 and those who were autoantibody positive showed impairment in acute phase insulin secretion demonstrated with oral glucose tolerance test.

B. In the Health, Aging and Body Composition Study, increased levels of inflammatory markers (C-reactive protein [CRP], interleukin 6 [IL-6], tumor necrosis factor α [TNF-α]) were found in elderly diabetic patients aged 70 to 79 years. The study also found that among diabetics, those with poor glycemic control had higher levels of CRP.

C. Additional defect in noninsulin-mediated glucose uptake. Insulin-mediated and noninsulin-mediated-glucose uptake (NIMGU) are the two mechanisms by which the human body uses glucose. Under basal conditions, noninsulin-mediated glucose uptake occurs primarily in the central nervous system. During hyperglycemia, NIMGU p. 775p. 776is enhanced to a greater extent in skeletal muscle. It is increasingly recognized that alterations in NIMGU play an important role in the pathogenesis of disorders of carbohydrate metabolism. In a study of patients aged 75 and older utilizing glucose clamps and Octreotide to suppress endogenous insulin release, glucose uptake was similar in diabetic and nondiabetic patients, but glucose clearance was reduced in diabetic patients at fasting glucose levels. In the hyperglycemic state, glucose uptake and peripheral glucose effectiveness were reduced in diabetic patients. Therefore, the effect of glucose on glucose uptake is impaired in elderly patients with type 2 diabetes and interventions that enhance NIMGU in younger diabetics (decrease in free fatty acid levels, exercise, certain oral antihyperglycemic agents, and glucagon-like peptide-1) may have important therapeutic implications in the

management of the elderly population afflicted with diabetes.

D. Effects of leptin and amylin

1. **Leptin**. Leptin, a hormone **secreted by fat cells, is a major regulator of adiposity** leading to anorexia and increased metabolic rate. In rodents that fail to produce this hormone, leptin has been demonstrated to decrease food intake and cure the obesity of the congenitally obese mouse. In humans, the level of leptin in the blood correlates strongly with body weight, percentage of body fat, and body mass index. Abdominal fat cells appear to produce more leptin per cell than do fat cells in the thigh. An analysis of 15-year longitudinal data from the New Mexico Aging Process Study found that **leptin levels were highly correlated with the development of insulin resistance in older persons**. In addition to the relationship between leptin and waist-to-hip ratio, leptin levels are also influenced strongly by sex hormones. Overall, leptin levels are higher in the elderly but with gender variability with males having lower leptin levels compared with females. In men, there is a negative correlation between testosterone and leptin, with increasing leptin levels being associated with lower testosterone levels which can be reversed with testosterone treatment. Current data suggest that high leptin levels are at least a marker for insulin resistance and the hyperglycemia of aging and may actually play a role in the pathogenesis of metabolic syndrome.
2. **Amylin.** Amylin is a peptide hormone **secreted along with insulin from pancreatic β cells**. Its effects include the inhibition of the second phase of insulin secretion, inhibition of glucagon, increasing satiety, slowing of gastric emptying, and modulation of memory processing. Edwards et al. demonstrated that amylin secretion follows a U-shaped curve with higher levels in younger (age 20 to 40) and older (age 61 to 90) nondiabetic individuals and reduced levels in middle age (age 41 to 60) at the time of an increase in adiposity. With aging, the appropriate decrease in amylin is no longer maintained. Amylin and leptin levels have been found to be highly correlated with elevated postprandial glucose levels. **Amylin levels are high in elderly leading to insulin resistance**—increased glucose and increased amylin secretion leading to deficient insulin response in older individuals. Leptin and amylin have a synergistic effect.

II. METABOLIC SYNDROME

Metabolic syndrome, popularized by Reaven as syndrome X after the original description by Camus, is a cluster of cardiovascular risk factors, including components of hyperinsulinemia, hypertriglyceridemia, hypertension, hyperglycemia, hyperuricemia, and altered clotting factors. Metabolic syndrome is **more prevalent with increasing age**, affecting 44% of adults age 60 to 69 and 42% age 70 and older. The prevalence of metabolic syndrome increases with advancing age because of increases in body fat and obesity. Also, the development of metabolic syndrome reduces life expectancy in the elderly. The pathophysiology centers around insulin resistance that is affected largely by genetics and also environmental considerations such as central obesity, a sedentary lifestyle, and excess caloric intake. Complex interactions between proinflammatory and endocrine markers modulate insulin signaling. Promoters of insulin resistance including leptin, resistin, free fatty acids, and proinflammatory cytokines including IL-6 and TNF-α are balanced against insulin sensitizers such as adiponectin. Lipid is redistributed to muscle, p. 776p. 777bone marrow, and other tissue. The elderly population may be particularly susceptible to metabolic syndrome and insulin resistance because of the aging of the adipocytes leading to an inability to store lipids accompanied by body composition changes resulting in increased fat mass and lower muscle mass. The treatment for metabolic syndrome is aimed primarily at reducing long-term risk of cardiovascular disease and diabetes. Current guidelines recommend focusing on intensive therapeutic lifestyle interventions (such as increased physical activity, dietary modification, and modest weight reduction 5% to 15%) that address many of the metabolic risk factors in metabolic syndrome, including insulin resistance. When necessary, pharmacologic agents should be used to achieve recommended therapeutic target goals set forth by guidelines. Among nursing home residents, 50% have either diabetes mellitus or metabolic syndrome.

III. MONITORING OF LONG-TERM DIABETIC CONTROL

A. Glycosylated hemoglobin (see Chapter 67). Hemoglobin is a protein that transports oxygen throughout the body and is located inside red blood cells (RBCs). The lifespan of an RBC is 120 days, and therefore the lifespan of hemoglobin is directly related to the

lifespan of the RBC in which it resides. During the 120 days, hemoglobin is exposed to glucose in the circulation resulting in glycosylation, where glucose binds to its amino groups. This nonenzymatic chemical reaction where glucose binds to the terminal valine of the beta-globulin chain is referred to as hemoglobin A_{1c} (HbA_{1c}), the most widely used measure for monitoring diabetic control. However, any condition that interferes with the RBC lifespan will affect the HbA_{1c}, and this should be taken into consideration when interpreting the value. Conditions such as hereditary spherocytosis, hemolysis, sickle cell anemia, thalassemias, and acute/chronic blood loss all decrease the time of exposure of hemoglobin protein to circulating glucose, therefore decreasing the glycosylation process, which results in a falsely low HbA_{1c}. On the other hand, any condition that lengthens the lifespan of the RBC, such as vitamin B_{12} deficiency, folate-deficiency anemia, asplenia, iron deficiency, uremia, increases the glycosylation process, and results in a falsely elevated HbA_{1c}.

B. Fructosamine (see Chapter 67). Fructosamine is a glycosylated albumin that provides information on shorter periods (3 weeks) of diabetic control than does HbA_{1c} (3 months). Results differ between the two measurements mainly because of the difference in turnover times of the underlying glycosylation targets, hemoglobin versus serum proteins. Fructosamine is inexpensive and performs well in elderly diabetic subjects when corrected for albumin. However, certain conditions such as paraproteinemias and nephropathies may interfere with the result.

C. Hyperglycemic crises. There are **three typical types of hyperglycemic crises**: ketoacidotic, hyperosmolar hyperglycemic state, and lactic acidotic. Approximately 10% of elderly persons with new-onset diabetes manifest the type 1 form of the disease and therefore may present with ketoacidosis, which usually occurs in young subjects. Moreover, older persons with long-standing type 2 diabetes can develop pancreatic β-cell "exhaustion" and convert to type 1 diabetes. Therefore, mixed hyperosmolar ketotic states may be seen in these older persons with diabetes. The diagnosis of ketoacidosis is confirmed by detection of ketones in the blood. Urine ketones are often a nonspecific marker of starvation if an elderly diabetic subject has negative ketones in the blood.

D. Ketoacidosis. In a retrospective study, Malone et al. analyzed the characteristics of ketoacidosis unique to the elderly and found that elderly diabetics were less likely to be on insulin before hospitalization and required longer time duration and higher mean insulin doses to achieve blood glucoses <300 mg/dL. The mortality rate was much higher in older patients than in younger patients.

E. Hyperosmolar hyperglycemic state. The first cases of hyperosmolar coma were described by von Frerichs and Dreschfeld in 1880s. It occurs predominantly in elderly type 2 diabetics in whom dehydration and severe hyperglycemia may occur without development of ketoacidosis and is associated with high mortality rates of 10% to 20%. The diagnosis is made by a serum osmolality >320 mOsm/L and a glucose >600 mg/dL. Associated findings may include severe azotemia, lactic acidosis p. 777p. 778(giving a mixed presentation), and hypernatremia or hyponatremia (secondary to hyperglycemia inhibiting arginine vasopressin). Two possibilities exist, hyperglycemia-induced hyponatremia and also hyperglycemia inhibiting arginine vasopressin which leads to hypernatremia. The parenthetical refers to hyperglycemia leading to elevated arginine vasopressin and hyponatremia. Acute infection, including pneumonia and urinary tract infection, is the most common precipitating factor. Severe hyperosmolarity, residence in a nursing home, and advanced age are the major prognostic factors associated with death.

F. Hypoglycemia. In general, hypoglycemia occurs when the capillary blood glucose level is <70 mg/dL. Hypoglycemia is a serious complication of therapy in elderly patients with diabetes. The frequency of these episodes increases with tight glycemic control as assessed by HbA_{1c}. In the elderly, hypoglycemia can have serious consequences in terms of cardiovascular and cognitive function, and thus can be life-threatening, in addition to increasing morbidity and causing a decline in quality of life. The major reason that clinicians undertreat diabetes in the elderly population is the fear of hypoglycemia, although in reality severe hypoglycemia is relatively rare. Therefore, the risk of hypoglycemia must be evaluated and balanced against the potential benefit of tight glycemic control in each

individual. Elderly diabetics are at risk for hypoglycemic events because they tend to experience fewer symptoms. Hypoglycemic unawareness (see Chapter 53) can be related to intensification of the insulin therapy and to repeated episodes of hypoglycemia, leading to defective counterregulation that is reversible by strict avoidance of hypoglycemic events. This can be worsened by the duration of diabetes and the presence of autonomic neuropathy. In general, the consequences of hypoglycemia can be more serious in the elderly subject: increased risk of myocardial infarction, ventricular rhythm disorders, and stroke (in a population with an already high cardiovascular risk), as well as the risk of injury and fractures in a predisposed population. Other predisposing risk factors for severe hypoglycemia include advanced age, recent hospitalization, black race, polypharmacy (more than five medications), lack of self-monitoring, unawareness of symptoms, decreased counterregulatory hormones, missed meals, renal insufficiency, increased number of injections, and the use of short-acting sliding scale insulin scales. Prevention requires reinforced education, knowledge of symptoms and signs of hypoglycemia, and appropriate management treatment.

IV. PREVENTION OF LONG-TERM COMPLICATIONS

A. Microvascular. Microvascular complications include retinopathy, which can lead to various degrees of visual impairment; neuropathy, leading to pain and numbness, which is a risk for infected skin ulcers that can lead to amputations; and nephropathy, which can ultimately lead to renal failure. In one study, nearly 10% of subjects had experienced a microvascular complication by 9 years after diagnosis. Nearly half of the cost of treating type 2 diabetes complications has been attributed to microvascular complications. Although tight glycemic control has been clearly demonstrated to significantly decrease long-term complications of diabetes by the Diabetes Control and Complications trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), the question of whether similar outcomes would occur in elderly type 2 diabetics was left unanswered. The Veterans Affairs Cooperative Trial demonstrated the feasibility of tight glucose control in middle-aged and elderly diabetics. Studies show that progression of retinopathy is markedly decreased with good diabetic control in persons over the age of 60 years. Almost no retinopathy progression was found in patients with HbA_{1c} levels <7%. In a

retrospective cohort study of 250 patients with at least one microvascular complication, tight glycemic control was associated with reduced risk of additional complications in other organ systems. The Wisconsin Eye Study demonstrated that for each 1% decrease in HbA_{1c} in type 2 diabetes, there is an exponential decrease in long-term diabetic complications. These data strongly support the concept that tight glycemic control is also important in elderly diabetic patients even if the resulting effort results in only minor changes.

B. Macrovascular. Whether tight glycemic control reduces macrovascular complications of diabetes is still uncertain.

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V. GLUCOTOXICITY

Hyperglycemia causes numerous signs and symptoms in elderly diabetic patients.

A. Osmotic diuresis. Elevated glucose levels lead to a hyperosmolar diuresis, which has three major consequences: nocturia, incontinence, and dehydration. Older persons have an impaired ability to recognize thirst and thus a blunted response to osmotic changes. With diabetes-induced polyuria, the failure to have a normal thirst response leads to mild dehydration, which in turn leads to a generalized feeling of malaise and orthostatic hypotension, increasing the risk of falls and syncope. Incontinence in many older diabetics is not caused by autonomic neuropathy, but rather by polyuria similar to diuretic-induced incontinence.

Osmotic diuresis leads to:

1. Nocturia, dehydration, and orthostasis
2. Incontinence
3. Hyperosmolar state
4. Trace mineral loss; decreased zinc and magnesium

Hyperglycemia leads to a loss of trace elements in the urine. Older diabetics tend to be zinc deficient. **Zinc deficiency** becomes important when the diabetic patient develops peripheral vascular disease or pressure ulcers. In this situation, zinc replacement is important for healing the ulcer.

B. Cognitive defects. Studies have shown that hyperglycemia is associated with cognitive difficulties. There is a high prevalence of cognitive dysfunction, depression, and functional impairment among

elderly diabetic patients, which causes challenges in their management. Elderly diabetics should be screened for barriers to safe and effective diabetes control. Goals for diabetes control need to adjusted and simplified based on the patients' cognitive abilities. In diabetic mice, hyperglycemia interferes with memory retention, and a single insulin injection that normalizes glucose levels reverses the retention deficit. Evidence indicates that treatment of diabetes in older persons improved cognitive function.

C. Increased infections. Diabetes has been associated with various alterations in immune function including decreased innate response by way of polymorphonuclear leukocyte function in addition to depressed humoral response with regard to T-cell function. There is conflicting evidence regarding whether common and rare infections are more prevalent among patients with diabetes in comparison with the general population. Patients with diabetes appear to have an increased risk of asymptomatic bacterial urinary tract infections, and skin and mucous membrane infections, including *Candida* infections and infections of the foot. Epidemiologic studies support the fact that patients with diabetes are at high risk for complications, hospitalization, and death from influenza and pneumococcal disease. Studies have shown that influenza and pneumococcal vaccines in patients with diabetes have the potential to significantly reduce morbidity and mortality related to influenza and pneumococcal disease. The current recommendation regarding immunizations is that patients should receive the influenza vaccine yearly and the pneumonia vaccine. According to CDC 2016 guidelines, adults 65 years or older who have not previously received PCV13 should receive a dose of PCV13 first, followed 1 year later by a dose of PPSV23.

1. If the patient already received one or more doses of PPSV23, the dose of PCV13 should be given at least 1 year after they received the most recent dose of PPSV23.

   Despite national goals, immunization rates for at-risk patient groups remain low; therefore, implementation of effective strategies to identify at-risk patients and closely monitor their immunization record is needed.

D. Increased pain perception. Hyperglycemia is associated with an increased perception of painful stimuli because elevated glucose levels interfere with the ability of β-endorphin to bind to the opioid receptor and downregulate pain impulses. A classic population-based study

found some degree of neuropathy in 66% of patients with diabetes. Among those with type 1 and type 2 diabetes, 54% and 45%, respectively, had diabetic peripheral neuropathy, and 15% and 13%, respectively, had subjective complaints. Several studies have demonstrated that the duration of diabetes correlates strongly with the risk of developing peripheral neuropathy. In p. 779p. 780addition, intensive glycemic control (maintaining HbA_{1c} <7%), particularly when initiated early in the disease process, has also been shown to reduce the prevalence of diabetic peripheral neuropathy. Among patients with type 1 diabetes, intensive glucose control also delays or prevents the development of clinical manifestations of peripheral neuropathy. Comorbidities associated with diabetic peripheral neuropathy include sleep disturbance, depression, and interference with activities of daily living, which has a huge impact on quality of life. The **treatment of diabetic peripheral neuropathy** includes tricyclic antidepressants, anticonvulsants, and analgesics, but there are no strict guidelines for treatment. Hence, the treatment should be geared to each individual patient, and the benefits versus the adverse effects of medications should be assessed and discussed in detail with the patient before prescribing any medication for treatment. This is extremely important in the elderly, in whom polypharmacy, declining renal function, and decline in cognitive skills are issues that can cause adverse events when prescribing any of the above medications.

E. Decreased responsiveness to sulfonylureas. Finally, glucotoxicity can lead to sluggish islet-cell response to sulfonylureas. Lowering the circulating glucose level with insulin can result in improved responsiveness to sulfonylureas.

VI. DIABETES AND FUNCTION

Diabetes mellitus has been identified as a major cause of functional impairment and activities-of-daily-living dependence. Diabetics are at risk for developing frailty at an earlier age, a condition referring to a predisability state where an older person functioning near the disability threshold is susceptible to any stressor sending him or her into the disabled category. Frailty can be defined by the following acronym:

A. Fatigue

B. Resistance (cannot climb 1 flight of stairs)
C. Ambulation (cannot walk 1 block)
D. Illness (more than 5)
E. Loss of weight (<5% over 1 year or less)

Falls are common in frail older persons, particularly those who are also diabetic. According to one nursing home study, 35% of residents fell during a period of 299 days with the incidence of falling being notably higher in diabetics versus nondiabetics (78% vs. 30%). Abnormal gait and balance and diabetes independently predicted falls. It is hypothesized that uncontrolled glucose may lead to increased **accumulation of advanced glycosylation end products** in bone collagen, which may increase bone stiffness and fracture susceptibility. Hyperglycemia may impair calcium deposition and subsequent mineralization, which decreases bone quality and increases fracture risk. Some studies have also reported an increased risk of fractures with insulin treatment, which might be explained by the fact that insulin treatment may suggest a longer duration of disease or insulin use increases the risk of hypoglycemic events, leading to increased fall risk.

Diabetics also have a decline in muscle function and an age-related decline in muscle mass referred to as sarcopenia. Fatty infiltration of muscle (myosteatosis) decreases muscle strength and leads to increased morbidity and mortality.

VII. CONGESTIVE HEART FAILURE

The incidence of congestive heart failure (CHF) has doubled in diabetics compared with nondiabetics, and age is one of the major risk factors. The occurrence of CHF in diabetics is probably related to the degree of glycemic control. In some studies, **every 1% increase in HbA_{1c} corresponds to a 15% increase in the risk of developing CHF**. Of 31 600 U.S. subjects 65 years and older hospitalized for CHF, 27% of whom were 85 years or older, 40% were diabetics. Through advanced glycosylation end products, chronic hyperglycemia has a specific role in the pathophysiology of myocardial fibrosis leading to diastolic dysfunction. Theoretically, at least at an early stage, strict blood sugar control may attenuate left ventricular remodeling. However, at this time, there is no evidence of this benefit. The use of antihyperglycemic agents on cardiac function is unknown. However, the use of **metformin can be complicated by lactic acidosis in the setting of acute CHF**. The insulin-

sensitizing effects of thiazolidinediones may p. 780p. 781have a positive effect on the prevention or treatment of myocyte hypertrophy related to hyperinsulinemia. However, a major side effect of these drugs is water and salt retention, leading to edema and weight gain, which increases the risk of CHF by 1.6 to 1.8 times. Therefore, current recommendations **advise against prescribing glitazones** to subjects with known left ventricular dysfunction, despite the stage, or to discontinue them if symptoms of CHF develop.

In conclusion, age, diabetes, and arterial hypertension are risk factors for CHF. Myocardial changes that are seen with normal aging are similar to those seen in patients with diabetes, with diabetes considered an accelerator of aging. At this time, there is no evidence on how to treat diastolic dysfunction, and prevention should be optimized utilizing tight blood pressure and glucose control.

VIII. DEPRESSION IN ELDERLY DIABETICS

Several cross-sectional studies have found an increased risk in the prevalence of depression among those with diabetes, usually secondary to either poor glycemic control or diabetes-related complications. In a study of elderly diabetic patients, 33% had depressive symptoms along with functional disabilities and undiagnosed cognitive dysfunction all of which are barriers to glycemic control.

IX. SEXUAL DYSFUNCTION

It is estimated that 40% to 60% of men with diabetes have erectile dysfunction (ED). ED in diabetics is often multifactorial and can result from impaired blood flow, nerve damage, or psychological factors. It is very important to inquire about ED and to take a comprehensive history. A physical examination and a thorough laboratory investigation should be conducted, including a complete blood count, basal metabolic panel, lipid profile, HbA_{1c}, total testosterone, prolactin, luteinizing hormone (LH), and thyroid-stimulating hormone. An endocrinologist should be consulted if hyperprolactinemia, abnormal thyroid function tests, or a low to normal LH in the setting, where a morning total testosterone of <200 is detected. There are no studies to confirm that intensive glycemic control prevents the progression of other complications of diabetes mellitus. Improvement in ED can usually be achieved with a phosphodiesterase-5 inhibitor, for

example, sildenafil, intracavernosal administration of PGE1, or a vacuum device. If none of these treatments is effective, a surgical prosthesis should be considered as an alternative. Diabetes produces a **decrease in testosterone** levels in men, which accelerates the onset of the androgen deficiency in aging men (ADAM) syndrome. The ADAM syndrome is associated with ED, retrograde ejaculation, and decreased libido, as well as decreased strength and cognitive abnormalities. In women, diabetes may result in vaginal dryness and vaginal infections, particularly *Candida* infections.

X. THERAPEUTIC MANAGEMENT

Diabetes management in the geriatric population should involve an individualized approach taking into consideration a patient's functional limitations, cognitive abilities, comorbidities, polypharmacy, and living environment. Comorbidities and barriers to management of diabetes mellitus in the elderly are listed in Table 58-1.

A. Medical nutrition therapy (MNT). Therapeutic management of diabetes, both type 1 and type 2, in the general population aims initially toward lifestyle modification p. 781p. 782by way of MNT. The goal of MNT is glucose homeostasis by means of weight management, if not weight loss, usually by way of decreased intake and increased energy expenditure while maintaining sufficient macronutrient as well as micronutrient intake. Although these principles may be appropriately applied to young and middle-aged patients, MNT in the elderly population is less clear because of insufficient data.

TABLE 58-1 Comorbidities and Barriers in the Management of Diabetic Older Individuals

Hypertension	Dementia
Depression	Foot problems
Congestive heart failure	Increased frailty
Stroke	Immobility
Decreased vision	Impaired communication
Food and medication allergies	Incontinence

1. Diet. Dietary restriction and subsequent weight loss in the

geriatric patient result in **inadequate micronutrient intake and increased frailty**. Moreover, studies in long-term-care facilities have not shown any utility of dietary intervention to control diabetes. Another single study demonstrated increased mortality in older persons with diabetes who lose weight. To date, the American Diabetes Association guidelines **do not recommend a therapeutic diet for diabetics in nursing homes**.

2. **Exercise.** Exercise is a key component of diabetes management. Exercise physiology is based on the shift of fuel usage by the muscle from a fatty acid source to an energy source progression/combination that includes muscle glycogen, circulating glucose, and fatty acids. Glucose uptake continues long after the activity is ceased. Furthermore, exercise, independent of body weight, is effective in reducing HbA_{1c}. For the older diabetic patient, aerobic exercise may be challenging, if not dangerous, considering individual issues including vision impairment or peripheral neuropathy. On the other hand, resistance exercise in older persons is highly recommended. Resistance exercise training increases muscle mass and endurance while improving body composition and functional status. Increasing evidence shows beneficial effects of resistance training and results in improved overall glucose management.
3. **Teamwork approach.** The best results are seen with an interdisciplinary approach that involves, most importantly, the patient and/or the patient's family, as well as the physician, nutritionist, and ancillary nursing staff. The patient should be educated about the complications, both short-term and long-term, of poor glucose control. This promotes patient autonomy and prevents hospitalization and incurrence of substantial medical cost.

B. Medical therapeutics. Therapeutic focus in the long-term-care population shifts toward medical management, ranging from insulin to noninsulin therapies including oral and injectectable options listed in Table 58-2. These treatment options have different safety profiles in the geriatric patient. Most of these drugs are well studied in general populations but not in elderly populations, so it is vital to be careful in choosing the specific agent to be implemented and the specific patient who will be taking the agent.

1. **Insulin.** Insulin is often used when oral hypoglycemic agents fail

after a long period of time, and its institution is often too long delayed to produce optimal results. Insulin therapy tends to carry some unnecessary stigmata in the general population, as well as among medical professionals. However, insulin can produce predictable glucose control in the geriatric population if it is implemented correctly. Insulin preparations vary according to structure and resulting half-life. The most common insulin and insulin analog preparations are listed in Table 58-2. Insulin initiation should be tailored to the patient (i.e., renal function, hypoglycemic unawareness) and requires regular blood glucose monitoring. There are a number of different approaches to insulin use in long-term facilities. One common method is the basal-bolus regimen with a long-acting insulin and use of short- or rapid-acting insulin with meals. For those working in long-term-care facilities, attention to meal timing is important in preventing hypoglycemia. Multiple insulin mixtures (not listed), either intermediate/rapid or intermediate/short, exist. Insulin mixtures, although convenient, are inflexible and do not allow "fine tuning" of therapy leading to extreme peaks and valleys in glucose. It is also important to reassess any previous oral or injectable diabetic medication once insulin therapy is initiated, to avoid hypoglycemia.

2. **Sulfonylureas.** Sulfonylureas are a class of drugs that target hyperglycemia through **enhancing insulin secretion from the *β* cells of the pancreas**. Their principal target is the adenosine triphosphate (ATP)-sensitive potassium (K-ATP) channel of the *β*-cell membrane. Inhibition of this channel, by either glucose or sulfonylureas, results in the triggering and opening of voltage-gated p. 782p. 783calcium channels, leading to calcium influx into the cell and insulin exocytosis. Members of this class vary mainly in half-time and potency, depending largely on the level of K-ATP channel activity and its subunits. Sulfonylureas should be used cautiously in elderly patients, as well as in anyone with hepatic and renal failure, for fear of hypoglycemia. **Glipizide** is the **preferred sulfonylurea in the elderly** because of the fact it has the least risk of hypoglycemia. It is also the least dependent on renal function. **Glyburide** is typically avoided because of prolonged risk of hypoglycemia and weight gain.

TABLE 58-2 Currently Available Diabetes Treatment Options for the Geriatric Patient

Medical nutrition therapy	Includes education, exercise, and multidisciplinary team approach
Insulin and insulin analogs	Rapid acting • Insulin lispo (Humalog) • Insulin aspart (Novolog) • Insulin glulisine (Apidra) • Insulin U-200 (Humalog) Short acting • Regular (Humulin R, Novolin R) Intermediate acting • NPH (Humulin N, Novolin N) Humulin R (U-500) • 5× the potency of U-100 Long acting • Insulin glargine U-100 (Lantus) • Insulin glargine U-300 (Toujeo) • Insulin detemir (Levemir)
Oral Agents	
Inhaled insulin	Insulin human (Afrezza)
Sulfonylureas	Glipizide (Glucotrol) Glyburide (Diabeta, Glynase) Glimepiride (Amaryl)
Meglitinides	Nateglinide (Starlix) Repaglinide (Prandin)
Biguanides	Metformin (Glucophage, Glumetza, Fortamet)
Thiazolidinediones (TZDs)	Rosiglitazone (Avandia) Pioglitazone (Actos)
α-Glucosidase inhibitors	Acarbose (Precose) Miglitol (Glyset)
DPP IV inhibitors	Saxagliptin (Onglyza) Sitagliptan (Januvia) Linagliptin (Tradjenta) Alogliptin (Nesina)
GLP-1 agonists	Exenatide (Byetta, Bydureon) Liraglutide (Victoza) Albiglutide (Tanzeum) Dulaglutide (Trulicity)
SGLT2 inhibitors	Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance)

DPP IV, dipeptidyl peptidase IV; GLP-1, glucagon-like peptide 1; SGLT2, sodium glucose cotransporter 2.

3. **Meglitinides**. A class of insulin secretagogues with rapid onset and short half-life are the meglitinides. Side effects of meglitinides are quite similar to p. 783p. 784those of sulfonylureas, and the meglitinides should be used cautiously, if at all, in geriatric patients.
4. **Biguanides**. **Metformin** is the sole available member of the biguanide class. The exact mechanism of action was not previously known, but a recent study hypothesizes that it inhibits the redox shuttle enzyme mitochondrial glycerophosphate dehydrogenase ultimately **decreasing hepatic gluconeogenesis without having any effect on insulin secretion**. Metformin is widely used in the general obese type 2 diabetic population for these hepatic effects. Anorexia and weight loss are common side effects, although not desirable in the geriatric patient caused by the risk of frailty. Metformin is not recommended for use in persons over the age of 80 years or in persons with renal failure. Older persons frequently have muscle breakdown, or sarcopenia, that can mask renal insufficiency, further limiting its use in this population.
5. **Thiazolidinediones (TZDs).** TZDs are a class of drugs that can also improve insulin sensitivity. **Rosiglitazone** and **Pioglitazone** are members of this class. TZDs work via the peroxisome proliferator-activated receptor-*γ* (PPAR-*γ*) to **promote insulin sensitivity** at the level of the liver as well as muscle. Previous research has focused on TZDs and adipokines, most importantly adiponectin. Adiponectin is produced by adipocytes and appears to enhance insulin effects on hepatic gluconeogenesis. Activators of PPAR-*γ* have also been shown to **increase adiponectin levels**, a concept that may be important to current research in diabetes prevention. Both the DREAM trial and the ACT NOW study showed substantial reductions in the incidence of diabetes in high-risk individuals with TZD treatment. In the long-term-care setting, insulin resistance is associated with a proinflammatory state, whereas TZD treatment has been observed, through ubiquitin-proteasome activity analysis, to decrease inflammation. Improvement in homocystinemia in diabetic patients was also recognized with the addition of this pharmacologic agent. Alternately, the benefits of TZDs have been questioned, especially in the older population, by research that shows that activation of

PPAR-γ may promote differentiation of bone marrow–derived progenitor cells toward adipocytes. A later clinical observational study supports the hypothesis that TZDs may **cause bone loss** in older women, thereby putting patients, already at risk for falls, at a superimposed increased risk of fracture. In addition, there is an increased **risk of edema leading to heart failure** and weight gain. It should also be noted that Pioglitazone has been associated with an increased **risk of bladder cancer**.

6. **α-Glucosidase inhibitors.** α-Glucosidase inhibitors are a class of drugs that target postprandial hyperglycemia by **decreasing carbohydrate absorption** at the intestinal brush border. The net result is an **increase in insulin sensitivity** as opposed to insulin release in elderly patients. Currently available class members are **acarbose** and **miglitol**. These drugs have a good overall safety profile for older populations, with the most common side effects being gastrointestinal, such as **bloating and loose stools, which limit their use** in some patients. **Postprandial hypotension** is a significant clinical condition that predisposes elderly patients to events such as syncope and falls. Also, postprandial hypotension severity tends to be augmented with greater carbohydrate content. The addition of α-glucosidase inhibitors appears to attenuate postprandial hypotension and its resulting effects, possibly by slowing gastric emptying.
7. **Glucagon-like peptide 1 receptor (GLP-1) agonists.** The gut hormones, GLP-1 and gastric inhibitory polypeptide, are **incretin** hormones that are released postprandially and appear to augment insulin secretion by way of β-cell glucose sensitization as well as decreasing hepatic glucose production. In healthy persons, GLP-1 dose-dependently inhibits gastric emptying. It is this effect that may decrease food intake through either neuronal or endocrine signaling. With increased aging and glucose impairment, insulin release patterns are altered and become more chaotic, which can be improved with GLP-1 infusion. The first clinically available incretin mimetic was exenatide. **Exenatide** has a significantly longer half-life as well as greater glucose-lowering potential compared with GLP-1. Statistically significant reductions in HbA_{1c} and both fasting and postprandial glucose levels, as well as body

weight, have been recognized in placebo-controlled studies p. 784p. 785performed by adding exenatide to regimens of inadequately controlled patients on metformin, a sulfonylurea, or both, to show significant reductions in HbA_{1c}, overall glucose control, and body weight. Despite improved glucose management, **this class of drugs should be avoided in the elderly** considering side effects of nausea, vomiting, and weight loss which could result in worsening frailty.

8. **Dipeptidyl peptidase 4 (DPP IV) inhibitors.** This class of medications increases GLP through inhibition of its degradation by the enzyme, DPP IV. In human studies, DPP IV inhibition appears to improve glucose homeostasis through stimulation of insulin secretion and inhibition of glucagon release without altering gastric emptying. **Sitagliptin** is a highly selective oral DPP IV inhibitor. Sitagliptin treatment up to 600 mg was generally well tolerated without side effects, such as increased hypoglycemia or gastrointestinal complaints, compared with placebo in healthy euglycemic men. Sitagliptin has been found to have similar HbA_{1c} reductions and side-effect profile compared with sulfonylurea without significant hypoglycemia. This class of medications is particularly **useful in the elderly** diabetic population given that it is well tolerated, weight neutral and has a favorable safety profile.
9. **Sodium glucose cotransporter 2 (SGLT2) inhibitors.** This novel group of medications inhibits the SGLT2 receptor located at the proximal tubule of the kidney resulting in increased urinary excretion of glucose. This medication has been of recent interest given evidence that it may have a cardiovascular mortality benefit, the mechanism of which is undetermined at this time. The adverse side effects are important to recognize and include hypovolemia, hypotension, syncope, mycotic urinary infections, polyuria, and urinary incontinence. It also promotes weight loss, which as discussed previously is not recommended in the elderly. There is also concern over the side effect of the phenomenon referred to as euglycemic diabetic ketoacidosis in patients on SGLT2 inhibitors. Because the mechanism of action is glycosuria, patients may not detect elevated blood sugars with self-monitoring and any

developing acidosis may worsen without recognition and result in life-threatening diabetic ketoacidosis. Moreover, there is apprehension over an increased risk of fractures notably in the second year of treatment with this medication. Overall, it should be **used cautiously and judiciously in elderly diabetic patients**.

XI. SUMMARY

Diabetes is a chronic progressive condition that becomes more common as well as more complicated in the older population. The management of diabetes should be approached from a number of different angles, and its management needs to be tailored to the individual patient to achieve the best results.

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59 Diabetes Mellitus Type 2, Obesity, Dyslipidemia, and the Metabolic Syndrome in Children

Norman Lavin

I. DIABETES MELLITUS TYPE 2

A. Introduction

1. Type 2 diabetes mellitus (DM) is no longer exclusively a disease of adults, as evidenced by an emerging epidemic of type 2 DM in children throughout the world. Twenty years ago, type 2 DM accounted for <3% of all cases of new-onset diabetes in children and adolescents, but now many more cases are attributed to it. Because of the close link between obesity and type 2 DM, there are comorbidities including hypertension, dyslipidemia, nonalcoholic fatty liver disease, and the metabolic syndrome, all of which are associated with increased cardiovascular risk. This disorder is polygenic, resulting from an interaction of genetics and environmental factors, such as obesity, inactivity, and a high-fat and/or high-calorie diet leading to insulin resistance.
2. There is an increased risk of type 2 DM in patients with polycystic ovary syndrome (PCOS) because of insulin resistance that can be independent of obesity. Thirty-one percent of these patients have impaired glucose tolerance, and 7% to 16% have or will develop overt type 2 DM.
3. **Mature-onset diabetes of the young/atypical diabetes mellitus**
   a. In addition to type 1 and type 2 DM, there is another specific type of diabetes: **mature-onset diabetes of the young (MODY)** (see Chapter 60) (Tables 59-1 and 59-2; Fig. 59-1). MODY is characterized by early-onset diabetes inherited in an autosomal dominant pattern, and it is believed to be a subtype

of non–insulin-dependent DM. Classic MODY occurs predominantly in Caucasians, presents before age 25 years, is nonketotic, and is generally not insulin requiring. Fewer than 5% of cases of childhood diabetes in Caucasians are caused by MODY. Mutations in five genes can cause this entity. These genes include hepatocyte nuclear factor-4α (HNF-4α, MODY 1), glucokinase (MODY 2), hepatocyte and nuclear factor-1α (HNF-1α, MODY 3), insulin-promoter factor-1 (IPF-1, MODY 4), and hepatocyte and nuclear factor-1β (HNF-1β, MODY 5).

b. Atypical diabetes mellitus (ADM) is a subtype of diabetes that occurs in approximately 10% of African Americans with youth-onset diabetes. In contrast to MODY in Caucasians, ADM presents clinically as acute-onset diabetes, often associated with weight loss, and occasionally ketosis. Approximately 50% of patients with ADM are obese. Initially, it is sometimes difficult to distinguish ADM from type 1 DM. Many months or years later, a non–insulin-dependent clinical course develops in patients with ADM that is clearly different from type 1 DM.

B. Incidence

The highest incidence of type 2 DM is evident in Native Americans, Hispanics, and African Americans. The peak incidence is age 13 to 14 years, probably secondary to physiologic insulin resistance during pubertal maturation. In lean African American children ages 7 to 11 years, insulin levels are significantly higher than in age-matched white children, which may predispose this group to obesity and type 2 DM. There is as much as a 30% decline in insulin action in comparison with preadolescent children or adults. Therefore, minority children may have a genetic predisposition to insulin resistance.

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TABLE 59-1 Diagnosis of Diabetes Mellitus

1. Signs and symptoms (polyuria, polydipsia) plus random glucose >200 mg/dL
   or
2. Fasting blood glucose ≥126 mg/dL
   or
3. Two-hour oral glucose tolerance test ≥200 mg/dL

TABLE 59-2 Classification of Diabetes Mellitus by Etiology

A. Type 1 diabetes mellitus (immune mediated)
B. Atypical diabetes mellitus (ADM)
C. Maturity-onset diabetes of youth (MODY)
D. Type 2 diabetes mellitus
  1. Insulin resistance; insulin deficiency; secretory defect
  2. MODY; genetic defects of β-cell function
  3. Lipotropic diabetes
  4. Cystic fibrosis
  5. Cushing syndrome
  6. Drug induced (glucocorticoids)
  7. Infections (congenital rubella)
  8. Gestational
  9. Other genetic defects

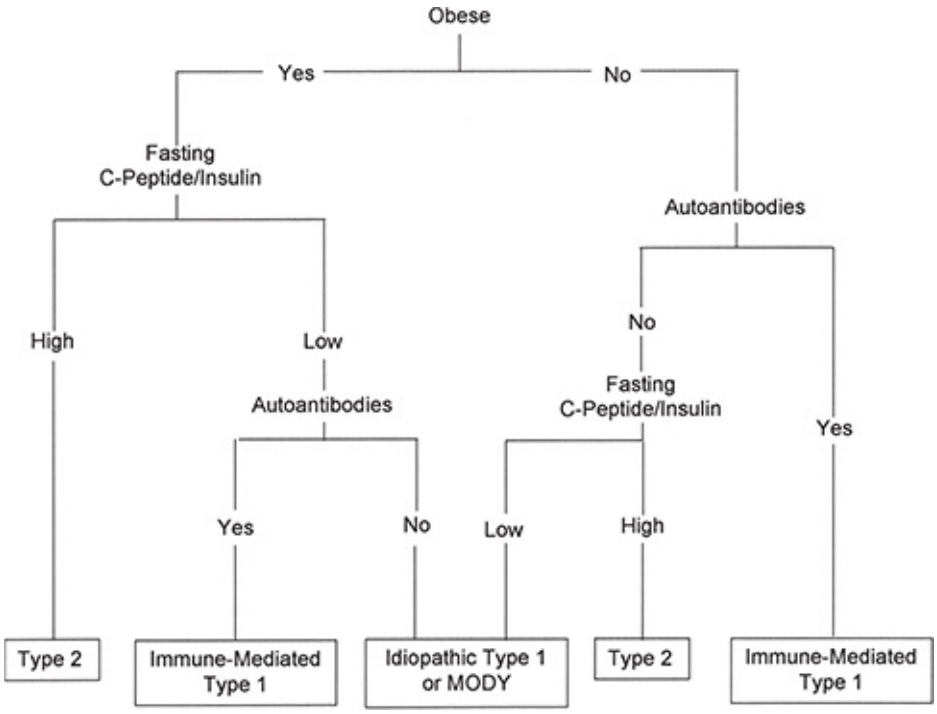

Figure 59-1. Classification of diabetes mellitus in children. MODY, mature-onset diabetes of youth.

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C. Insulin resistance syndrome/metabolic syndrome

1. Definition

Risk factors for the development of the insulin resistance

syndrome/metabolic syndrome are more prevalent during childhood than was previously thought. This syndrome reflects a wide array of factors, including adiposity, dyslipidemia, hypertension, hyperinsulinemia, impaired glucose metabolism, microalbuminuria, and abnormalities in fibrinolysis and inflammation. Many health organizations define the metabolic syndrome differently, but most agree that a low high-density lipoprotein (HDL) level and a high triglyceride level are two characteristics. Most agree that obesity prevention and treatment in childhood should be the first-line approach to this problem. In addition to the body mass index (BMI) percentile, the inclusion of waist circumference is a fairly good surrogate marker for insulin resistance. That is, the greater the circumference, the greater is the likelihood of insulin resistance.

2. **Obesity**

   Elevated fasting serum insulin concentration correlates significantly with serum lipids and blood pressure, which, in turn, are linked to obesity and diabetes. Obesity in teens is associated with an increased risk of premature death from coronary heart disease, especially among males. High birth weight is also a marker for subsequent cardiovascular risk. Larger infants born to diabetic mothers have an increased incidence of hypertension and hyperinsulinemia at ages 10 to 16 years in comparison with controls.

3. **The fetus**

   Fetal life is a critical time for the ultimate development of cardiovascular risk factors in later life. Many studies have shown that insulin resistance in adults is related to birth weight—either small for gestational age or large for gestational age (a U-shaped curve). The long-term effects of fetal nutritional abnormalities may result in later insulin resistance, or certain genes may cause both low birth weight and insulin resistance. Low birth weight is associated with increased risk for the insulin resistance syndrome, probably evolving from under nutrition in utero. When these infants become adults, they may ultimately have high blood pressure, hyperglycemia, hyperinsulinemia, and elevated triglyceride levels.

4. **Measure of insulin resistance**

   a. A biochemical measure of insulin resistance is the Homeostasis

Model of Insulin Resistance (HOMA-IR) index. The formula is as follows:

$$\text{HOMA-IR} = \frac{(\text{FPI} \times \text{FPG})}{22.5}$$

That is,

$$\frac{\text{Fasting insulin } (\mu\text{U/L}) \times \text{fasting glucose (mmol/L or mg/dL)}}{22.5}$$

Although the data are not absolute, consider the diagnosis of insulin resistance if the quotient is over 2.0.

D. Diabetes pathophysiology

1. Type 2 DM emanates from a combination of insulin resistance, increased hepatic glucose output, and progressive decline of insulin sensitivity in response to glycemic stimulation. Chronic hyperglycemia gradually impairs *β*-cell function and leads to more insulin resistance and more hyperglycemia. The *β* cell loses its ability to compensate, leading to lower insulin concentration despite the presence of hyperglycemia. The failure of the *β* cell to continue to hypersecrete insulin underlies the transition from insulin resistance to clinical type 2 DM. Insulin resistance within the peripheral tissues leads to hypersecretion of insulin from pancreatic *β* cells. This compensatory secretion is thought to lead to overtaxing of the *β* cells, which contributes to further decline in overall *β*-cell function, p. 790p. 791paving the way for glucose intolerance. In the liver, insulin resistance leads to less regulation of glucagon concentrations.
2. A new study published in *Diabetologia* investigated whether Forkhead Box Protein O (FOXO) transcription factor could help understand the pathophysiology of diabetes and potentially lead to the design of new therapies. Their review included many biologic functions of FOXO and metabolism, such as the regulation of hepatic glucose production, liver lipids, and bile acids. They focused on the role of FOXO in hepatic insulin resistance and *β*-cell failure.

   In the regulation of hepatic glucose production, FOXO-1 can drive the G6PC gene, which is encoding glucose 6-phosphatase, and glucose 6-phosphatase is the rate-limiting enzyme in

glycogenolysis, and hepatic insulin resistance can be correlated with excessive FOXO activity. The study also concludes that hepatocyte FOXO-1 can be inactivated by insulin and then G6PC expression is repressed. At the same time, FOXO is also linked to β-cell failure. FOXO nuclear translocation can indicate β-cell stress, and loss of FOXO can lead to loss of insulin. In conclusion, the researchers hope a new treatment of diabetes can be derived by understanding the function of FOXO and the pathophysiology of diabetes.

E. Screening for diabetes or prediabetes (adapted from Yale University)

The first step in evaluating an obese child is to measure fasting glucose and insulin levels as well as hemoglobin A_{1c} (HbA_{1C}). The HbA_{1C} may be in the normal range despite abnormal glucose metabolism, but if it is >6, this should be considered a "red flag" that warrants further evaluation. Insulin levels may be elevated during puberty. Fasting insulin levels that are >20 μU/mL indicate insulin resistance, and prepubertal fasting insulin levels of 10 to 15 are a cause for concern. But actual glucose values are more important than insulin levels. A fasting glucose of 100 to 125 mg/dL indicates impaired fasting glucose. A level of 126 mg/dL or higher is consistent with a diagnosis of diabetes. A 2-hour postchallenge blood sugar of 140 to 199 mg/dL indicates impaired glucose tolerance. A blood sugar of 200 mg/dL or higher indicates diabetes (Table 59-1). A recent pediatric study found that half of the cases of impaired glucose tolerance were missed using fasting assessments of glucose alone. They recommend that any adolescent who is obese, who has acanthosis nigricans, and who has a family history of diabetes, should undergo a 2-hour oral glucose tolerance test even when the fasting blood glucose is <100 mg/dL. Although not everyone agrees, I consider an HbA_{1C} of 6.6 or higher diagnostic of diabetes.

A diagnosis of type 2 DM in children and adolescents focuses on blood glucose concentrations and the presence of signs and key symptoms, which include polyuria, polydipsia, blurred vision, and weight loss in association with glucosuria and potentially ketonuria.

Unfortunately, a diagnosis of diabetes is often delayed until complications are present. Therefore, children who have a high BMI, signs of insulin resistance, such as acanthosis nigricans, or

comorbidities of insulin resistance, such as hypertension, dyslipidemia, and PCOS, are considered high risk and should be screened for type 2 DM.

F. Clinical presentation and differential diagnosis

Type 1 and type 2 DM may have clinical presentations that are indistinguishable from each other, so distinguishing between them may be difficult at the onset. Nevertheless, whether a patient is type 1 or type 2 is usually but not always established by the clinical presentation. Children with type 1 DM present with weight loss rather than obesity, as in type 2. Polyuria and polydipsia and a high incidence of diabetic ketoacidosis (DKA) are more typical of type 1. Insulin administration is required for survival in type 1, and 5% of these children have a first- or second-degree relative with the same disorder. Some children with type 2 DM present with DKA, and they initially require insulin as well. Acanthosis nigricans, found in 90% of children with type 2 DM, is a darkened skin lesion that is prominent around the neck and in the intertriginous areas. There is a high correlation with insulin resistance. PCOS is also associated with insulin resistance and may be more p. 791p. 792common in children with type 2 DM as well. Lipid disorders and hypertension are also found in such children.

In children with type 2 DM, 15% to 25% have hypertension and 4% to 32% manifest elevated triglyceride levels (Table 59-14).

G. Clinical presentation of type 2 DM in children

Unrecognized hypoglycemia 42%	HbA_{1C} 9.3%
Polyuria 58%	Average insulin level 76.8 mIU/L
Hispanic 47%	C-peptide 5.5 ng/dL
Black 37%	Elevated total cholesterol
Caucasian 11%	Elevated low-density lipoprotein (LDL)
Mean age 14.3 yr	Centripetal obesity
Acanthosis nigricans 90%	Weight >120% of ideal body weight or
Type 2 family history 80%	BMI >85th percentile for age and sex
Hypertension 15% to 25%	No recent weight loss
Mean glucose 397 mg/dL	DKA 30%

H. Diabetes diagnosis and evaluation

For high-risk populations, such as obese members of minority groups, I order a fasting glucose, insulin level, and C-peptide level, and, if needed, a 2-hour glucose tolerance test. If I have a strong index of suspicion, I order the glucose tolerance test even with a normal fasting blood glucose (Fig. 59-1). I also order a HbA_{1C} (if between 5.7 and 6.5 = prediabetes).

At presentation, the child with type 2 DM has hyperglycemia, which is usually not as high as in type 1. There are also high insulin and C-peptide levels, as well as absence of autoimmune markers, such as the islet-cell and glutamic acid decarboxylase antibody and the tyrosine phosphatase insulin antibody (1A-2 and 1A-2β), which argues strongly against type 1.

I. Acute complications of type 2 DM

1. **Diabetic ketoacidosis.** Children often present with ketonuria and hyperglycemia.
2. **Hyperglycemic hyperosmolar state** (see Chapter 54). This is a life-threatening emergency. Standard diagnostic criteria are blood glucose concentrations >600 mg/dL and serum osmolality >330 mOsm/L with mild acidosis (serum bicarbonate >15 mmol/L and mild ketonuria ≤15 mg/dL). Precipitating causes include infections, medications, nonadherence to diabetes treatment, undiagnosed diabetes, substance abuse, and coexisting chronic illness. In the literature, 29 cases have been reported of adolescents with a hyperglycemic hyperosmolar state, of whom 26 were African American and 22 were male. As in adults, this complication is associated with substantial mortality.
3. **Malignant hyperthermia-like syndrome with rhabdomyolysis.** This is a rare syndrome that includes the hyperglycemic hyperosmolar state complicated by a malignant hyperthermia-like event with fever, rhabdomyolysis, and severe cardiovascular instability after administration of insulin. Mortality is a common outcome.

J. Diabetes management

1. **Weight reduction and exercise.** Reducing weight and increasing physical exercise can reduce the incidence of type 2 DM as well as improve control in children who already have type 2 DM.

   a. Goal. The goal is to normalize blood sugar values and $HgbA_{1C}$

as well as to control hypertension and dyslipidemia. If weight loss and normalizing glucose are not achieved by diet and physical exercise, then pharmacologic therapy should be considered.

b. **Lifestyle changes.** The treatment of every child with type 2 DM should begin with lifestyle modifications, including physical activity and nutrition. Only 10% of pediatric patients achieve their blood sugar goals with lifestyle modifications alone. This is perhaps secondary to a loss of follow-up, a higher rate of depression, and peer pressure steering toward unhealthy eating habits. p. 792p. 793Many factors will increase insulin sensitivity, and most can be accomplished through lifestyle changes. These include the following:
   i. Institute aerobic and resistance exercise.
   ii. Increase muscle mass.
   iii. Reduce body fat, particularly visceral fat.
   iv. Reduce levels of circulating fats, including triglycerides and free fatty acids.
   v. Eat foods rich in antioxidants.
   vi. Increase physical activity.
   vii. Reduce mental and physical stressors.
   viii. Increase intake of dietary fiber.
   ix. Decrease consumption of saturated fats and *trans*-fats.
   x. Decrease consumption of highly refined foods with high glycemic index values.
   xi. Eat a healthy breakfast every day.
   xii. Get adequate sleep.
   xiii. Treat sleep apnea.

2. **Oral drugs.** Most pediatric diabetologists now use oral agents for type 2 DM after insulin is administered on admission to the hospital.
   a. **Metformin** (biguanide) decreases hepatic glucose production and enhances hepatic and muscle insulin sensitivity. The first oral agent I generally recommend is metformin, because it can contribute to weight loss and not cause hypoglycemia. Compared with placebo, metformin was associated with a loss of 4.8% of total body weight and statistically significant reductions in BMI, waist circumference, fasting glucose, and

fasting insulin. LDL and triglyceride concentrations decrease as well. It may also normalize ovulatory abnormalities in girls with PCOS. Metformin should be discontinued during administration of radioactive material if a patient has impaired renal function, hepatic disease, serious infection, alcohol abuse, or pregnancy. Side effects are usually gastrointestinal disturbances, but these usually diminish with time. The correct dosing in children has not been fully evaluated. I start at low levels, such as 250 mg at dinner for 1 week, and then titrate upward to 2 000 mg/day maximum.

If monotherapy with metformin is unsuccessful, then consider adding a sulfonylurea, insulin, or other drugs listed below.

For patients with high levels of glucose who are very symptomatic or ketonuric, I begin with insulin administration as for a type 1 patient. Then, when glucose control is established, I add metformin while reducing the insulin dose.

One study shows that metformin plus rosiglitazone was superior to therapy with metformin alone in children. However, use of rosiglitazone was previously restricted owing to concerns of increased cardiovascular ischemic risks observed in a meta-analysis. Therefore, we do not recommend that medication.

b. Sulfonylureas promote insulin secretion and are used in both adults and children with MODY. Although not labeled for use in pediatrics, sulfonylureas have been used safely in this population. Dosage used in studies in children includes glimepiride 1 to 8 mg once daily and glipizide 2.5 mg twice daily. The most common adverse events associated with sulfonylureas include weight gain and hypoglycemia. Recent studies state that glimepiride was as effective as metformin in reducing HbA_{1C} but with more weight gain in pediatric patients.

c. Meglitinide (repaglinide) causes short-term promotion of glucose-stimulated insulin secretion. Repaglinide and nateglinide work by stimulating insulin release from the pancreas in a glucose-dependent manner, but they are **not approved for children**. The most common adverse events are hypoglycemia, upper respiratory tract infection, diarrhea, and headache.

d. **Glucosidase inhibitors** (acarbose and miglitol) slow carbohydrate absorption and slow the hydrolysis of complex carbohydrates, which decreases postprandial rise in glucose. Glucosidase inhibitors have not been well studied in children.
e. **Thiazolidinediones** improve peripheral insulin sensitivity and reduce triglyceride concentration. Triglitazone has been associated with hepatic failure and is no longer recommended. Rosiglitazone (Avandia) and pioglitazone p. 793p. 794(Actos) are now available but, as of 2007, there were reports of cardiac side effects with Avandia.
f. **Exenatide and Liraglutide** belong to a class of drugs called **incretin mimetics**, so-called because they imitate natural hormones known as incretin. The incretins are released from cells in response to food. One of these is glucagon-like peptide-1 or GLP-1. GLP (or exenatide) lowers blood glucose in the following ways: **(a)** it improves the normal release of insulin from the pancreas; **(b)** it decreases glucagon release; and **(c)** it slows the speed with which food leaves the stomach and promotes a feeling of fullness.

   Exenatide can be used in type 2 patients along with a sulfonylurea or metformin and is given by injection. Side effects include moderate nausea, which is most common when first starting. It rarely causes hypoglycemia, and it tends to cause gradual weight loss. **Exenatide and liraglutide** work as GLP-1 agonists. **Neither agent is approved for pediatric patients**. Liraglutide has not been studied in children. The most common adverse events associated with GLP agonists include nausea, hypoglycemia, vomiting, headache, and diarrhea. They should not be used in patients with a history of pancreatitis or severe renal impairment.
g. **Sitagliptin (Januvia)** and **vildagliptin (Galvus).** GLP-1 is rapidly broken down by enzymes called dipeptidyl peptidase-4 (DPP-4). These two drugs act by inhibiting DPP-4, which increases the level of GLP-1 in the body. They improve insulin production and suppresses glucagon secretion, as does exenatide. These drugs reduce blood glucose levels after meals

and affect the signal to the liver to stop producing glucose. They are once-a-day medications and are given orally. The most commonly reported side effects include stuffy or runny nose, sore throat, headache, diarrhea, and joint pain. Neither medication has been associated with weight gain.

h. **Pramlintide (Symlin).** A healthy pancreas releases both insulin and amylin in response to food intake. Without enough amylin, as seen in diabetes, glucose from food enters the bloodstream more quickly than normal, causing blood glucose levels to rise. Pramlintide, a synthetic analog of human amylin, prevents the rise in blood glucose after meals in the following ways: **(a)** it slows the speed with which food leaves the stomach; **(b)** it suppresses the secretion of glucagon after meals, which decreases the amount of glucose released from the liver; and **(c)** it decreases appetite. Pramlintide is approved for use in type 1 and type 2 DM. As of this writing, it is **approved only for adults**. It is also an injectable medication. The most common side effect is mild to moderate nausea.

3. **Insulin.** Insulin may aggravate an existing hyperinsulinemic state with problems of hypoglycemia and weight gain. Some endocrinologists recommend the use of oral agents in the morning and insulin at bedtime, which decreases nocturnal hepatic glucose (reducing fasting glucose) and enhances the effects of the sulfonylureas.

   Rapid acting or a combination of rapid/ Neutral protamine Hagedorn (NPH), for example, Humalog 75/25, helps to lower postprandial elevated glucose levels. More recently, basal insulin (Lantus, Levemir) is combined with Bolus insulin (Humalog or Novolog).

4. **Chronic complications**

   a. **Hypertension.** There is a prevalence of hypertension at presentation of type 2 DM, varying between 10% and 32%. Hypertension at diagnosis is eight times more frequent in adolescents with type 2 DM than in those with type 1 DM.

   b. **Nephropathy.** Microalbuminuria can also occur at presentation, particularly in Pima Indians, of whom 21% demonstrated this finding. The rate of progression of microalbuminuria and nephropathy seems to be rapid in adolescents with type 2, whereas the rate of progression of

microalbuminuria in adolescents with type 1 DM for the same duration was significantly less.

c. **Retinopathy.** Similar to nephropathy, retinopathy can be present at diagnosis of type 2 DM. Retinopathy is significantly more frequent in individuals with type 1 DM than in those with type 2 (20% vs. 4%).
d. **Dyslipidemia.** Many adolescents had substantial dyslipidemia at time of diagnosis of type 2 DM.

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e. **Nonalcoholic fatty liver disease.** This is the most frequent cause of chronic liver disorder in obese and diabetic individuals.
f. **Cardiovascular and atherosclerotic complications.** As many as 71% of patients with type 2 DM had diminished nocturnal decline in blood pressure, which is a known predictor of cardiovascular risk. Ultrasonographic variables indicating posterior and septal wall thickness were above the reference range in 47% of the children in one study. Another study reported left ventricular hypertrophy in 20% of adolescents with type 2 DM.
g. **Neuropathy.** There are few systemic reports on the incidence of neuropathy in children and adolescents with type 2 DM.
h. **Psychiatric disorders.** A significant number of patients had neuropsychiatric disease at presentation of type 2 DM, including depression, schizophrenia, bipolar disorder, autism, mental retardation, attention-deficit disorder, obsessive–compulsive disorders, and behavior disorders.
i. **Conclusion.** Unfortunately, early onset of type 2 DM is associated with risk for complications qualitatively similar to that seen in adult patients.

5. **Treatment algorithm**

Evidence from the Truday studies indicates that treatment failure with monotherapy (e.g., metformin) was higher in children than in adults. In patients with moderate hyperglycemia, metformin alone, metformin plus insulin, or insulin alone would all be reasonable choices. As discussed, many of the medications used to treat type 2 DM have not been studied in children, and data are often extrapolated from data in adults.

6. **Conclusion**

Type 2 DM has emerged as a serious epidemic in the pediatric population. Lifestyle interventions, including exercise and nutrition, should be a cornerstone in therapy. The American Academy of Pediatrics (AAP) guideline recommends metformin and/or insulin as first-line therapy in children with a diagnosis of type 2 DM. Metformin and insulin are the only anti-diabetic medications completely approved for children. With limited pediatric data, the choice of an additional agent presents a unique challenge for the healthcare practitioner.

II. OBESITY

A. Introduction

1. Childhood obesity has risen at an alarming pace over the past decade, making obesity the most prevalent health problem among children in the majority of the developed countries. One in three children is overweight or obese. The International Obesity Task Force estimates that >300 million individuals worldwide are obese, and a billion are overweight. Childhood obesity may shorten life expectancy. If current trends in obesity among children continue, life expectancy will begin to decline for the U.S. population. This generation of children could become the first in modern history to live shorter and less healthy lives than their parents' generation. Statistics show that the problems of overweight in U.S. children ages 6 to 11 years rose from 4% to 15.3% between 1963 and 2000, and during the past 10 years, the prevalence of overweight also increased among children ages 2 to 5 years, to as much as 10%. About 66% of adult Americans are either obese or overweight.

Our current Western food environment has become highly "insulinogenic," as demonstrated by food with increased energy density, high fat content, high glycemic index, increased fructose composition, decreased fiber, and decreased dairy content. As a result, insulin increases and acts on the brain to encourage eating through two separate mechanisms: **(a)** it blocks the signals that travel from the body's fat stores to the brain by suppressing the effectiveness of the hormone **leptin**, resulting in increased food intake and decreased activity and **(b)** it promotes the signal that seeks the reward of eating, carried by the chemical dopamine, which makes a person want to eat to get the pleasurable "rush."

Calorie intake and expenditure are regulated by leptin. When

leptin is functioning properly, it increases physical activity, decreases appetite, and increases p. 795p. 796feelings of well-being. Conversely, when leptin is suppressed, feelings of well-being and activity decrease and appetite increases, a state called “leptin resistance.”

Metabolic consequences of obesity often begin in childhood. According to adult studies, obesity is one of the most important risk factors in the development of type 2 DM and is often associated with elevated insulin levels. Childhood obesity may lead to adult cardiovascular diseases that are independent of adult weight. Early onset of obesity is found in many groups, including Native Americans (Pima, Cherokee, Mescalero, Apache, Onondaga, and Navajo), African Americans, and Hispanics.

As in adults, it is visceral fat rather than total body fat that correlates with basal and stimulated insulin levels and inversely correlates with insulin sensitivity. The Bogalusa Heart Study showed that African American teens were more obese and had higher insulin levels.

There are also current reports correlating childhood weight with an adult abnormal atherogenic lipid profile. The Bogalusa Heart Study, the Muscatine Study, and the Minneapolis Children’s Blood Pressure Study showed evidence of these abnormalities in children developing into cardiovascular disease in adults.

2. Epigenetic and genetic considerations

Epigenetic issues are those that relate to cellular changes during intrauterine development that lead to risk factors for the development of obesity.

Infants of diabetic mothers, especially type 2 and gestational diabetes, are at increased risk for diabetes. Infants with intrauterine growth restriction are also at increased risk of developing obesity. The mechanism of this is related to insulin resistance, created by the intrauterine growth retardation state that continues throughout life. Infants born to obese mothers are also at an increased risk of developing obesity, as well as those infants born large for gestational age. Maternal smoking has also been shown as a risk factor for obesity in the offspring. There are several genetic syndromes that are associated with obesity in childhood that need to be considered when evaluating the obese child. These are listed

in Table 59-3. There are also single-gene defects that can lead to obesity in childhood, referred to as monogenetic human obesity syndromes (Table 59-4).

B. Incidence

Thirty-three percent of U.S. adults are above the 80th percentile for BMI. According to the National Health and Nutritional Examination Surveys (NHNES) 1, 2, and 3, 23% of U.S. children aged 6 to 17 years are above the 85th percentile for BMI and 11% are above the 95th percentile. Obesity is more prevalent among African Americans and Native Americans and among poor or less educated families. The prevalence of pediatric obesity is increasing at the rate of approximately 30% per decade. This significant change over a single decade must reflect major changes in nongenetic factors. Therefore, obesity results from the interactions of genetic susceptibility to store excess calories as fat, as well as heritable predilections toward insulin resistance, impaired β-cell function, dyslipidemia, and hypertension, with an environment that favors the expression of these susceptibilities. Low-income families have less access to healthy food choices and safe, affordable opportunities for physical activity for their children.

C. Definition

A child is **overweight** if his or her BMI is above the 80th percentile and **obese** if the BMI is above the 95th percentile. BMI is calculated by dividing the child's weight (kg) by the square of the height (m), or kg/m^2. Standard graphs are also used by most pediatricians to plot weight for height and age to determine whether a child is obese.

BMI	Weight status
Below 18	Underweight
18.5–24	Normal
25.0–29	Overweight
30.0 and above	Obese

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TABLE 59-3 Genetic Syndromes Associated with Obesity

Syndrome	Gene locus	Clinical features
Prader-Willi	15q	Microcephaly, short stature, hypotonia, almond-shaped eyes, high-arched palate, narrow hands and feet, delayed puberty, early failure to thrive with hyperphagia and increased weight gain by 2–3 yr, mild to moderate cognitive deficit
Pseudohypoparathyroidism type 1a (Albright hereditary osteodystrophy)	20q13	Short stature, short metacarpals and metatarsals, round facies, delayed dentition, ±hypocalcemia and/or poor mineralization, precocious puberty, mild cognitive deficit
Alstrom	2p13	Blindness, deafness, acanthosis nigricans, chronic nephropathy, type 2 diabetes mellitus, cirrhosis, primary hypogonadism in males only, normal cognition, obesity develops at age 2–5 yr
Bardet-Biedl	Multiple loci	Mental retardation, hypotonia, retinitis pigmentosa, polydactyly, hypogonadism ± glucose intolerance, deafness, renal disease
Beckwith-Wiedemann	11p15.5	Hyperinsulinemia, hypoglycemia, hemihypertrophy, intolerance of fasting
Carpenter	6p11	Mental retardation, short stature, brachycephaly, polydactyly, syndactyly of feet, cryptorchidism, umbilical hernia, high-arched palate, hypogonadism in males only
Cohen	8q22	Mental retardation, microcephaly, small hands and feet, cryptorchidism, hypotonia and failure to thrive in infancy, prominent central incisors, long, thin fingers and toes

TABLE 59-4 Gene Defects Associated with Obesity

Single-gene disorder	Gene locus	Clinical features
Leptin deficiency	7q31.3	Severe, early-onset obesity, hypometabolic rate, hyperphagia, pubertal delay, impaired glucose tolerance, hypothalamic hypogonadism
Proopiomelanocortin (POMC) deficiency	2p23.3	Severe, early-onset obesity, red hair, hyperphagia, adrenal insufficiency, hyperpigmentation
Prohormone convertase impairment	5q15-q21	Early-onset obesity, abnormal glucose homeostasis, hypogonadotropic hypogonadism, hypocortisolism, elevated plasma proinsulin and POMC
Melanocortin-4 receptor haploinsufficiency	18q21.3-q22	Early-onset, moderate-to-severe obesity, early-onset hyperphagia, increased bone density

Leptin receptor deficiency	1p31-p22	Severe, early-onset obesity, hypometabolic rate, hyperphagia, pubertal delay, hypothalamic hypogonadism

Body fat distribution is usually defined on the basis of waist circumference. Central distribution of body fat is an independent predictor of insulin resistance and dyslipidemia in prepubertal and pubertal children and of type 2 DM, cardiovascular disease, stroke, and death in adults. Free fatty acids from omental fat drain directly p. 797p. 798into the portal circulation, exposing the liver to circulating free fatty acids, which results in increased hepatic glucose production and decreased insulin clearance and which, in turn, leads to insulin resistance and dyslipidemia.

D. Complications

In children, as in adults, there are many complications associated with obesity (Tables 59-5 and 59-6).

1. **Insulin resistance.**
2. **Non–insulin-dependent DM or type 2 DM.**
3. **Dyslipidemia.**
4. **Premature atherosclerosis.** The Bogalusa Heart Study showed that atherosclerosis can be found in early childhood and that a high BMI is associated with early plaque formation—hence, the necessity of early intervention to prevent p. 798p. 799cardiovascular disease in the adult. C-reactive protein and lipoprotein (a) [Lp(a)] show promise as markers in children of future atherosclerosis.

TABLE 59-5 Complications Associated with Obesity

Signs and symptoms	Disorder	Additional findings
Snoring	Sleep apnea	Hypertrophy of tonsils or adenoids
Daytime somnolence	Pickwickian syndrome or sleep apnea	
Abdominal pain	Gallbladder disease	
Hip pain or limp	Slipped capital femoral	

	epiphysis	
Irregular menses or amenorrhea	Polycystic ovary disease	Hirsutism, visceral adiposity, insulin resistance
	Prader-Willi syndrome	Short stature, hypogonadism, small hands and feet, infantile hypotonia
Short stature or growth arrest	Hypothyroidism, Cushing syndrome	
Developmental delay	Prader-Willi syndrome, other genetic syndromes	
Fatigue/tiredness	Depression	
Elevated blood pressure	Cardiovascular disease	Consider Cushing syndrome
Postaxial polydactyly	Bardet-Biedl syndrome	Retinitis pigmentosa, hypogonadism, mental retardation
Eyes		
Papilledema	Pseudotumor cerebri	
Retinitis pigmentosa	Bardet-Biedl syndrome	
Skin		
Acanthosis nigricans	Obesity, glucose intolerance, metabolic syndrome	
Violaceous striae	Cushing syndrome	
Hirsutism	Polycystic ovary disease, Cushing syndrome	
Hepatomegaly	Nonalcoholic fatty liver disease	Elevated serum aminotransferases
Genitalia		
Undescended testicles	Prader-Willi syndrome	
Delayed puberty	Cushing syndrome	
	Prader-Willi syndrome in girls	
	Bardet-Biedl syndrome	
Bowed legs	Blount disease, bowed femurs	Bowed tibias

TABLE 59-6 Major and Minor Comorbid Conditions Associated with Obesity

Respiratory	Obstructive sleep apnea Central hypoventilation syndrome Exercise intolerance Worsening of asthma
Cardiovascular	Hypertension

	High triglyceride, low HDL, high LDL
Endocrine	Polycystic ovary syndrome Type 2 diabetes mellitus
Gastrointestinal	Nonalcoholic fatty liver disease Gallstones Gastroesophageal reflux disease Constipation
Genitourinary	Kidney stones
Orthopedic	Slipped capital femoral epiphysis Blount disease Back, foot, knee, and hip pain
Skin	Acanthosis nigricans Impetigo
Psychiatric	Depression Anxiety Eating disorder

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

5. **Hypertension** (even as young as 2 to 5 years in overweight children). In one study, 10.6% of overweight and obese children had elevated blood pressure values in comparison with normal subjects.
6. **The insulin resistance syndrome/metabolic syndrome** is a clustering of factors, including hypertension, dyslipidemia, and insulin resistance. This entity is the most common cause of early cardiovascular disease (see Chapter 55).
7. **Low self-esteem.**
8. **Pseudotumor cerebri.**
9. **Sleep apnea.**
10. **Slipped capital femoral epiphysis.**
11. **NASH or NAFLD.** Nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease in adults. In adolescents, the most common cause of elevated liver enzymes is obesity. Up to 10% of obese children may have abnormal alanine aminotransferase levels. Abnormal liver enzymes in overweight children may emanate from a combination of hyperinsulinemia, hyperlipidemia, and a decrease in antioxidant levels. These elevated enzymes often reflect NAFLD.

    In NAFLD, hepatosteatosis is present without evidence of significant inflammation, whereas in NASH, hepatosteatosis is

associated with hepatic inflammation.

Expert opinions suggest that in an obese child with transaminase elevation, evaluation for other common causes of liver disease be performed. This includes, but is not limited to, hepatic ultrasound with Doppler, viral hepatitis studies, Wilson disease, α1-antitrypsin deficiency, and autoimmune hepatitis.

NASH may progress to cirrhosis even in children. NAFLD occurs most commonly in conditions associated with the insulin resistance syndrome.

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There are some data by Levine and others suggesting that vitamin E and milk thistle may normalize aminotransferase levels in these patients. In addition, modest alcohol ingestion may exacerbate obesity-associated liver disease. Therefore, in a child with elevated liver enzymes, I recommend immediate weight loss and exercise, vitamin E supplements, milk thistle, and, obviously, no ingestion of alcohol.

12. **Hyperuricemia.** It has been mentioned that obesity/overweight is an important promoter of independent risk factors for cardiovascular disease from early childhood. In addition, there are some emerging risk factors for both cardiovascular and chronic kidney disease from early childhood, such as high plasma levels of uric acid. Hyperuricemia has been reported in overweight children with a significant association with the metabolic syndrome. An association between childhood plasma uric acid levels and adult blood pressure was described in the Bogalusa Heart Study, and abnormal plasma uric acid levels may be used to discriminate between healthy and unhealthy obese children. An improvement in the plasma uric acid levels may improve body weight and related cardiovascular risk factors in young patients with hyperuricemia. Therefore, we suggest that plasma uric acid levels require more attention in the evaluation of the metabolic risk profile of children and adults.

E. Evaluation and workup (Tables 59-7, 59-8, and 59-9)

1. Rule out various conditions of which obesity is a sign, including hypothyroidism, Cushing syndrome, and certain genetic syndromes (e.g., Prader-Willi, Laurence-Moon-Biedl, Alstrom, and Cohen syndromes) (Table 59-3).

Also, rule out certain medications as a cause, such as anticonvulsants, corticosteroids, antipsychotics, and tricyclics.

2. **Laboratory tests**
   - **a.** Lipid profile
   - **b.** Serum chemistries
   - **c.** Fasting glucose
   - **d.** HbA_{1C}
   - **e.** Glucose tolerance test
   - **f.** Fasting insulin
   - **g.** C-peptide
   - **h.** T4 and TSH
   - **i.** Cortisol levels (serum; 24-hour urine)
   - **j.** Repeat electrolytes and the lipid profile 6 to 12 weeks after the first test and after initiating the dietary program.

F. Management

Management of obesity in children includes an increase in physical exercise, reduction in television or computer time, and a decrease in caloric intake. Drug therapy to reduce weight has not been well studied in children. Intensive lifestyle modification remains the primary treatment. Carefully selected patients with severe comorbidities may benefit from the addition of pharmacotherapy and/or bariatric surgery. Because treatment is difficult, prevention is the ultimate goal. For a child age 2 to 6 years who has a BMI at or above the 95th percentile, the goal of treatment is to achieve weight maintenance. Weight loss is indicated for this age group if there are weight-related complications. For older children, weight reduction is the goal if the BMI is at or above the 95th percentile, whether or not there is a weight-related complication, including pseudotumor cerebri, sleep apnea, orthopedic abnormalities, type 2 DM, hypertension, as well as major psychological or social issues.

1. **Recommendations**
   - **a.** Studies suggest that exclusive breast-feeding up to 6 months of age is associated with decreased risk of obesity later in childhood. With children ages 2 years and up, a low-fat (skim or 1%) milk should be used, and families should limit their child’s consumption of sugar-sweetened beverages. Studies suggest children and adolescents who skip breakfast do not, on average, make up nutrient deficits at other meals and overall have

decreased micronutrient intake.

b. Discourage ingestion of high-fat snacks and beverages that are high in calories and sugar. Obesity rates among the poor are substantially higher than the rates seen in higher-income groups. The CARDIA study showed that frequent fast-food p. 800p. 801consumption is associated with weight gain and risk of insulin resistance. Very low-calorie or high-protein diets are not recommended.

TABLE 59-7 Physical Examination in Primary Care Settings

System or condition assessed	Assessment
Anthropometric features	Calculation of BMI (weight in kilograms and height in centimeters)
Vital signs	Pulse and blood pressure (use correct cuff size; often must be checked manually because of "white coat hypertension")
General	Body fat distribution and affect
Skin	Acanthosis nigricans, keratosis pilaris, skin tags, intertrigo, excessive acne, hirsutism, or violaceous striae of Cushing syndrome
Eyes	Papilledema
Throat	Tonsillar size and abnormal breathing
Neck	Goiter
Chest	Auscultation for rhythm and sounds (heart) and rhonchi, rales, and wheezes (lungs)
Abdomen	Palpation for liver size, right upper quadrant tenderness, and epigastric tenderness
Secondary sexual characteristics	Premature/abnormal appearance of pubic hair, breast development, testicular enlargement, acne or comedones, axillary odor, appearance of microphallus because penis is buried in fat, or gynecomastia
Extremities	Abnormal gait, hip or knee tenderness, limited range of motion in hip (slipped capital femoral epiphyses), Blount disease, joint and foot pain, small hands and feet, polydactyly, lower back pain or limited motion, deep tendon reflexes, or edema
Prader-Willi syndrome	Short stature, acromicria, characteristic facies, hypotonia, and development delay
Proopiomelanocortin mutation	Red hair, pale skin, low blood pressure or rapid pulse, and corticotropin deficiency/adrenal insufficiency
Albright hereditary osteodystrophy	Developmental delay, short stature, and short fourth and fifth metacarpals

Laurence-Moon or Bardet-Biedl syndrome	Short stature, developmental delay, retinitis pigmentosa, and polydactyly
Melanocortin 4 receptor gene mutation	Tail stature and rapid growth, early-onset obesity
Down syndrome	Typical phenotypic features
Fragile X syndrome	Large head and ears and developmental delay

BMI, body mass index.

c. Drinking of skim milk is not associated with any negative effect on growth in early childhood.

d. Sixty minutes of physical activity every day is recommended for children, and 30 minutes for adults.

e. Do not recommend a semi-starvation diet. Such diets usually lead to failure because the body defends itself against starvation by metabolic, hormonal, and behavioral processes establishing a set point of weight that the body attempts to maintain. Because of a lowered metabolic rate, the patient may regain weight back rapidly—even more than that was lost ("Yo-Yo" dieting).

f. Consider the "stoplight" diet, in which foods are grouped as red, yellow, or green lights according to their lipogenic potential.

i. Green-light food (unlimited quantities) includes fruits, nonstarchy vegetables, fat-free dairy products, and baked or broiled skinless poultry and fish.

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TABLE 59-8 Review of Systems for Weight-Related Problems

Symptoms	Explanation	Potential consequences/comments
Sleep Problems		
Loud snoring or apnea (prolonged intervals without respiratory effort)	Obstructive sleep apnea	Poor sleep efficiency, poor attention, poor academic performance, pulmonary hypertension, right ventricular hypertrophy, or enuresis
Shorter sleep time, later onset of sleep, daytime sleepiness, or restlessness	Disordered sleep	Depression, poor attention, poor academic performance, food cravings, or difficulty responding to satiety cues

Respiratory Problems		
Shortness of breath, exercise intolerance, wheezing, or cough	Asthma	Progression of disease, resistance to treatment, exacerbation of excessive weight gain, or exacerbation of asthma with weight gain
Gastrointestinal Problems		
Vague recurrent abdominal pain	Nonalcoholic fatty liver disease	Fatty deposits in liver, small percentage progresses to steatohepatitis, cirrhosis, and future hepatocarcinoma
Heartburn, dysphagia, regurgitation, or chest or epigastric pain	Gastroesophageal reflux	Increased abdominal pressure or esophagitis
Abdominal pain and/or distention, flatulence, fecal soiling/encopresis, anorexia, or enuresis	Constipation	Disordered eating pattern, physical inactivity, or decreased social interaction
Right upper quadrant or epigastric pain or vomiting and colicky pain	Gallbladder, with or without gallstones	Cholecystectomy (most patients with gallstones are asymptomatic)
Endocrine Disorders		
Polyuria and polydypsia	T2DM	Lack of symptoms is normal for T2DM; unexpected weight loss may occur and may not indicate compliance with treatment of obesity
Menstrual Irregularities		
Oligomenorrhea (<9 menses/yr) or dysfunctional uterine bleeding (anovulation)	Polycystic ovary syndrome	Insulin resistance, metabolic syndrome, T2DM, infertility, or worsening obesity with worsening of aforementioned conditions
Orthopedic Problems		
Hip pain, groin pain, thigh pain, painful gait, or waddling gait	Slipped capital femoral epiphysis	Permanent hip deformity and dysfunction, decreased physical activity, or worsening obesity
Knee pain	Slipped capital femoral epiphysis or Blount disease	Decreased physical function, decreased physical activity, or worsening obesity
Foot pain	Increased weight-bearing	Decreased physical activity or worsening obesity
Mental Health		
Psychiatric conditions		
Flat affect or sad mood, loss	Depression or	Worsening obesity, suicide, or

of interest/pleasure, or worries/fears	anxiety	eating disorder
Psychosocial conditions		
Body dissatisfaction, school avoidance, problems with social interactions, poor self-esteem, or neglect	Depression or anxiety	Worsening obesity
History/ongoing sexual abuse	Depression or anxiety	Worsening obesity
Hyperphagia or binge eating, eating “out of control,” or bulimia	Disordered eating	Worsening obesity; medications may cause/exacerbate obesity
Genitourinary Problems		
Nocturia or nocturnal enuresis	Disordered sleep	Worsening Obesity
Skin Conditions		
Rash or irritations acne	Impetigo attributable to increased skin-to-skin contact with persistent moisture	More serious skin infections and abscesses

T2DM, type 2 diabetes mellitus.

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ii. Yellow-light foods (moderate quantities) are the starchy vegetables (potatoes, corn, peas), rice, pasta, and breads.

iii. Red-light foods (infrequent ingestion) are high in fat and sugar; these include cakes, fatty meats, pizza, fruit juices, and other fast foods.

g. Behavior modification may be helpful.

h. Individuals who ate meals from fast-food restaurants more than twice a week gained 4.5 kg more weight and had a greater increase in insulin resistance.

i. All children above age 9 years should be universally screened for dyslipidemia. Clinicians should counsel children’s families to:

i. limit their child’s consumption of sugar-sweetened beverages;

ii. eat breakfast daily;

iii. limit eating out, especially eating at fast-food restaurants;
iv. adjust portion sizes appropriately for age;
v. avoid television for children younger than 2 years; and
vi. limit television and screen time to less than 2 hours/day for children older than 2 years.

j. The American Academy of Pediatrics recommends no juice under the age of 6 months, no more than 4 to 6 ounces of juice per day for 1 to 6 years of age, and no more than 8 to 12 ounces/day for 7 to 18 years of age.

k. All children should have blood pressure checked annually, starting at age 3 years.

2. Questionable treatment

a. Weight-loss summer camps are not always successful.

b. Herbal diet products containing ma huang or ephedrine should be avoided.

3. Pharmacotherapy

Most pediatric obesity centers do not use medications for obesity, at least initially, because long-term safety and efficacy have not been shown. A few drugs have p. 803p. 804proven to be harmful, such as fenfluramine (Pondimin) and dexfenfluramine (Redux), and have been discontinued.

TABLE 59-9 Further Clinical Comorbidity Assessment

If cardiac disease is suspected	Electrocardiography, assessing length of QTe interval and cardiac rhythm, and echocardiography; consider measurement of lipoprotein (a)
If blood pressure is elevated	24-hr ambulatory blood pressure monitoring
If nonalcoholic fatty liver disease is suspected	Ultrasonography of liver and *α*-I antitrypsin, ceruloplasmin, antinuclear antibody, and hepatitis antibody measurements, liver biopsy if recommended by pediatric gastroenterologist
If goiter is present or hypothyroidism is suspected	Serum-free thyroxine measurement or total thyroxine measurement with resin triiodothyronine uptake, serum thyroid-stimulating hormone measurement, and anti-thyroid peroxidase and anithyroglobulin antibody measurements
If diabetes is suspected	Glucose tolerance test (measuring insulin levels as well as glucose over 3 hr) and urinary microalbumin (first morning void) or microalbumin/creatinine ratio measurement
If sleep apnea is suspected	Polysomnography, oxygen saturation measurement, and carbon dioxide measurement for carbon dioxide retention

If orthopedic disease is suspected	Radiographs of hip, knee and foot
If Cushing syndrome is suspected	24-hr urinary-free cortisol measurement or salivary cortisol measurement at bedtime or midnight
If Albright hereditary osteodystrophy is suspected	Serum calcium and phosphate measurements
If hirsutism and oligomenorrhea is present	Plasma 17-hydroxyprogesterone (basal or corticotropin-stimulated), plasma DHEAS (basal or corticotropin-stimulated), androstenedione, testosterone, and free testosterone, and sensitive (third-generation) LH and FSH measurements
If precocious puberty is suspected	Sensitive (third-generation) LH and FSH, sensitive testosterone (for boys) or estradiol (for girls), and DHEAS measurements
If specific syndrome is suspected (see Genetics section)	MCR4 evaluation, fluorescent in situ hybridization for Prader-Willi syndrome, or fragile X evaluation (high-resolution chromosomal analysis)

DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Currently, some centers are exploring the use of **sibutramine (Meridia)**, a psychostimulant, and **orlistat (Xenical)**, a lipase inhibitor that prevents fat absorption.

a. Orlistat. It is approved by the U. S. Food and Drug Administration for treatment of childhood obesity. It is approved for children older than 12 years. No weight-loss medications are approved for use in children younger than 12 years. Orlistat is a reversible lipase inhibitor that binds lipase on the lumen of the stomach, making it unavailable to hydrolyze dietary fat (triglycerides) and cholesterol to free fatty acids and glycerol. Intact triglycerides and cholesterol cannot be absorbed, thereby reducing fatty acid absorption by 30%. The adverse effects of orlistat include fatty and oily stool, fecal urgency, and oily spotting in up to 30% of patients.

b. Sibutramine. The side effects of sibutramine are nervousness, irritability, headache, dry mouth, nausea, and constipation. The safety and efficacy of sibutramine have not been established for patients younger than 16 years. It has, however, been associated

with a small increase in blood pressure and pulse rate; therefore, it is not recommended for patients with uncontrolled hypertension, preexisting cardiovascular disease, or tachycardia.

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c. **Metformin** reduces food intake, inhibits lipogenesis, and reduces fasting glucose and insulin concentrations, all of which may lead to some weight loss. Metformin is currently approved for the treatment of type 2 DM in children who are at least 10 years of age, but does not have approval as a weight-loss drug. The main adverse effects of metformin are diarrhea, nausea, vomiting, and flatulence, which are usually transient and mild to moderate.

d. **Rimonabant.** The ability of recreational marijuana to stimulate appetite generated interest in the use of endogenous cannabinoid agonists and antagonists for weight-related disorders. The endocannabinoid system includes two major receptors, the CB-1 and CB-2 receptors. Endocannabinoids increase motivation to eat and stimulate food intake. Rimonabant, the first **CB-1 receptor blocker**, enhances thermogenesis, diminishes hepatic and adipocyte lipogenesis and augments adiponectin concentrations. It significantly reduces weight (in one study by 4.6 kg), reduces waist circumference, and improves triglyceride and HDL cholesterol profiles. Adverse effects include nausea, dizziness, diarrhea, and insomnia in a small percentage of patients.

e. **Octreotide** may be of potential benefit in children with hypothalamic obesity who demonstrate insulin hypersecretion.

f. **Leptin** therapy in patients with mutations of the leptin gene resulted in extraordinary loss of weight and fat mass, along with reduction in hyperphagia, resolution of obesity, and reduction of puberty. These conditions, however, are very rare.

g. **Benefits.** There are no definitive data showing benefit of one anti-obesity drug over another. Drugs that improve surrogate endpoints, such as weight loss, might not necessarily improve endpoints judged to be more clinically relevant.

h. **Future therapy.** New drugs are being tested, including some that act on the central melanocortin pathway, a group of neurons centered in the arcuate nucleus and hypothalamus that controls

appetite and energy expenditure. Examples include ciliary, neurotrophic factor, and other melanocortin-4 receptor agonists, ghrelin, neuropeptide Y antagonists, melanin-concentrating hormonal antagonists, and peptide YY.

4. **Treatment for morbidly obese adolescents**
   - **a.** Ketogenic (carbohydrate-restricted) diet
     - **i.** Improved lipid profile
     - **ii.** Decreased insulin resistance
   - **b.** Bariatric surgery (see Chapter 57): Recommendations suggest limiting its use to adolescents with a BMI of at least 40 or more who also have obesity-related coexisting illnesses. Most clinicians suggest bariatric surgery for adolescents with a BMI above 50 kg/m^2 or above 40 kg/m^2 with severe comorbidities in whom lifestyle modifications and/or pharmacotherapy have failed. There is limited information on the long-term efficacy and safety of bariatric surgery in children and adolescents. Consideration for bariatric surgery should be given only under the following conditions:
     - **i.** The child has a BMI >40 kg/m^2 or has a BMI >35 kg/m^2 and significant severe comorbidities, such as type 2 DM, obstructive sleep apnea, or pseudotumor cerebri.
     - **ii.** A child has attained at least Tanner stage 4 or 5 pubertal development.
     - **iii.** Failure of over 6 months of organized attempts at weight management.
     - **iv.** Bariatric surgery should not be performed for preadolescent children, for any patient who has not mastered the principles of healthy dietary activity habits, and for those with unresolved eating disorders, untreated psychiatric disorder, or Prader-Willi syndrome. Pregnant, breast-feeding adolescents, and those planning to become pregnant within 2 years of surgery should not be considered candidates for bariatric surgery.
5. **Risks of treatment.** Lowering of dietary fat in infancy does not alter growth patterns during the first 3 years of life according to the special turku coronary risk factor intervention project (STRIP) Study in Finland. Likewise, the Dietary Intervention Study in Children shows no negative effect of lowering dietary fat on

growth in preteens.

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III. LIPID DISORDERS

A. Introduction

1. Prevention

Cardiovascular disease in adults has its roots in childhood. I believe that by correcting lipid disorders at an early age, we can help prevent coronary heart disease. Atherosclerotic cardiovascular disease begins in childhood and is progressive. There is still not total agreement regarding when to measure lipids in children, how to interpret them, and what medications to use, if any, in pediatric dyslipidemias.

2. Fetus

Fatty streak formation can begin in the fetus and is greatly increased by maternal hypercholesterolemia leading to subsequent atherosclerosis, according to the FELIC (Fate of Early Lesions in Children) study. Cholesterol-lowering intervention of hypercholesterolemia in pregnancy may reduce the incidence of atherogenesis in children. (Of course, **the use of statins is contraindicated during pregnancy**.) During fetal life, the placenta may be permeable to certain fatty acids or native lipoproteins. Maternal hypercholesterolemia may also increase oxygen radical production and peroxidative compounds that may permeate the placenta.

3. Excess lipids

Hyperlipidemia or dyslipidemia means that high levels of fats or lipids are found in the blood. Fats do not dissolve in water. In order for them to be carried in the blood, which is mostly water, they combine with a protein to create a lipoprotein. There are three kinds of lipoproteins in the body: LDL, HDL, and triglycerides. Hyperlipidemia can run in families as a genetic disorder.

There are medications that can lower LDL cholesterol and triglycerides or raise HDL. *Statins* are the most common medications for lowering LDL cholesterol. *Fibrates* and *niacin* are used to lower triglycerides and to raise HDL cholesterol (Table 59-10).

a. Familial hypercholesterolemia—LDL levels are high.

b. Familial hypertriglyceridemia—triglyceride levels are high.
c. Familial combined hyperlipidemia—levels of cholesterol, triglycerides, or both are high, and HDL is low.

B. Lipoprotein physiology

Triglyceride and cholesterol are combined with apolipoproteins and phospholipids and then are transported through the body as lipoproteins.

Lipoproteins are classified according to their density and their ratio of cholesterol and triglycerides to protein. The five main classifications of lipoprotein are chylomicrons, very low-density lipoprotein (VLDL), LDL, intermediate-density lipoprotein (IDL), and HDL (Table 59-11).

Chylomicrons are the largest, most buoyant lipoproteins, with relatively more triglyceride within their core and less cholesterol than LDL and HDL particles. They are composed of approximately 90% triglyceride, which is less dense than cholesterol and gives them their buoyancy. They are made in the intestines following the absorption of digestive fat. From there, they are transported to the bloodstream to tissues such, as skeletal muscle, body fat, and the liver. In these tissues, an enzyme p. 806p. 807called **lipoprotein lipase** breaks down the triglycerides within the chylomicrons into free fatty acids. These free fatty acids are then either used by muscle cells to create energy, stored in muscle or fat tissues, or broken down and transported into other substances by the liver. The lipoproteins enter two major pathways.

TABLE 59-10 Goals for Lipid Levels in Children

Lipid	Goal (mg/dL)
Cholesterol	<170
Low-density lipoprotein	<110
High-density lipoprotein	>45
Triglycerides	<125

TABLE 59-11 Classification of Lipoproteins

Phenotype (old classification)	Particles with elevated levels	Major lipid abnormality	Frequency
I	Chylomicron	TG	Very rare
IIA	LDL	LDL-C	Common
IIB	LDL and VLDL	LDL-C, TG	Common
III	IDL	TC, TG	Rare
IV	VLDL	TG	Common
V	Chylomicron	TG	Uncommon

IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL, very-low-density lipoprotein.

1. **Exogenous pathway.** Triglycerides hook onto chylomicrons and circulate systemically, where they are acted on by lipoprotein lipase. The triglycerides are then released as free fatty acids and monoglycerides, which are resynthesized in fat tissue where they are stored, subsequently resulting in production of chylomicron remnants.
2. **Endogenous pathway.** VLDL produced in the liver also interacts with lipoprotein lipase to release IDL particles, which are either removed by the liver or metabolized to LDL. Some of the LDL is brought to the subintimal space, where atheromas develop, causing atherosclerosis. Elevated LDL cholesterol (LDL-C), decreased HDL cholesterol (HDL-C), and an elevated ratio of total cholesterol to HDL predict increased risk for atherosclerosis in adults.

C. Evaluation

1. Studies to exclude secondary dyslipidemia should be instituted, including thyroid function tests as well as liver and renal function tests.
2. Lipids in all first and secondary relatives of the affected child should be measured.
3. I recommend ordering a lipid panel that includes total cholesterol, HDL, LDL, and triglycerides, as well as measurement of the size of the LDL particles.
4. Measurement of total cholesterol and HDL does not require fasting. Triglyceride and LDL levels should be measured following an overnight fast, but new methods to measure LDL directly do not require fasting specimens (these methods can be used to measure

LDL when the triglyceride level is >400 mg/dL) (Table 59-10).

D. Interpreting and managing abnormal lipid levels

1. Evaluation of elevated cholesterol

a. If the total cholesterol is between 170 and 199 mg/dL, repeat the test in 2 to 4 weeks and average the two levels (Tables 59-12, 59-13, and 59-14).

b. If the average is >170 mg/dL, or if the initial total cholesterol is >200 mg/dL, I recommend ordering a complete lipid profile (Table 59-13).

i. If the LDL is between 110 and 129 mg/dL, I recommend the Step 1 diet developed by the National Cholesterol Education Program (NCEP), which provides for <30% total fat (of which <10% is saturated fat and <300 mg cholesterol per day), 55% carbohydrate, and 15% to 20% protein. This diet is safe and does not interfere with growth. The goal is to achieve an LDL level <110 mg/dL by beginning the Step 1 diet and changing to the Step 2 diet if significant improvement has not been achieved in 3 months. This latter diet reduces saturated fat to <7% of total calories and dietary cholesterol to <200 mg/day. If dietary and exercise interventions have not p. 807p. 808p. 808p. 809reduced LDL to <160 mg/dL in 6 to 12 months, then pharmacotherapy should be considered.

TABLE 59-12 Treatments for Elevated LDL and TG in Children

Elevated LDL-C: Child 2 LDL		
2–21 yr	Refer to a registered dietician for family medical nutrition therapy: • 25%–30% of calories from fat, ≤7% from saturated fat, ~10% from monounsaturated fat; <200 mg/d of cholesterol; avoid *trans*-fats as much as possible	Grade B strongly recommended
	Supportive actions: • Plant sterol esters and/or plant stanol esters[a] up to 2 g/d as replacement for usual fat sources can be used after age 2 yr in children with familial hypercholesterolemia. • Plant stanol esters as part of a regular diet are marketed directly to the public. Short-term studies show no harmful effects in healthy children.	Grade A recommended

	• The water-soluble fiber psyllium can be added to a low-fat, low saturated fat diet as cereal enriched with psyllium at a dose of 6 g/d for children 2–12 yr, and 12 g/d for those ≥12 yr.	
Elevated TG or Non-HDL-C: Child 2—TG		

2–21 yr	Refer to a registered dietitian for family medical nutrition therapy:
	• 25%–30% of calories from fat, ≤7% from saturated fat, ~10% from monounsaturated fat; <200 mg/d of cholesterol; avoid *trans*-fats as much as possible
	• Decrease sugar intake:
	  • Replace simple with complex carbohydrates
	  • No sugar-sweetened beverages
	• Increase dietary fish to increase ω-3 fatty acids
		Grade B strongly recommended
		Grade A recommended
		Grade B recommended
		Grade D recommended

[a]Can be found added to some foods, such as some margarines.
HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

TABLE 59-13 Dyslipidemia and Atherosclerosis

Dyslipidemia that increases the risk of atherosclerosis	Dyslipidemia that decreases the risk of atherosclerosis
Elevated levels of the following:	**Decreased levels of the following:**
TC	TC
LDL	LDL
ApoB	ApoB
TC/HDL-C ratio	TC/HDL-C ratio
ApoB/HDL-C ratio	ApoB/HDL-C ratio
ApoB/apoA-I ratio	ApoB/apoA-I ratio
Lipoprotein(a), or Lp(a)	Lipoprotein(a), or Lp(a)
Decreased levels of the following:	**Elevated levels of the following:**
HDL	HDL
HDL-C	HDL-C
ApoA-I	ApoA-I
LDL-C/apoB ratio	LDL-C/apoB ratio

apoA-I, apolipoprotein A-I; apoB, apolipoprotein B; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

TABLE 59-14 Pharmacotherapy for Dyslipidemia

I. Children with type IIA or IIB hyperlipoproteinemia

- **A.** LDL >160–190 + family history of early CV disease
- **B.** LDL >160–190 + risk factors for CV disease (e.g., hypertension), HDL <35 mg/dL, obesity, diabetes mellitus
- **C.** LDL >190

II. Children with fasting hypertriglyceridemia

Triglyceride level (mg/dL)	Management
125–300	Weight reduction, exercise
300–500	If HDL <35 mg/dL, consider medication
500–1 000	Medication
>1 000	Medication

CV, cardiovascular; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

ii. Adding fiber to the diet is benign and can lower total cholesterol and LDL.

iii. If the LDL is >130 mg/dL, consider familial dyslipidemias and secondary causes of dyslipidemia (Table 59-15).

iv. Restriction of dietary cholesterol, saturated and *trans*-fat, along with liberal intake of dietary fiber and plant sterols, can lower LDL. High intake of p. 809p. 810ω-3 fatty acids can reduce serum triglycerides. A 28% reduction in LDL cholesterol levels with a diet that is low in saturated fat and cholesterol and rich in soluble fiber, plant sterols, soy proteins, and nuts.

TABLE 59-15 Clinical Characteristics and Treatment Options for High-Risk Adolescents with Hyperlipidemia

	Familial combined hyperlipidemia	Metabolic syndrome	FH heterozygote	FH homozygote
Total cholesterol (mg/dL)	200–250	200–250	250–350	600–700
Triglycerides (mg/dL)	175–350	>150	100–150	100–150
LDL cholesterol (mg/dL)	150–200	130–200	160–250	600–650

HDL cholesterol (mg/dL)	25–35	<35	45–55	45–55
Xanthomata	Rare	None	10% of teens	Common
Adolescent's 10-yr risk of myocardial infarction	<1%	<1%	15%–20%	Very high, 90%
Treatment used if TLC fails	Extended-release niacin, ω-3 fatty acids, fibrates, statins	Extended-release niacin, ω-3 fatty acids fibrates, statins	Statins with or without ezetimibe, extended-release niacin, or bile acid sequestrant	Biweekly apheresis

FH, Familial Hyperlipidemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TLC, therapeutic life change

v. The original adenosinetriphosphate (ATP)-3 guidelines were updated in 2004 and introduced an optimal LDL goal of <70 mg/dL for patients at very high risk of heart disease and also recommended drug therapy for these patients even at baseline LDL cholesterol levels <100. A meta-analysis of the four recent trials suggested a 16% reduction in the incidence of coronary death or any cardiovascular event with LDL cholesterol reduction to 75 mg/dL with high-dose statin therapy.

2. Management of elevated triglycerides (Tables 59-10, 59-14, 59-15, 59-16, 59-17). If the triglyceride level is >300 mg/dL, especially with an HDL level <35 mg/dL, pharmacotherapy can be instituted. Triglycerides are most responsive to lifestyle interventions, such as diet, and particularly low-fat diets. If there is no resolution, then pharmacologic intervention should be instituted with **fibrates, niacin, and/or *ω*-3 polyunsaturated fatty acids**. Key points to remember for lipoproteins and the significance of hypertriglyceridemia are the following:

a. Triglyceride levels >1 000 to 2 000 mg/dL are associated with an increased risk for **pancreatitis**.

b. Consider familial or inherited forms of hypertriglyceridemia.

c. Consider underlying diseases that could cause hypertriglyceridemia (such as DM, renal insufficiency, obesity, and alcoholism).

3. Dyslipidemias Tables 59-16 and 59-17

Concurrent with instituting a diet and exercise program, eliminate secondary causes of lipid disorders. These include obesity, poor diet, lack of exercise, smoking, alcohol, DM, hypothyroidism, liver and renal diseases, as well as drugs, such as diuretics, β-blockers, glucocorticoids, retinoid acid derivatives, and interferons ($-\alpha$, $-\beta$, $-\gamma$). These are all well known to **increase serum triglycerides**. Cyclosporine can increase LDL cholesterol levels, and **sirolimus** and **HIV-1 protease inhibitors** can cause severe hypertriglyceridemia. **Tamoxifen** can cause hypertriglyceridemia

p. 810p. 811in certain individuals but reduces LDL cholesterol levels. **Aromatase inhibitors** can modestly raise LDL cholesterol levels.

TABLE 59-16 Dyslipidemias—Frederickson Classification

Phenotype	Elevated particle	Lipid disorder	Frequency	Etiology
I	Chylomicron	Triglycerides >1 000 mg/dL	Rare	Lipoprotein lipase deficiency
IIA	LDL	LDL >130 mg/dL	Common	Familial hypercholesterolemia, familial combined hyperlipidemia (also DM, hypothyroidism, and nephrosis)
IIB	LDL VLDL	LDL >130 mg/dL Triglycerides >125 mg/dL	Common	
III	IDL	Total cholesterol >200 mg/dL Triglycerides >125 mg/dL	Rare	Apolipoprotein E2 homozygosity (also diabetes and kidney disease)
IV	VLDL	Triglycerides >125 mg/dL	Common	Familial combined hyperlipidemia, familial hypertriglyceridemia (also diabetes, hypothyroidism, Cushing, nephrosis, drugs, e.g., glucocorticoids, GH, androgens)
V	VLDL chylomicron	Triglycerides >1 000 mg/dL	Uncommon	

DM, diabetes mellitus; GH, growth hormone; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

TABLE 59-17 American Heart Association Statement for the Treatment of Children with High-Risk Lipid Disorders

Lipid	Frederickson class	Medication	
		First choice	Second choice
LDL	IIA	Statins (lovastatin, simvastatin, pravastatin, atorvastatin)	Bile acid–binding resin or niacin
LDL + triglycerides	IIB	Statins	Niacin or fibric acid derivatives
Triglycerides	IV	Statins	Fibric acid derivatives

Types I, III, and V are uncommon.
LDL, low-density lipoprotein.

a. Familial hypercholesterolemia is an autosomal dominant lipid disorder marked by an elevated LDL with or without a concurrent hypertriglyceridemia (1 in 500 people). Cord-blood LDL and total cholesterol are elevated in babies with familial hypercholesterolemia. Coronary heart disease can begin in the third decade in this disorder.

Homozygous familial hypercholesterolemia is caused by loss-of-function mutations in both alleles of the LDL receptor gene. Patients have a poor response to conventional drug therapy.

A potentially effective therapy for homozygous familial hypercholesterolemia is to reduce LDL production. In certain patients, there is a rare disorder of an absence of this protein; it is called **abetalipoproteinemia** and leads to the absence of all lipoproteins containing apolipoprotein B in the plasma. Therefore, an inhibitor was developed.

The **microsomal triglyceride transfer protein inhibitor** was effective in reducing cholesterol levels. There were, however, major side effects on liver enzymes. Therefore, this type of medication will need to be carefully studied to determine its safety.

b. Familial combined hyperlipidemia (1 in 200 to 300 people) is autosomal dominant, with elevated total cholesterol or

triglyceride in some and increased LDL and triglyceride in others. Premature coronary heart disease occurs in this group as well.

c. Lipid disorders in type 1 and type 2 DM. In a study called SEARCH one of three children with type 2 DM had elevated total cholesterol levels, and 50% of either type 1 or type 2 DM had elevated LDL levels. The optimal levels are the same as in nondiabetic children, which include an LDL <100, HDL >35, and triglycerides <125. The American Diabetes Association recommends initiation of **pharmacologic treatment in children 10 years or older with type 1 or type 2 DM if the LDL is >160 mg/dL** after glycemic control is established and other nonpharmacologic interventions fail. It should also be considered if the LDL is >130 to 159.

E. Pharmacotherapy for pediatric dyslipidemias

1. **Bile acid–binding resins** are poorly tolerated in children. The use of statins, therefore, is an obvious therapeutic choice. The American Heart Association says that ***statins*** **should be the first-line therapy in these children**. Statins have similar safety and efficacy in lipid disorders in children as in adults (Tables 59-18 and 59-19).

   Cholestyramine and **cholestipol** are taken with meals, when bile acids are secreted. Begin with one or two packets or scoops per day, given in p. 811p. 812orange juice or water with meals (breakfast and dinner). The dose is increased monthly until LDL is <130 mg/dL. They are not indicated in the condition of hypertriglyceridemia found in type 2B hyperlipoproteinemia. The child should not take other medications for at least 1 hour before or 3 hours after consuming resins.

TABLE 59-18 Dosing of HMG-CoA-Reductase Inhibitors

Statin	Adult dose	Pediatric dose
Lovastatin (Mevacor)	Initial: 20 mg/d PO qhs Followed by 10–80 mg/d PO qhs or divided b.i.d.	10–17 yr: 10 mg/d PO; not to exceed 40 mg/d
Simvastatin (Zocor)	Initial: 5–10 mg/d PO qhs Followed by 5–80 mg/d PO qhs or	10–17 yr: 10 mg/d PO; not to exceed 40 mg/d

	divided b.i.d.	
Pravastatin (Pravachol)	Initial: 10–20 mg/d PO qhs Followed by 5–40 mg/d PO qhs	8–13 yr: 10 mg/d PO initially; not to exceed 20 mg/d 14–17 yr: 10 mg/d PO initially; not to exceed 40 mg/d
Fluvastatin (Lescol)	Initial: 20–30 mg/d PO qhs Followed by 20–80 mg/d PO qhs; divide 80 mg into b.i.d.	<18 yr: not established
Atorvastatin (Lipitor)	Initial: 10 mg/d PO qhs Followed by 10–80 mg/d PO qhs	10–17 yr: 10 mg/d PO initially; not to exceed 20 mg/d

HMG-CoA-reductase, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase.

2. **Niacin** (nicotinic acid) has been effective in adults for types 2A, 2B, 4, and 5 hyperlipoproteinemia and is also effective in children. Beginning at a dose of p. 812p. 81350 mg/day, increase the dose gradually at monthly intervals until the LDL is <160 mg/dL (types 2A, 2B), or the triglycerides are <300 mg/dL (type 4), or until a maximal dose of 1 500 to 3 000 mg/m^2 is reached without liver toxicity. Split the dose as soon as you reach 100 mg/day. Once the LDL falls to <130 mg/dL, or the triglycerides fall to <125 mg/dL, either reduce the niacin dose or attempt a trial off medication.

TABLE 59-19 Medications for Dyslipidemia

Drug class	Examples	Action	Contraindications and side effects
Statins	Atorvastatin Fluvastatin Lovastatin Pravastatin Rosuvastatin Simvastatin	Inhibits hepatic cholesterol synthesis	Myalgia, myositis, raised aspartate, aminotransferase (AST [SGOT]) and alanine aminotransferase (ALT [SGPT])
Niacin	Extended-release niacin	Impairs VLDL (high TG)	Flushing, elevated AST and ALT
Fibrate	Gemfibrozil Fenofibrate	Impairs VLDL (high TG)	Dyspepsia, constipation, myositis, anemia
Bile acid sequestrant	Cholestyramine Colesevelam	Binds intestinal bile acids, interrupts	Gas, bloating, constipation, cramps

		enterohepatic recirculation	
Cholesterol absorption inhibitor	Ezetimibe	Inhibits cholesterol absorption from small intestine	Gas, bloating, constipation

TG, triglyceride; VLDL, very-low-density lipoprotein.

Side effects of niacin include liver disease, nausea, gastrointestinal upset, and facial flushing. The flushing may be reduced by ingestion of aspirin, but this is not generally recommended for children, especially if a viral illness is present or suspected.

Slow-release preparations of niacin include Slo-niacin, Niacor, Nicolar, and Niaspan, but these may be associated with a higher incidence of liver toxicity because higher niacin levels are sustained for longer periods. Liver function tests should be performed every 3 months in all children treated with niacin products.

3. **"Statins"** (3-hydroxy-3-methylglutaryl, coenzyme A [HMG-CoA] reductase inhibitors) (Tables 59-18 and 59-19). These "statins" inhibit production of HMG-CoA reductase, which controls the rate-limiting step in cholesterol biosynthesis. We begin treatment in children at the lowest dose available, which increases every 6 to 12 weeks until the LDL is <160 mg/dL or the maximal adult dose is reached without toxicity. Remember to scale back the dose in proportion to the child's weight compared with that of an adult. Using lovastatin as an example, I would not exceed 40 mg/day in a young child, compared with the maximal adult dose of 80 mg/day. If the LDL drops to <130 mg/dL, consider reducing the statin dose or discontinuing the medication. This group of drugs has been shown to be **effective and safe in children**. Included in the group are lovastatin (Mevacor), pravastatin (Pravachol), simvastatin (Zocor), fluvastatin (Lescol), and atorvastatin (Lipitor) (Table 59-19). The primary efficacy variable was change from baseline of carotid intima-medial thickness (IMT) as measured by ultrasound. The mean carotid IMT was attenuated after 2 years of treatment, although there was a trend toward an increase in the placebo group. LDL levels were reduced in the treatment group,

whereas HDL, triglyceride, and lipoprotein (a) levels remained unchanged. This statin was both effective and well tolerated, with minimal observable side effects. There were no negative effects on growth or sexual development. Resins were poorly tolerated in this age group; therefore, the use of statins is an obvious therapeutic choice. Lovastatin in teenage boys with familial hypercholesterolemia showed no adverse effects on growth or sexual development over the 48-week course of the study. Side effects include hepatocellular toxicity and, rarely, rhabdomyolysis. Liver functions should be monitored every 3 months.

4. **Fibric acid derivatives.** These drugs are useful in adults for treating types 2A, 2B, 4, and 5 hyperlipoproteinemias, but there are **few data on their use in children**. They include chlofibrate (Atromid-S), gemfibrozil (Lopid), and fenofibrate (Tricor). Tricor is indicated as adjunctive therapy in patients with primary hypercholesterolemia or mixed dyslipidemia (Frederickson types 2A and 2B). It increases HDL, reduces triglycerides, reduces LDL, reduces total cholesterol, and reduces apolipoprotein (apoB). The combined use of Tricor and statins should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk. This combination has been associated with rhabdomyolysis, marked elevated creatine kinase levels, and mild globulinuria, leading to acute renal failure.

   Before using fibric acid derivatives in children to treat a type 2 lipid disorder, I recommend using statins, bile acid–binding resins, or niacin. With elevated triglyceride levels, niacin, gemfibrozil, and atorvastatin should be considered.

   Side effects include myalgias, myositis, myopathy, rhabdomyolysis, liver toxicity, gallstones, and glucose intolerance. Gemfibrozil is less likely to cause gallstones than gemfibrate. I recommend monitoring liver functions every 3 months in children treated with this group of drugs.

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F. Summary

Occasionally, combination medications are indicated. For those with high LDL levels, various combinations of statins, bile acid–binding sequestrants, ezetimibe, and niacin can be used. For severe hypertriglyceridemia, a combination of statins, fibrates, and fish oils

may be used. The combination of statins and fibrates, however, may be associated with increased risk of serious myopathy and rhabdomyolysis and therefore should be used with great caution. Evaluate children with dyslipidemias every 3 months. Because premature cardiovascular disease is increasing, studies of the safety and efficacy of lipid-lowering drugs in children should be expanded.

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60 Type 1.5 Diabetes: Overlay between Type 1 and Type 2 Diabetes

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I. INTRODUCTION

Diabetes ketoacidosis (DKA [see Chapter 54]) is often associated with a stressful condition such as infection or trauma that is pathognomonic for type 1 diabetes (T1DM); however, new data suggest an increasing incidence of DKA cases without precipitating cause in children and adults with T2DM. These cases present with hyperglycemia along with ketosis which requires insulin to treat, but insulin can be discontinued after a few months and the patient can be maintained on diet control and oral hypoglycemic agents. This clinical presentation has been reported primarily in African Americans (AAs), Latinos, and other minority ethnic groups. This variant of T2DM has been referred to in the literature as idiopathic T1DM, atypical diabetes, Flatbush diabetes, diabetes type 1.5, and more recently as ketosis-prone type 2 diabetes mellitus (KPDM).

II. HISTORY AND CLINICAL PRESENTATION

In 1994, DKA was noted in young, obese AAs of Caribbean descent who lived in the Flatbush area of Brooklyn, New York. They showed elevated serum C-peptide levels and negative islet cell antibodies or glutamic acid decarboxylase (GAD) antibodies that led to the creation of the name “Flatbush diabetes.”

It was initially thought that KPDM was exclusively present among AAs; however, different studies reported different ethnicities affected worldwide, including Caucasians, Hispanics, Chinese, South Asians, and sub-Saharan Africans. AAs and Hispanics appear to have the highest risk, and Caucasians and Asians have a much lower risk of developing the disease (<10%).

Most patients with new-onset KPDM present with polyuria, polydipsia, and weight loss. They may also show signs of nausea,

vomiting, and abdominal pain. The latter is usually seen when hyperglycemia accompanies urinary ketonuria and acidosis (DKA). The majority of patients are overweight or obese but will notice a recent weight loss between 4 and 12 kg. Most of these patients have a family history of T2DM. Physical examination is commonly significant for acanthosis nigricans and abdominal adiposity in both adult and pediatric populations.

A majority of KPDM patients present with hyperglycemia and no precipitating factor for ketoacidosis. Mean blood glucose (BG) is usually very high (>500 mg/dL) along with a pH of <7.30 and a mean hemoglobin A_{1c} >12%. It is important to note that only 17% of these patients have positive antibodies at the time of diagnosis, which is significantly lower compared with lean DKA patients in whom 65% have at least one antibody present.

III. PATHOPHYSIOLOGY

Insulin sensitivity is low at the time of diagnosis in the above-mentioned patients; however, their condition improves at the time of remission when normoglycemia occurs. Likewise, C-peptide levels decrease at the time of DKA but returns to normal levels later in the course. The improvement in both insulin sensitivity and *β*-cell function is the main characteristic of the disease.

It is also suggested that in such patients glucose toxicity plays an important role—a metabolic phenomenon that happens when there is desensitization of *β*-cells and impaired insulin secretion in response to sustained elevations of plasma glucose. p. 815p. 816When insulin binds to its membranous receptors, it activates a cascade of intracellular signaling molecules via phosphorylation. As a result of this interaction, protein kinase enzyme Akt becomes activated. This enzyme is responsible for glucose transport and glycogen accumulation in skeletal muscle cells. Studies have shown that AKT response to insulin is decreased in KPDM patients, which is likely one of the etiologies of insulin resistance in these patients.

IV. TREATMENT

A. Acute management

Diabetic ketoacidosis consists of three major components: BG > 250

mg/dL, pH ≤7.3, HCO_3 <18 mEq/L, and the presence of ketones in serum or urine. Treatment includes intravenous (IV) hydration, continuous IV insulin administration, and electrolyte replacement. The response to treatment in KPDM patients is similar to that in the T1DM treatment course and usually takes less than 14 hours. After DKA resolves, a higher insulin dose at about 0.7 to 0.8 U/kg of subcutaneous insulin is needed to achieve normoglycemia. Like T1DM, a combination of multiple daily injections, including short- and long-acting insulin, is effective in controlling BG in the initial phase.

B. Long-term management

It is suggested to monitor patients every 2 weeks for the first 2 months to adjust insulin therapy and then every 2 or 3 months depending on glycemic control. Patients with negative GAD and with fasting C-peptide level > 1.5 ng/dL or stimulated C-peptide level >2.25 ng/dL can start low-dose sulfonylurea (glyburide 1.25 to 2.5 mg/day), pioglitazone 30 mg/day, or metformin (500 mg b.i.d.) therapy. Insulin may be tapered when fasting BG levels are ≤130 mg/dL for 2 weeks or if the patient experiences hypoglycemia, defined as a BG <70 mg/dL. The majority of patients can taper insulin dose by 25% at each follow-up visit and discontinue insulin entirely after 3 months.

Negative antibody status and positive β-cell reserve as determined by a fasting C-peptide level of >1.0 ng/dL or a glucagon-stimulated C-peptide of >1.5 ng/dL correlate with the ability to discontinue insulin therapy during follow-up. Continuation of insulin treatment is recommended in patients with low β-cell reserve, and most of these patients require multiple daily insulin injections to avoid hyperglycemic relapse. The best predictor of remission in KPDM appears to be stimulated C-peptide response to glucagon. AA or Hispanic ethnicity, newly diagnosed diabetes, obesity, family history of T2DM, and a lower insulin requirement are all potential predictive factors that support remission.

V. REMISSION

Remission is defined as A_{1c} of ≤7% and a fasting BG of <130 mg/dL that is maintained after the discontinuation of insulin. Even if remission has been achieved, studies have reported that such individuals have variable β-cell function, and if treated solely with diet and lifestyle modification,

they develop an increasing insulin dependence over time. Similar to T2DM patients, individuals with KPDM have gradual loss of β-cell function. Recurrence of hyperglycemia or ketosis after the discontinuation of insulin occurs within 12 to 24 months in nearly 60% of patients who are on diet alone.

Lifestyle and dietary modifications remain an important aspect of long-term KPDM management; however, oral hypoglycemic agents are recommended as an adjuvant treatment. Glipizide (2.5 mg/day), glyburide (1.25 to 2.5 mg/day), or pioglitazone (30 mg/day) has shown to be successful in maintaining normoglycemia and preventing acidosis. There is ongoing research on other oral hypoglycemic agents, such as metformin, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1.

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61 C-Peptide

Åsa Davis

I. C-PEPTIDE INTRODUCTION

The measurement of connecting (C)-peptide is now a well-accepted method for the quantification of endogenous insulin secretion and β-cell function. C-peptide is generated as a by-product when proinsulin is converted to insulin by proteolytic cleavage. It is released by the β-cells at a 1:1 molar ratio to insulin and is considered to reliably reflect the endogenous insulin production. C-peptide circulates at a concentration of approximately 10 times higher than that of insulin, as in contrast to insulin itself, it escapes hepatic retention. Furthermore, the administration of exogenous insulin does not affect the measurement of C-peptide levels as it would insulin. C-peptide can be measured by highly sensitive assays in both serum and urine, and the two methods have been shown to correlate well.

II. C-PEPTIDE IN THE NATURAL HISTORY OF T1D

A. C-Peptide in recently diagnosed individuals

Type 1 diabetes (T1D) is the result of an immune-mediated destruction of the pancreatic β-cells, caused by a combination of genetic, environmental, and immune factors. The measurement of C-peptide before, at, and after diagnosis of T1D has helped elucidate the natural history of β-cell function in T1D. Studies have shown that most individuals have some residual insulin secretion at the time of diagnosis, although the absolute C-peptide levels at diagnosis varies greatly depending on how the patient is diagnosed. Studies such as Diabetes TrialNet in which antibody-positive individuals are closely monitored with serial oral glucose tolerance testing usually diagnose T1D early, before the development of clinical symptoms. As a result, C-peptide levels in study participants are usually higher than those in individuals diagnosed with clinical symptoms and/or those hospitalized, both of which indicate that an individual has progressed to a later stage in the disease course. C-peptide levels at the time of diagnosis also depend on age and the level of insulin resistance, with

younger individuals having lower C-peptide levels compared with adults, and those with higher body mass index (BMI) and thus a higher likelihood of insulin resistance, often presenting with higher C-peptide levels compared with those with lower BMI. At the time of diagnosis, preteen children have lower levels of C-peptide than older children and adults, which may reflect a lower baseline β-cell mass. However, the rate of fall of insulin secretion is greater in children of all ages when compared with adults, suggesting a more aggressive destruction of the β-cells. C-peptide levels fall rapidly in the first 2 years after diagnosis, with a more rapid decline during the first year. This rate of fall is significantly attenuated in adults. Other factors that impact the change in secretion postdiagnosis have also been described, and these are glycemic control, BMI, antibodies, and human leukocyte antigen type; however, these factors have not been found in all studies, suggesting that age is the key variable. Indeed, while intensively treated subjects in the Diabetes Control and Complications Trial (DCCT) had preserved C-peptide as compared to those randomized to conventional care, a recent clinical trial using state-of-the-art insulin delivery was unable to show differences in C-peptide between treated and control individuals, suggesting that only markedly abnormal glycemic control contributes to β-cell dysfunction.

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B. C-peptide in individuals with longer T1D duration

It has been generally accepted that there is a linear decline in β-cell function both before and after diagnosis, as proposed by the Eisenbarth model, and that this eventually leads to complete β-cell dysfunction in all individuals with T1D. However, this dogma has been challenged by several recent studies suggesting that T1D is a more heterogeneous and complex disease than what was previously described, that the fall in insulin secretion prior to diagnosis is not linear, and that the majority of individuals with T1D have some residual β-cell function even many years after diagnosis.

In a recent study, we determined the frequency of detectable ($\geq$0.017 nmol/L) C-peptide in a nonfasting serum sample of 919 individuals with established T1D from clinics across the United States. The overall frequency of detectable C-peptide was found to be 29%. Among patients diagnosed with T1D >18 years of age, the percentages of individuals with detectable C-peptide were 78, 60, 35, 19, and 16,

respectively, in the different T1D duration groups (3 to 5, 6 to 9, 10 to 19, 20 to 40, and >40 years). Contrastingly, in individuals diagnosed ≤18 years of age, 46%, 20%, 9%, 7%, and 6% in the respective duration group had detectable C-peptide. Although the levels of nonfasting C-peptide were consistently higher in participants diagnosed as adults (>18 years of age) than those diagnosed as children (≤18 years of age), the proportion of subjects with detectable C-peptide decreased with longer T1D duration. Surprisingly, although diagnosis later in life was associated with a greater frequency of detectable C-peptide, a small percentage of participants in both groups were found to still have detectable C-peptide many years after diagnosis. The presence of C-peptide in individuals with more advanced T1D and the association with age at diagnosis and disease duration has also been demonstrated in other recent studies. Researchers in the United Kingdom found that 80% of patients in a cohort of 924 individuals, with a diabetes duration >5 years, had detectable endogenous C-peptide production as measured by urine C-peptide-to-creatinine ratio. Furthermore, in a cohort of individuals with a T1D duration >50 years, investigators from the Joslin Diabetes Center showed that more than 67% of these patients had detectable random serum C-peptide levels. Using assays with lower limits of detection, one can find that even more individuals are likely to have some indication of detectable C-peptide. Evidence of residual β-cell function in long-standing T1D is also supported by early as well as more recent histological findings demonstrating insulin positive β-cells in postmortem pancreata from individuals with longer duration of T1D. Moreover, recent work has noted that although β-cells may be devoid of insulin, proinsulin may be present in islets of those with long-standing disease.

Collectively, studies using C-peptide as a measure of β-cell function suggest continued function of insulin-producing β-cells even long after T1D diagnosis, and thereby contradict the description of T1D by the American Diabetes Association 2014 Standards of Care as "β-cell destruction, usually leading to absolute insulin deficiency." This description has led to the common notion among many nonspecialty clinicians that residual insulin secretion is very unusual in individuals with long-standing T1D. As a result, some clinicians erroneously exclude the diagnosis of T1D on the basis of the presence of residual secretion, which can lead to inappropriate treatment with

oral hypoglycemic therapies in lieu of insulin. Furthermore, in the United States, one of the criteria used by the Centers for Medicare and Medicaid Services for covering the use of insulin pumps for individuals with T1D is low or absent C-peptide, thus potentially depriving individuals from using such well-accepted technology to manage their disease.

C-peptide has been used as a biomarker for monitoring T1D disease course, but also in intervention trials, where a mixed meal tolerance test–induced C-peptide is considered a reliable primary endpoint for evaluating the effect of drugs meant to maintain or improve the function of the insulin-producing β-cells. The data from our study and others, showing a variable disease course in people with T1D, stress the importance of selecting the appropriate participants in prevention trials, including participants who have a steady, as opposed to a steep, C-peptide decline and are thus more likely to benefit from treatment, recognizing heterogeneity in the loss of C-peptide and disease progression among individuals with T1D.

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III. CLINICAL BENEFIT OF RESIDUAL C-PEPTIDE IN T1D

Several studies have suggested that preserved β-cell function in T1D as measured by residual C-peptide may have clinical significance and could help identify individuals at risk for diabetes-related complications and faster disease progress. In the groundbreaking DCCT, it was established that intensive treatment (three or more insulin injections per day and frequent blood glucose checks) could delay the start, and slow the progression, of diabetes-related complications, such as retinopathy, nephropathy, neuropathy, and cardiovascular disease. This benefit, however, came along with the added complication of a higher incidence of severe hypoglycemia. DCCT investigators hypothesized that residual insulin secretion among those randomized to intensive therapy could preserve the clinical benefits of reduced long-term complications without an increase in hypoglycemia. This was indeed found. Among the participants in the intensively treated group, individuals with C-peptide levels ≥0.2 nmol/L had a reduced risk of developing retinopathy and microalbuminuria, as well as a lower risk of severe hypoglycemia compared with individuals with C-peptide levels <0.2 nmol/L. More recent analysis of DCCT subjects found that any level of C-peptide

secretion in the intensively treated group was associated with reduced incidence of retinopathy and nephropathy, whereas the rates of hypoglycemia in this group were significantly lower in individuals with higher C-peptide levels compared with those with modest C-peptide levels.

The correlation between residual C-peptide and clinical benefits in T1D points to C-peptide as a useful biomarker. Although not widely accepted, one group has also suggested that the peptide itself is bioactive and may directly decrease diabetes-induced defects, leading to possible complications, such as inflammatory vascular responses, reduced microvascular circulation, and renal and nerve dysfunction.

It is noteworthy that improvements in clinical care have led to an overall reduction in macro- and microvascular complications for those with diabetes. However, the increasing incidence of T1D, as well as the increasing prevalence of hypoglycemic unawareness (see Chapter 53), particularly in those with long-standing disease, emphasizes the importance of endogenous β-cell function. It has been shown that even a small increase in endogenous insulin production as measured by C-peptide after an islet transplant can lead to clinical improvements, such as fewer severe hypoglycemic events and lower HbA_{1c} values. Additional efforts are ongoing to preserve β-cell function before or soon after clinical diagnosis.

IV. CONCLUSIONS

Taken together, recently performed functional studies using sensitive C-peptide assays and earlier histology work showing intact, insulin positive, β-cells in pancreata from individuals with several years of T1D duration have shown that many individuals with T1D will continue to secrete low levels of insulin decades after being diagnosed with T1D and have led to a better understanding of the heterogenic nature of this disease. Yet, it remains unknown as to whether or not such low levels of C-peptide are clinically meaningful. Studies are underway to explore this in further detail by assessing β-cell function and its relationship with islet function, β-cell stress, β-cell death, glycemic control, and insulin sensitivity. Additional longitudinal studies evaluating the change in C-peptide over time in individuals with varying disease duration are also ongoing. This work will help determine whether residual function stems from cells that have evaded immune-mediated destruction or regenerating β-cells.

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62 Cystic Fibrosis Related Diabetes

Katie Larson Ode and Andrew W. Norris

I. INTRODUCTION

Cystic fibrosis (CF) is a severe multisystem autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) anion channel. CF leads to early mortality primarily caused by pulmonary disease and respiratory failure. Cystic fibrosis related diabetes (CFRD) is a unique form of diabetes mellitus with high prevalence in patients with CF. Uncontrolled CFRD speeds the rate of lung function decline in those with CF and increases morbidity and mortality in this population.

II. PATHOGENESIS OF CFRD

A. Insulin deficiency

1. **Insufficient insulin secretion is the primary cause of CFRD.** Insulin secretion in response to glucose challenge is delayed and blunted. Unlike type 1 diabetes, there is **no *β*-cell autoimmunity** in CFRD. The mechanisms underlying poor insulin secretion are multifactorial.
2. **Exocrine pancreatic disease** is likely a major factor underlying impaired insulin secretion in CFRD. Individuals with CF who escape exocrine pancreatic destruction have markedly lower risk of CFRD. In animal models, there is a marked inflammation of the pancreas early in the course of CF. This inflammation is associated with a partial loss of *β*-cell mass and ultimately a marked structural remodeling of islets.
3. ***β*-Cell mass is reduced** in CFRD. Although the loss of exocrine acinar tissue is extensive in CF, islet mass is not as severely affected. Postmortem pancreatic specimens show partial, but variable, loss of *β* cells in CF. The average degree of *β*-cell loss is typically estimated at about 50%, which is generally not thought sufficient alone to induce diabetes. Furthermore, the degree of *β*-

cell loss does not predict which CF patients develop diabetes.

4. **Amyloid deposits** are common in islets among many CFRD patients. It is not known whether amyloid deposits cause *β*-cell loss/dysfunction or whether the deposits are merely a marker of stressed *β* cells.
5. **Defects in *β*-cell function** are thought to contribute to poor insulin secretion in CFRD. This long-standing suspicion has been borne out in studies of cultured islets from CF animals and in islets with acute disruption of CFTR.

B. Insulin resistance

1. **Clinically apparent insulin resistance is not inherent to CFRD.** Patients with CFRD typically respond to conventional doses of insulin commensurate with their degree of insulin deficiency (See VIII. B. for more details).
2. **Transient insulin resistance.** A degree of insulin resistance is common during CF exacerbations and during glucocorticoid administration. Insulin doses typically need to be increased during such periods. The reduction in insulin sensitivity during exacerbations is thought to be related to inflammation and cytokine actions on insulin-sensitive tissues.
3. **Clinically subtle insulin resistance may be common in CFRD.** Hepatic insulin resistance has been repeatedly demonstrated by hyperinsulinemic euglycemic clamp studies in pancreatic insufficient CF patients. More generalized insulin resistance, demonstrable by clamp, is present in some with CFRD. The involved mechanisms are unclear, but may be secondary to poor health and/or glucose toxicity.

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C. Altered alimentary function

1. Altered gut function in CF is postulated to contribute to CFRD in several manners. Incretin levels are often low in CF, and this may contribute to reduced *β*-cell function. Gastric emptying can be accelerated in CF, and this may contribute to a pattern of early hyperglycemia during oral administration of glucose.

D. Genetic contributions

1. **A family history of type 2 diabetes** increases the risk of CFRD by approximately threefold. Genetic polymorphisms in several genes have been shown to increase the odds of developing

CFRD. Many of these are established type 2 diabetes susceptibility polymorphisms, whereas other loci modify CF exocrine pancreatic disease.

E. Diabetes complications unique to CFRD

1. CFRD induces several complications not common with other forms of diabetes. These complications are worsening of lung disease and impairment of proper weight gain/maintenance even when the diabetes is not severe. The mechanisms involved are not well understood. Possible mechanisms include loss of insulin's anabolic effects, nitrogen catabolism, advanced glycation end products, and hyperglycemia-induced oxidative stress.

III. PREVALENCE

A. Prevalence of CF. CF is most prevalent in individuals of Northern European descent. However, CF can be found in people of all ethnic backgrounds. It occurs in 1 of 3 500 live births in the United States and in 1 of every 2 000 to 3 000 live births in the European Union. Life expectancy has improved dramatically and people with CF now regularly live to adulthood.

B. Prevalence of CFRD. CFRD has an extremely high prevalence in those who have CF. Prevalence increases dramatically with age. Approximately 2% of children have CFRD. This rises to 15% of adolescents and 40% of those >18. Those with the most severe and most common CF gene mutations have a nearly 80% prevalence of CFRD by the age of 40 years.

C. Risk factors for CFRD

1. CFTR mutation—Severe CFTR gene mutations increase the risk for CFRD, with the most common mutation, deltaF508, being extremely high risk.
2. Exocrine pancreatic disease—Pancreatic insufficiency is a major risk factor for CFRD.
3. Liver disease—CF-associated liver disease also increases the risk for CFRD.
4. Female sex—Female sex is associated with increased morbidity in the presence of CFRD.
5. Age—Increasing age is associated with an increased risk for CFRD.
6. Family history of type 2 diabetes—A family history of type 2 diabetes is associated with an increased risk for CFRD.

D. Prevalence of prediabetes. Prediabetic states are common in those with CF. Impaired glucose tolerance and abnormal findings on oral glucose tolerance test (OGTT)are typically found for an extended period prior to the development of CFRD. Glucose tolerance often waxes and wanes with illness status and glucocorticoid exposure prior to the development of stable CFRD. Measured rates of prediabetes range from 10% to 40% in the nondiabetic CF population, depending on age.

IV. SCREENING

A. Need for screening in the CF population. Early CFRD is almost always clinically silent, but is accompanied by clinical decline years prior to the development of clinical symptoms. **Because of this, screening is the standard of care in CF.**

B. Recommended screening tests

1. **Routine screening—OGTT.** This is the recommended screening test in patients with CF for routine screening. Results of OGTT predict long-term outcomes in those with CF. Although OGTT values vary for any given CF patient, the worst p. 824p. 825recorded values on OGTT for a given patient correlate with long-term clinical outcomes.
   a. **Protocol for OGTT.** Consensus guidelines recommend that OGTT screening start at age 10 and that OGTT be performed yearly in all CF patients at a time when they are at baseline health, excluding those who have an established diagnosis of diabetes. 1.75 g/kg (maximum 75 g) of glucose is administered orally after a fast. Blood glucose levels are checked at 0 and 120 minutes. Many centers also include insulin levels or intermediate (e.g., 60 minute) time points as well in their screening protocol. Diagnostic interpretation of OGTT results are detailed below.
2. **Screening during inpatient admissions.** CFRD diagnosed during inpatient admission for pulmonary exacerbation predicts the development of diabetes complications and lung function decline in patients with CF. Because of the increase in inflammation associated with pulmonary exacerbation, it is not uncommon for patients with CF to develop new diabetic-range blood sugars while

they are hospitalized. This can be worsened by drug therapies, such as glucocorticoids, used in the context of inpatient therapy.

a. **Protocol for screening during inpatient admissions.** The guidelines recommend point-of-care blood glucose testing done fasting, prior to meals, 2 hours after meals, and at bedtime for the first 48 hours of admission for all CF patients admitted for pulmonary exacerbation treated with intravenous antibiotics or glucocorticoids.
b. **Screening results.** The presence of blood glucose levels persistently >200 for 48 hours is considered abnormal and diagnostic of CFRD. Such patients may require insulin therapy for the duration of diabetic-range hyperglycemia, which often resolves with illness resolution—allowing cessation of insulin therapy when blood glucose levels normalize.

3. **Continuous glucose monitor.** This technology has not yet been endorsed by the official guidelines for screening as there are no consensus criteria for diagnostic interpretation. Nonetheless, some CF centers use this methodology for screening. Ultimately, this technology may prove to be the most sensitive method to detect glycemic abnormalities in CF.

C. Tests not recommended for screening.

1. **HbA_{1c}**. For various and partly unexplained reasons, **HbA_{1c} is often not fully elevated in CFRD.** Because of this, CF patients with diabetic blood sugars can still have a normal HbA_{1c}. Therefore, a normal HbA_{1c} cannot rule out diabetes in a patient with CF and makes a very poor screening test in this population. HbA_{1c} **should not be used** to screen for diabetes in patients with CF.
2. **Fasting blood glucose.** Fasting hyperglycemia is a late finding in CFRD. Patients typically have normal fasting blood sugars well past the point of significant clinical decline from diabetes. Because of this, the use of fasting blood glucose to screen for diabetes in CF will miss a large and clinically relevant number of patients. Therefore, fasting glucose **should not be used** for diabetes screening in CF patients.

V. DIAGNOSIS

A. Prediabetes—Prediabetes in CF is associated with more rapid

progression to CFRD and problems maintaining weight/body mass index (BMI) (Table 62-1).

1. **Indeterminate glycemia**
   - **a.** Fasting blood sugar <126 mg/dL, 2-hour blood sugar <140 mg/dL with blood sugar at intermediate time point of OGTT test ≥200 mg/dL
2. **Impaired glucose tolerance**
   - **a.** Fasting blood sugar <126 mg/dL and 2-hour blood sugar on OGTT testing >140 to under 200 mg/dL
3. **Impaired fasting glucose**
   - **a.** Fasting blood sugar >100 and <126 mg/dL
   - **b.** When isolated, this abnormality is not associated with worsened outcomes in patients with CF.

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TABLE 62-1 Criteria for Glucose Tolerance Category Based on OGTT Results

Glucose tolerance category	Fasting glucose (mg/dL)	Mid-point glucose (mg/dL)	120-min glucose (mg/dL)
CFRD	≥126[b]	N/A	≥200[a]
IGT	<126	N/A	≥140 and <200
INDET	<126	≥200	<140
IFG	≥100 and <126	<200	<140
Normal	<100	<200	<140

CFRD, cystic fibrosis related diabetes; IGT, impaired glucose tolerance; INDET, indeterminate glycemia; IFG, impaired fasting glucose; OGTT, oral glucose tolerance test.

[a]Fasting blood sugar ≥126 is sufficient for the diagnosis of diabetes as a single criterion and 120-minute glucose ≥ 200 mg/dL is sufficient for the diagnosis of diabetes as a single criterion.

B. CFRD

1. **Fasting blood sugar ≥126 mg/dL**
2. **Two-hour glucose on OGTT ≥200 mg/dL**
   - **a.** The subject may have 2-hour elevation without fasting elevation.
   - **b. Must be confirmed** by additional testing
     - **i.** Some centers confirm by home self-blood glucose

monitoring showing recurrent blood glucose levels >200 mg/dL.

ii. Some centers confirm with second OGTT.

iii. Some confirm with continuous glucose monitoring.

3. **Random blood sugar ≥200 mg/dL in the presence of symptoms of diabetes**
4. **HbA_{1c} >6.5**
   a. **HbA_{1c} cannot be used to rule out diabetes in a patient with CF**—This is because patients with CF who have diabetes commonly have HbA_{1c} levels in the normal or borderline range (even when their diabetes is uncontrolled on the basis of chronic-marked abnormal elevation of serum glucose levels). Therefore, although **an HbA_{1c} >6.5 does rule in diabetes** in a patient with CF, **an HbA_{1c} <6.5 cannot rule out diabetes** in a patient with CF.
5. **Date of diagnosis**—The date of diagnosis is the date the patient first met criteria for CFRD even if the patient has subsequent normalization of blood sugar levels.

VI. COMPLICATIONS

A. Microvascular complications. Microvascular complications—diabetic retinopathy, nephropathy, and neuropathy—can occur in CFRD and are directly related to the duration of diabetes and glycemic control, similar to type 1 diabetes. Guidelines for screening, follow-up, and treatment of microvascular complications in patients with CFRD are derived from those for patients with type 1 diabetes, detailed below.

B. Macrovascular complications. Cardiovascular disease has not been documented in association with CFRD. The reason for this is unknown, but is speculated to be related to the lack of hyperlipidemia in CF patients. This may change as rates of obesity increase in this population and as life spans lengthen.

C. Diabetic ketoacidosis. This acute complication does not typically occur in CFRD. However, just like the general population, patients with CF can develop type 1 diabetes, including markers of islet autoimmunity and risk of diabetic ketoacidosis.

D. Hyperosmolar coma. Does not occur in typical CFRD.

E. Hypoglycemia. Hypoglycemia is a common acute complication of

CFRD and is discussed in greater detail further below.

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VII. GOALS OF TREATMENT

A. Preservation of lung function

1. CFRD and prediabetic states are associated with increased lung function decline in CF.
2. Prevention of glycemic excursion and the use of insulin treatment decrease the rate of lung function decline.

B. Suppression of catabolism

1. BMI and weight maintenance are intimately linked with mortality in CF. CF disease promotes excess catabolism, which is worsened by insulin insufficiency and hyperglycemia. Insulin therapy helps reverse catabolism and improves weight and BMI in CF patients.

C. Prevention of microvascular complications

1. Tight glycemic control can be presumed to prevent diabetic microvascular complications, just as in common forms of diabetes.
2. Yearly screening for retinopathy, microalbuminuria, and neuropathy beginning at 5 years from diagnosis is recommended.

VIII. THERAPY

A. Nutritional therapy

1. **CF patients diagnosed with CFRD should continue to follow the high-calorie, high-fat, and high-sodium diet recommended for all CF patients.** This is due to the fact that most patients are at high risk for nutritional failure. Attainment and preservation of good nutritional status is paramount for survival in CF.
2. **Usual dietary management for type 1 diabetes and type 2 diabetes does not apply in CFRD.**
3. **Sugar-containing beverages**—Expert consensus recommends avoidance of sugary beverages devoid of other nutritive substances. If the patient does intake these, they must be taken only with meals and snacks.
4. **Carbohydrate counting**—Carbohydrate counting is essential to the management of CFRD if the patient requires insulin therapy, as glycemic stress with meals is the major cause of hyperglycemia in CFRD, and patients typically must consume large amounts of

carbohydrates to meet caloric goals for the CF diet.

5. **Oral supplements/enteral feedings**—Patients with CF often require oral supplements/enteral feedings to maintain/increase weight. Patients with CFRD often require these as well. The oral supplements used should be those best appropriate for typical CF nutrition therapy. **"Diabetic" supplements or feeds should not be used**.

B. Insulin therapy (see Table 62-2 for example regimens)—A variety of insulin regimens are used to treat CFRD. Common general approaches are outlined here.

1. **Dosing**—Patients with CFRD typically maintain partial endogenous insulin secretion, so **insulin doses are modest compared with those required by a patient of similar age/weight with type 1 diabetes**.
2. **Bolus-only insulin therapy**—Patients with CFRD without fasting hyperglycemia can typically be treated with bolus insulin therapy prior to meals and snacks, without the use of long-acting insulin. The patient is given short- or rapid-acting insulin prior to all meals and snacks on the basis of an insulin-to-carbohydrate ratio. This ratio is adjusted on the basis of 2-hour postprandial glucose levels.
3. **Basal-bolus insulin therapy**—Patients with CFRD that have fasting hyperglycemia are treated with a basal-bolus insulin regimen. Basal insulin requirements are typically lower than required in type 1 diabetes. As in a bolus-only regimen, an insulin-to-carbohydrate ratio is used and short- or rapid-acting insulin is given prior to all meals and snacks.
4. **Insulin pump therapy**—Insulin pumps have been shown to be effective in CFRD and can result in better compliance because of more convenient coverage of the frequent large snacks that patients with CF typically consume. Insulin pump regimens are very similar to those for type 1 diabetes mellitus, except for the lower doses needed.

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TABLE 62-2 Example Insulin Regimens for CFRD

Standard CF diet

18-yr-old male with fasting and prandial hyperglycemia and normal BMI (weight 75 kg)

Insulin pump

Insulin aspart

- Basal rate
  0.5 U/hr
- Insulin-to-carbohydrate ratios:
  1 U for every 10 g of carbohydrate with breakfast
  1 U for every 20 g with lunch and supper
  1 U for every 25 g with all snacks
- Sensitivity:
  1 U to drop blood sugar by 60 mg/dL

21-yr-old female with prandial but without fasting hyperglycemia and normal BMI, weight 60 kg

Bolus-only regimen

Insulin lispro

- Meal coverage:
  1 U for every 30 g with all meals and snacks
- Correction dose:
  0.5 U for every 50 mg/dL blood sugar is over 150 mg/dL
- No long-acting insulin

40-yr-old female with fasting and prandial hyperglycemia, long history of CFRD, weight 50 kg

Basal-bolus regimen

Insulin glargine

- Basal dose:
  20 U daily

Insulin aspart

- Meal coverage:
  1 U for every 15 g of carbohydrate with all meals and all snacks
- Correction dose:
  1 U for every 50 mg/dL blood sugar is over 150

Supplemental feedings

Overnight enteral feeds are initiated on an 18-yr-old male with CFRD without fasting hyperglycemia. Daytime glycemia is well controlled on meal boluses of insulin lispro of 1 U for every 15 g of carbohydrate. His 8-hr overnight continuous feed contains a total of 150 g of carbohydrate.

Continuous/Overnight regimen

In addition to his previous regimen:

NPH mixed with regular insulin

- Overnight meal dose
  7 U of NPH mixed with 3 U of regular insulin given at the beginning of the feed
  Covers 150 g of carbohydrate at a ratio of 1 U for every 15 g of carbohydrate (could also be given as 10 U of NPH/Regular 70/30 at the beginning of the feed)

Three daytime bolus feeds are added to the nutrition regimen of a 24-yr-old female with CFRD without fasting hyperglycemia, a person who is already on overnight feeds. She is reasonably controlled on coverage of all meals and snacks with 1 U of insulin aspart for every 10 g of carbohydrate and 10.5 U of NPH and 4.5 U of regular insulin mixed and administered prior to the 150-g 8-hr continuous overnight. Each bolus feed contains 50 g of carbohydrate.

Bolus supplement regimen

In addition to her previous regimen: Insulin aspart • Bolus supplement (meal) 1 U for every 10 g prior to the bolus feed (5 U prior to each feed of 50 g of carbohydrate)
BMI, body mass index; CF, cystic fibrosis; CFRD, cystic fibrosis related diabetes; neutral protamine Hagedorn insulin (NPH, an intermediate-acting insulin)

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5. **Basal only**—The guidelines **do not recommend basal-only** therapy for patients with CFRD.
6. **Timing of insulin**—As postprandial elevations are the most significant blood sugar elevations in most patients with CFRD, insulin should always, except in very exceptional cases, be administered **before** meals and snacks.
7. **Enteral feeds**—Insulin regimens, coupled to overnight enteral feeds, are very effective in reversing weight loss in CF. In some cases, CF patients may be able to have good glycemic control and reversal of weight loss utilizing insulin only with overnight feeds.
    a. **Insulin dosing for enteral feeds**—Insulin dosing should be based on the duration of the feed and the total amount of carbohydrate to be provided.
        i. **Bolus feeds**—These can be treated as a typical meal and covered with short- or rapid-acting insulin utilizing the patient's typical meal insulin-to-carbohydrate ratio.
        ii. **Overnight or continuous feeds**—These are treated as a lengthened meal. The total amount of carbohydrate to be consumed is calculated and the units of insulin to be given are determined on the basis of the patient's insulin-to-carbohydrate ratio. The type of insulin used is determined by the duration of the feeding. Because enteral feeds provide a steady and continuous supply of carbohydrate, these are well matched by basal insulins of similar duration to the feed. An example would be an 8-hour overnight feed, which is usually well covered by covering the total amount of carbohydrates with a 70/30 mixture of NPH/regular insulin given at the time the feed is started. The dose is subsequently adjusted on the basis of the mid-feed blood sugar and the postfeed blood sugar. Twenty-four-hour feeds

are well covered with insulin glargine. The calculated units for carbohydrate coverage can be added to the units calculated to be needed for basal insulin if glargine is used.

8. **Insulin therapy and illness**—Patients with CFRD typically experience more frequent hospitalizations for pulmonary exacerbations than CF patients without diabetes.
    a. **Insulin requirements increase dramatically during illness**—The increase will be typically three- to fourfold. Once illness resolves, it may take 4 to 6 weeks for insulin requirements to return to baseline, but can improve more quickly.
    b. **Glucocorticoid therapy**
        i. **Methylprednisolone**—A single dose can cause hyperglycemia lasting 6 to 12 hours. Some authors recommend administration of supplemental NPH insulin at the time of the methylprednisolone dose.
        ii. **Prednisone**—The hyperglycemic effect can lag with increased blood glucoses lasting for 24 to 48 hours post discontinuation. Increased insulin doses, often two to four times higher than baseline dosing, are generally needed to normalize blood glucose levels.
        iii. **Induction of CFRD in patients without preexisting diabetes**—Some patients without previous CFRD diagnosis may develop diabetes, requiring insulin initiation during glucocorticoid therapy. This often resolves upon completion of glucocorticoid therapy, but often will recur with future glucocorticoid administration.

C. Other antidiabetic medications

1. **No noninsulin antidiabetic medications are recommended for the treatment of CFRD**—Insulin reverses nutritional and lung function decline in CF. No other therapy has been associated with improved outcomes. This is an area under active investigation.

D. Blood glucose monitoring

1. **Self-monitoring of blood glucose** is recommended for all patients with CFRD. The frequency of monitoring depends upon circumstances, as discussed below.
2. **Glycemic goals**—Currently, blood glucose goal ranges in CFRD are based on recommendations for type 1 and type 2 diabetes, with

most practitioners using the goal ranges typical for type 1 diabetes mellitus.

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3. **Insulin therapy**—It is recommended that those on bolus-only, basal-bolus, and/or pump-based insulin therapy monitor blood glucose fasting, before meals, and 2 hours after meals and at bedtime (six to seven times daily) plus as needed for symptoms of hyper or hypoglycemia. An overnight check is recommended after adjustments are made in basal insulin therapy.
    a. **Illness**—Blood glucose should be checked as above, but when patients are unable to eat, blood sugar should be checked at least every 4 hours.
    b. **Enteral feeds**
        i. **Bolus feeds**—Check prior to feed and 2 hours after feed.
        ii. **Overnight feeds**—Check prior to feed, in mid-feed, and at end of feed.
        iii. **Continuous feeds**—If eating, check before and 2 hours after meals. If not eating, check every 4 to 8 hours.
4. **Exercise**—Exercise is essential for the treatment of CF, and patients with CFRD should follow the usual guidelines for exercise in CF including recommendations for maintained/increased exercise with illness. Exercise should not be avoided because of concerns regarding hypoglycemia. Rather, techniques for prevention of exercise-related hypoglycemia used for other forms of insulin-dependent diabetes should be used, such as the administration of supplemental carbohydrate prior to exercise and close monitoring of glucose levels.

E. Hypoglycemia

1. **The risk for hypoglycemia in CFRD is similar to that with type 1 diabetes or type 2 diabetes requiring insulin**
    a. **Treat with fat-free and protein-free quick-acting carbohydrate**—A typical recommendation is 15 g of quick-acting carbohydrate with a recheck of blood sugar in 15 minutes.
2. **Reactive hypoglycemia**—This is commonly seen in CF patients who are nondiabetic or prediabetic.
    a. **Recommendation**—avoidance of large carbohydrate loads with high glycemic index

F. Prediabetes

1. **Impaired glucose tolerance**
   a. **Nutrition therapy**—No overall restriction in carbohydrate intake is recommended, but carbohydrates might ideally be spread through the day and empty calorie carbohydrates replaced with nutrient-dense carbohydrates.
   b. **Insulin therapy**—Although there is no formal recommendation for insulin therapy for simple impaired glucose tolerance, some centers do prescribe low-dose insulin therapy, using either long-acting or prandial insulin, with the goal of improving anabolism.

IX. CLINICAL MANAGEMENT

A. Clinic visits

1. **Clinic visits should occur quarterly**
   a. Patients should be followed by an endocrinologist/pediatric endocrinologist or advanced practice provider familiar who is knowledgeable about CFRD.
   b. Blood glucose monitoring should be reviewed.
   c. Nutrition status should be reviewed in every visit with at least yearly monitoring by a nutritionist who is competent in dealing with CF and CFRD.
   d. Diabetes self-management education should be ongoing.
   e. HbA_{1c} should be measured quarterly, although specific cutoffs cannot be directly correlated to average blood glucose levels. Increase or decrease in HbA_{1c} over time is consistent with changes in glycemic control. Elevated values are predictive of poor control; however, low values are not always predictive of good control.

B. Pregnancy

1. **Diagnosis**—Diagnosis of gestational diabetes mellitus (GDM) should be made on the basis of standard guidelines (not CF-specific).
   a. CF patients with GDM are not considered to have CFRD while pregnant.

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2. **Nutritional management**—Nutritional management of GDM in

CF pregnancy is complex and requires increased energy intake even above standard CF recommendations, often requiring supplements or enteral feeding.

3. **Insulin**—Aggressive initiation of insulin must occur rather than calorie or carbohydrate restriction. Insulin pump therapy is optimal.
4. **Screening**—CF patients should be aggressively screened for CFRD prior to pregnancy. CF patients with the diagnosis of GDM require CFRD screening 6 to 12 weeks after the end of pregnancy.

C. Disordered eating

1. **Both CF and diabetes are associated with increased risk for disordered eating**—There is no literature specific to CFRD, but it is important to be aware of this possibility in a population where adequate weight gain is so essential to survival.

X. CONCLUSION

CFRD is a unique form of diabetes mellitus with major implications for all patients with CF. With the increasing life span of patients with CF and increased rates of CFRD with age, this disease becomes ever more important to the practice of diabetes care in general and the care of CF patients in particular. Given the unique pathophysiology and presentation of this disease, it is important to be aware of specific recommendations for the screening, diagnosis, and management of this disease. Screening is essential and specific to CFRD, with OGTT being the recommended modality. Treatment is with insulin, focusing on adequate coverage of carbohydrates, but requiring lower insulin doses than in other forms of diabetes. Nutrition and weight maintenance are an essential aspect of CF care. Caloric and carbohydrate restriction is not recommended, given the strong relationship between the lack of weight gain and mortality in CF. Aggressive appropriate treatment of glycemic abnormalities in CF improves outcomes and reduces morbidity and mortality.

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63 Diabetes in Pregnancy

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I. GENERAL PRINCIPLES

A. The presence of diabetes of any type during pregnancy confers a higher risk to both the mother and her fetus. Although continued advances in both medical and obstetrical management of the woman with diabetes during pregnancy have led to improved outcomes, the potential for problems to immediate and long-term health still exists. Careful management is necessary to optimize glycemic control, so that mother and fetus, and subsequently her neonate, avoid harm.

B. Pregestational diabetes is a term that can be applied to either *type 1* or *type 2 diabetes* that is present in the mother before conception. Although many of the risks are similar, the management between these two conditions may differ (see below).

C. Gestational diabetes mellitus (GDM) was previously a diagnosis given to any woman who had glucose intolerance discovered during pregnancy; however, this failed to account for the possibility that undiagnosed diabetes existed prior to conception. Currently, GDM is distinguished from overt diabetes, a term that signifies that although maternal diabetes has been diagnosed during pregnancy, it is presumed to have existed prior to pregnancy (see Section D). There is a lack of consensus regarding both the diagnosis and management of GDM, so it is best to refer to local or institutional guidelines when caring for this patient population.

Briefly, diagnosis of GDM can be made with either a one-step or two-step approach, generally performed between 24 and 28 weeks gestation. The one-step approach involves the administration of 75 g of oral glucose to the patient, with serum glucose measured at fasting, 1 and 2 hours. This approach is the more common test used by international groups. The two-step approach is more widely used in the United States. It involves a 50-g oral glucose challenge with serum glucose checked at 1 hour. If the screening test is positive, it is followed by a 100-g oral glucose test with glucose values measured

fasting, and 1, 2, and 3 hours after the administration of glucose. If two of three values are above threshold, the diagnosis of GDM is made.

There is further lack of consensus about ideal target glucose values as well as optimal pharmacologic treatment should medical nutritional management alone fail to control glucose levels. Recently, metformin has been identified as the first-line therapy over the only other oral agent comprehensively studied for use in pregnancy, glyburide. Ultimately, many women require insulin treatment, and both human insulin and its analogs are thought to be equally safe. There is agreement that even slight increases above normal glucose values can lead to both obstetrical and fetal complications, including an increased risk of Cesarian sections, macrosomia, and neonatal hypoglycemia.

D. Overt diabetes should be considered in any woman with risk factors for diabetes outside of pregnancy, including obesity, increased maternal age, history of GDM, family history of diabetes, or belonging to an ethnic group that has increased risk for developing type 2 diabetes mellitus (Hispanic, Native American, South or East Asian, African American, or Pacific Island descent). The diagnosis of overt diabetes can be made when any of the following are observed in the first half of pregnancy: a hemoglobin A_{1c} of ≥ 6.5%, a fasting glucose of ≥126 mg/dL, or a random glucose of ≥200 mg/dL. Most patients with overt diabetes are likely to have had pregestational type 2 diabetes prior to conception, and management recommendations reflect this assumption.

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E. Maternal adverse outcomes include those related to preexisting diabetes: an increased risk for hypoglycemia, because of both hormonal changes in the first trimester and an intensification of glycemic control throughout pregnancy; a precipitation or acceleration of microvascular and macrovascular complications, specifically underlying retinopathy and nephropathy or cardiovascular disease; and an increased risk for diabetic ketoacidosis in the setting of an enhanced ketogenic state. Moreover, women with pregestational diabetes are at increased risk for obstetrical complications, including preterm labor, polyhydramnios, preeclampsia, the need for Cesarian section, and subsequent problems with wound healing.

F. Fetal and neonatal adverse outcomes include major

congenital malformations, intrauterine growth restriction (particularly in women with concomitant hypertension and nephropathy), macrosomia, preeclampsia, stillbirth, preterm birth, and neonatal hypoglycemia as well as other metabolic derangements. Aggressive control of maternal glucose can help lower these risks.

II. PHYSIOLOGIC CHANGES OF PREGNANCY

A. Changes in metabolism related to glucose utilization

1. **Fasting state**—During pregnancy, fasting levels of plasma blood glucose are lower due to insulin-independent uptake of glucose by the placenta. Early in pregnancy, glucose tolerance is normal and there may be slightly increased overall peripheral insulin sensitivity. As pregnancy progresses, insulin resistance increases because of rising levels of human placental lactogen (hPL, also known as human chorionic somatomammotropin, or hCS), cortisol, prolactin, progesterone, and human placental growth hormone. Human placental growth hormone (pGH or growth hormone-variant, GH-V), a member of the growth hormone family, is secreted by the placenta throughout gestation and causes severe insulin resistance during pregnancy. It almost entirely **replaces pituitary growth hormone in pregnant women by week 20** of pregnancy. Basal endogenous hepatic glucose production also increases to supply the needs of the placenta and fetus.

   Initially during pregnancy there is an increase in lipid deposition. During late pregnancy, hPL and pGH contribute to the mobilization of lipids as free fatty acids and glycerol that serve as an alternate energy source for the mother, allowing glucose to be used preferentially by the growing fetus.

   Pregnancy is a ketogenic state, and women with Type 1 diabetes in particular are at greater risk of developing diabetic ketoacidosis after periods of fasting and at lower blood glucose levels than in the nonpregnant state.

2. **Fed state**—Postprandial hyperglycemia occurs more frequently in pregnancy because of the effects of placental hormones. During normal pregnancy, insulin levels take longer to reach peak level after a glucose load, and pregnant women produce more insulin for a given amount of glucose when compared with nonpregnant women, reflecting progressive insulin resistance. This is to enable the provision of more carbohydrate nutrients for the fetus. Women

without diabetes are generally able to compensate by increasing insulin production sufficiently to maintain normal glucose levels during pregnancy.

B. Cardiovascular and renal changes

Starting early in the first trimester, total body plasma volume increases by approximately 45%, reaching a maximal volume of 4.7 to 5.2 L at 32 weeks. There is a lesser increase in red blood cell (RBC) mass, resulting in a **physiologic anemia** during pregnancy. Pregnant women tend to have lower HbA_{1c} values related to a fall in mean RBC age as the RBC mass increases along with volume expansion that is independent of average glucose levels. **Cardiac output also increases** 30% to 50% above baseline, primarily related to an increase in stroke volume and secondarily to an increase in maternal heart rate by 15 to 20 beats/minute.

Systolic and diastolic **blood pressures tend to decline** early in pregnancy through the second trimester because of a reduction in systemic vascular resistance.

During normal pregnancy, **glomerular filtration rate increases** by up to 50% related to increased renal blood flow and cardiac output. Normally in pregnancy, **urine albumin excretion increases** only by a small amount (up to 30 mg/day); p. 834p. 835however, total protein excretion can increase up to 300 mg/day with a concomitant decrease in tubular reabsorption of protein. This can be an important consideration when assessing renal function in women with pregestational diabetes.

The diagnosis of overt diabetic nephropathy in pregnancy is therefore based on persistent proteinuria ≥300 mg/day during the first 20 weeks of pregnancy, in the absence of bacteriuria. After 20 weeks, the development of preeclampsia should be considered as a potential cause of increasing proteinuria.

C. Obesity

The incidence of pregnant, obese women has increased significantly over the past several decades, and is estimated to range from **18.5% to 38.3%** in the United States. Obese women without preexisting diabetes may experience higher degrees of insulin resistance and are at greater risk for developing gestational diabetes.

They also have a higher risk of cesarean deliveries with macrosomia, increased incidence of congenital anomalies such as neural tube defects, increased risk of postoperative complications such as wound infection and venous thromboembolism, and increased perinatal mortality.

III. PRECONCEPTION MANAGEMENT OF THE WOMAN WITH DIABETES

Women with diabetes planning to become pregnant should meet early with healthcare providers in order to discuss the importance of glycemic control prior to pregnancy as well as understand the associated risks. Studies have shown that women with diabetes who seek preconception counseling or who are followed for longer periods of time during pregnancy experience less perinatal morbidity and mortality, when compared with women who first present to care later in gestation. A prospective observational cohort study of women with type 1 diabetes who delivered over a period of 11 years in the United Kingdom found that prepregnancy care resulted in improved glycemic control in the first half of pregnancy and reduced the risks of spontaneous abortion, congenital malformation, and very premature delivery.

The following should be discussed with women with pregestational diabetes prior to conception:

A. Counsel regarding the health risks of pregnancy

The healthcare provider should assess for possible complications from preexisting medical conditions related to diabetes including diabetic nephropathy, retinopathy, and hypertension. Medications should be evaluated and any potentially teratogenic medications or those that are contraindicated in pregnancy should be discontinued, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and statins. Other medications that are commonly used in the setting of diabetes, such as aspirin, vitamin D, or antihypertensives such as beta-blockers or calcium channel blockers, may be continued if benefits outweigh the risks.

B. Counsel regarding the risk of adverse pregnancy outcomes

Risks to the fetus and neonate include fetal congenital malformation, macrosomia or fetal growth restriction, fetal demise, premature delivery, shoulder dystocia, and the potential for neurologic birth injuries. The risks for such complications are increased in the setting of poorly controlled diabetes.

C. Optimizing glycemic control

In order to minimize the risk of congenital anomalies and other complications to the growing fetus such as macrosomia or to the neonate such as hypoglycemia, tight glycemic control should be achieved. The American Diabetes Association (ADA) has recommended that in order to lower the risk of congenital anomalies, preconception HbA_{1c} should be <6.5% as long as this can be accomplished safely without significant hypoglycemia. During pregnancy, the target A_{1c} should be 6.0% to 6.5%, and ideally <6% if this degree of intense control can be achieved without severe hypoglycemia. In women with a history of recurrent, severe hypoglycemia, hypoglycemia unawareness, or an unacceptable frequency of hypoglycemia during pregnancy, the target A_{1c} can be relaxed to <7%.

D. Optimize medically

Prior to conception, women should undergo a comprehensive, dilated eye exam and be treated for any high-risk proliferative or preproliferative diabetic retinopathy, as the risk of progression of untreated proliferative diabetic retinopathy in p. 835p. 836pregnancy is high. There is no contraindication to laser photocoagulation therapy during pregnancy if needed. The first-line treatment for diabetic macular edema in pregnancy is also tight blood glucose control and laser photocoagulation. There are currently no long-term safety data in pregnancy for the use of anti-VEGF therapy for diabetic macular edema.

Diabetic nephropathy can have a significant impact on perinatal outcome, including the increased risk of intrauterine growth restriction, premature delivery, and preeclampsia. All women should have a random urine albumin-to-creatinine ratio or protein-to-creatinine ratio checked early in pregnancy. Microalbuminuria during pregnancy is diagnosed on the basis of urine albumin-to-creatinine ratio of 30 to 299 mg/day. As pharmacologic interventions during pregnancy are limited, healthcare providers should optimize blood glucose control and blood pressure control to reduce the risk of progression of nephropathy.

Women with chronic hypertension should be continued on

antihypertensive agents for blood pressure control, with preferred agents being labetalol, methyldopa, and long-acting calcium channel blockers such as nifedipine. Antihypertensives contraindicated in pregnancy include ACE inhibitors and ARBs; these should be discontinued prior to pregnancy (Table 63-1).

IV. MANAGEMENT DURING PREGNANCY

A. Medical nutrition therapy: Caloric intake should be adjusted to achieve the desired pregnancy weight gain on the basis of prepregnancy body mass index (BMI) following the 2009 updated recommendations of the Institute of Medicine (IOM) (Table 63-2). Women with preexisting diabetes mellitus should be counseled to p. 836p. 837gain weight within the IOM recommendations to avoid large-for gestational age, or macrosomic newborns.

TABLE 63-1 Stages of Care in Diabetes of Pregnancy

Preconception
- Achieve Hgb A_{1c} < 6.5%, normalize glucose control
- Evaluate for complications of diabetes and their severity, and start treatment
- Lifestyle changes—smoking cessation, diet and exercise, prenatal supplements, and 400–800 μg of folic acid per day

First trimester (glycemic targets in preexisting type 2 diabetes: fasting BG ≤90 mg/dL, 1 hr PPBG ≤130–140 mg/dL, 2-hr PPBG ≤120 mg/dL. In type 1 diabetes, target an A_{1c} of <6.0% without hypoglycemia.)
- Reduce spontaneous abortion risk and anomalies
- Monitor for ketonemia in the setting of hyperglycemia or gastrointestinal illness
- First-trimester fetal screening for anomalies (biochemical markers and ultrasound)

Second trimester (glycemic targets in preexisting type 2 diabetes: fasting BG ≤90 mg/dL, 1 hr PPBG ≤130–140 mg/dL, 2-hr PPBG ≤120 mg/dL. In type 1 diabetes, target an A_{1c} of <6.0% without hypoglycemia.)
- Optimize blood glucose control to reduce the risk of macrosomia
- Second-trimester fetal screening for anomalies at 18–22 wk
- Fetal echocardiogram at 18–22 wk

Third trimester (glycemic targets in preexisting type 2 diabetes: fasting BG ≤90 mg/dL, 1 hr PPBG ≤130–140 mg/dL, 2-hr PPBG ≤120 mg/dL. In type 1 diabetes, target an A_{1c} of <6.0% without hypoglycemia.)
- Reduce the risk of macrosomia
- Reduce the risk of stillbirth
- Reduce the risk of neonatal respiratory distress syndrome

Postpartum

• Discuss and counsel regarding breastfeeding, contraception, future pregnancies, and child development
BG, blood glucose; PPBG, postprandial blood glucose.

TABLE 63-2 2009 Institute of Medicine Recommendation for Total and Rate of Weight Gain during Pregnancy, by Prepregnancy BMI

Prepregnancy BMI	BMI (kg/m^2) (WHO)	Total weight gain range (lb)	Rates of weight gain second and third trimester (mean range in lb/wk)
Underweight	<18.5	28–40	1 (1–1.3)
Normal weight	18.5–24.9	25–35	1 (0.8–1)
Overweight	25.0–29.9	15–25	0.6 (0.5–0.7)
Obese (includes all classes)	≥30.0	11–20	0.5 (0.4–0.6)

BMI, body mass index.

Obese women with preexisting diabetes are encouraged to reduce their calorie intake by approximately one third (compared with their usual intake before pregnancy) while maintaining a minimum intake of 1600 to 1800 kcal/day. All women with preexisting diabetes should limit carbohydrate intake to 35% to 45% of total calories, distributed in three small- to moderate-sized meals and two to four snacks including an evening snack. Weight loss is not recommended in general for obese women during pregnancy. However, in women with a BMI of > 40, weight loss during pregnancy showed no significant increase in the risk of poor outcome for infants.

B. Self-monitoring of blood glucose: Women with preexisting diabetes generally require more frequent monitoring of blood glucose values. This includes preprandial glucose levels in type 1 diabetes to modify premeal insulin doses, and postprandial/bedtime glucose levels in both type 1 and type 2 diabetes to avoid hyperglycemia and reduce the risk for macrosomic fetal growth.

Optimal glycemic goals, if they can be achieved without excessive hypoglycemia, are fasting ≤90 mg/dL, 1-hour postprandial ≤130 to 140 mg/dL, and 2-hour postprandial ≤120 mg/dL. If preprandial glucoses levels are checked, they should be maintained at ≤110 mg/dL; however, for women with gestational or type 2 diabetes,

adjustments based on postprandial values are more effective in preventing obstetrical and neonatal complications.

If women with diabetes cannot achieve these targets without significant hypoglycemia during the first trimester because of increased insulin sensitivity and symptomatic nausea and hyperemesis, then slightly higher targets should be considered, such as fasting <105 mg/dL, 1-hour postprandial <155 mg/dL, and 2-hour postprandial <130 mg/dL.

Women should be cautioned not to over-treat hypoglycemic episodes so as to minimize rebound hyperglycemia. For moderate symptoms, 8 oz of nonfat milk is generally sufficient; for glucose levels <60 mg/dL, 10 g of fast-acting carbohydrate (e.g., dextrose tablets or liquid, 4 oz of orange juice followed by crackers or 6 oz of milk) are recommended. Because of the risk of severe hypoglycemia or unconsciousness, patients and their family members must be educated on the use of glucagon and should keep a current kit on hand.

Continuous glucose monitoring (CGM) can be used during pregnancy in women with preexisting diabetes when self-monitored blood glucose is not sufficient to assess glycemic control or episodes of postprandial hyperglycemia or overnight hypoglycemia are problematic. Current evidence on the efficacy of CGM on improving glycemic control during pregnancy, as well as on the effectiveness on pregnancy outcome, is limited with mixed results. Evidence on the cost-effectiveness is also lacking. Further proper randomized controlled trials on the effectiveness and p. 837p. 838cost-effectiveness of CGM in pregnancy are required before wide implementation in practice can be recommended.

C. Medical treatment

1. General principles of insulin use

All pregnant women with preexisting type 1 diabetes and the majority with type 2 diabetes require insulin therapy to achieve adequate blood glycemic control. Pregnant women with preexisting diabetes already successfully taking insulin detemir or glargine before pregnancy are recommended to continue the same type of insulin during pregnancy for basal coverage. For prandial coverage, rapid-acting insulin analogs lispro and aspart are preferred over regular (soluble) insulin in pregnant women with diabetes. **Glulisine has not received U.S. Food and Drug**

Administration (FDA) approval for use in pregnancy and does not appear to offer a proven advantage over insulin lispro or insulin aspart. Although insulin **glargine is also not FDA-approved during pregnancy**, a meta-analysis of observational data from 331 pregnancies with glargine exposure during the first, second, or third trimester showed no statistical increase in any maternal or neonatal adverse outcomes compared with the use of neutral protamine Hagedorn (NPH) insulin. For insulin-naïve women, NPH may offer some advantages both in terms of cost and long-term safety data.

2. **Continuous subcutaneous insulin infusion (CSII, insulin pump therapy)**

   Because of the potential risk of temporarily worsened blood glucose control, ketoacidosis, and hypoglycemia when CSII is initiated, its use during pregnancy should be limited to those patients already successfully using this method of insulin administration before pregnancy, to those women who, during pregnancy, have not succeeded with other insulin strategies, including multiple daily doses of insulin, or finally to women who choose to transition to CSII after understanding the above risks. The pregnant patient who is using an insulin pump will generally require a minimum of three basal rates over a 24-hour period. An increased early morning basal infusion is often required to counteract the anti-insulin effect of the early morning physiologic release of cortisol, which has been reported in both Type 1 and Type 2 diabetes and which is potentiated in pregnancy.

3. **Dosing**

   Frequent titration of insulin is needed to match changing requirements throughout pregnancy. In the first trimester, there is often a decrease in the total daily dose of insulin by 15% until 10 weeks. In the second trimester, rapidly increasing insulin resistance requires weekly or every other week increases in insulin dose to achieve glycemic targets. The total daily dose may triple from preconception to term. In general, a smaller proportion of the total daily dose should be given as basal insulin and a greater proportion as prandial insulin; bolus insulin increases from approximately 50% of the total daily dose of insulin before conception to 75% of the total daily dose at 36 weeks gestation (Fig. 63-1).

   Women with type 2 diabetes occasionally require **very large**

doses of insulin (200 to 1 000 U) toward the end of pregnancy. In such instances, the use of **U-500 insulin** in three premeal injections per day should be considered.

When considering women with type 2 diabetes who have not achieved glycemic targets through medical nutrition therapy and who are also insulin naïve, note that most recommendations include initiating insulin doses between 0.7 and 1.0 U/kg, depending on the trimester. Randomized, controlled trials to determine the optimal initial dose of insulin have not been conducted, and following such recommendations may lead to prescribing insulin in excess of 100 to 200 U for women with high BMIs. It may be safer to start with an initial dose closer to 0.2 U/kg and then make changes to target specific time points with hyperglycemia. For example, if the patient has elevated fasting but normal postprandial glucose levels, only a dose of bedtime NPH may be required to achieve target glycemic control. Likewise, women with normal fasting glucose levels but elevated postprandial hyperglycemia may benefit from injections of premeal fast-acting insulin.

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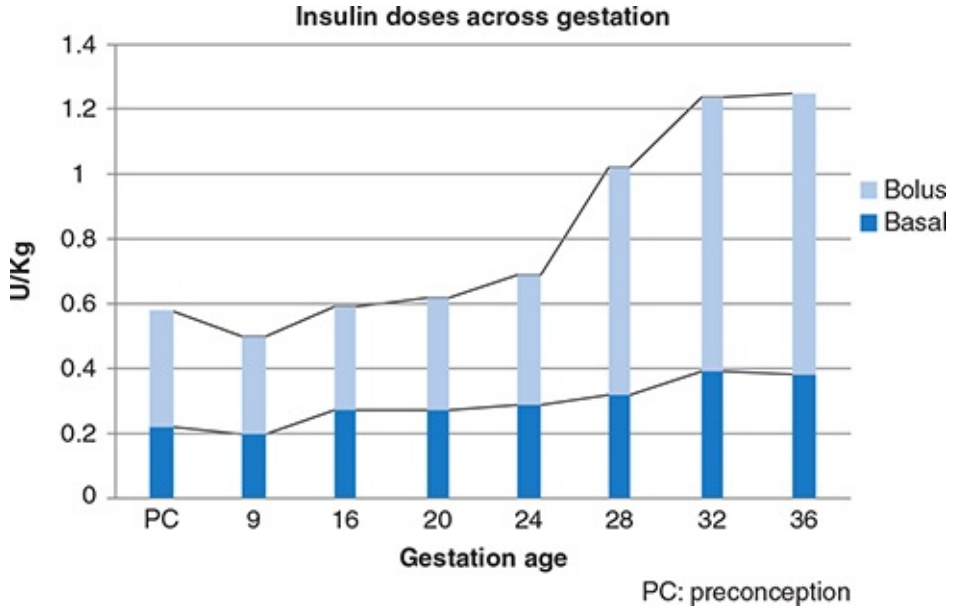

Figure 63-1. Total daily insulin dose increased threefold across gestation. Bolus doses of insulin constitute most of the rise; basal rates of insulin change minimally. PC, preconception. Modified from Castorino K, Jovanovic L. Pregnancy and diabetes management: advances and

controversies. *Clin Chem* 2011;57:221–230.

V. FETAL DEVELOPMENT

A. Incidence of major congenital anomalies: Infants born to diabetic mothers have **three to eight times greater incidence of congenital anomalies** than those born to nondiabetic mothers. Women with the greatest risk for congenital anomalies are those who have poorly controlled preexisting diabetes prior to conception or during the first trimester (HbA_{1c} > 8.5%), with major birth defects observed in up to 22% of all live births. During the critical period of organogenesis early in pregnancy, hyperglycemia can have teratogenic effects. The most frequent anomalies in diabetic pregnancies include neural tube defects and cardiovascular malformations.

Strict glucose control during preconception and the first trimester can reduce the rate of malformations, along with the use of **folic acid** and prenatal multivitamin supplements. Preventing obesity prior to pregnancy can also help decrease the risk of birth defects.

B. Screening for congenital abnormalities: First-trimester aneuploidy screening can be done using biochemical markers such as free β-hCG and pregnancy-associated plasma protein-A along with an early ultrasound to assess the fetal nuchal translucency. In the second trimester, the quadruple serum aneuploidy screening can be done, which includes maternal serum α-fetoprotein, hCG, unconjugated estriol, and inhibin A. Newer testing for women at increased risk for aneuploidy, such as women at 35 years or greater, can also include noninvasive prenatal screening in the form of cell-free fetal DNA testing or invasive diagnostic procedures such as chorionic villus sampling or amniocentesis. At 18 to 22 weeks, all women should have an ultrasound for detailed fetal anatomical evaluation. In addition, fetal echocardiography is often done at 18 to 22 weeks in insulin-dependent diabetic patients to further evaluate for cardiac malformations.

C. Effects of diabetes on intrauterine growth of the fetus: Maternal hyperglycemia during the second and third trimester can result in **macrosomic infants**, because the fetus responds to maternal high blood glucose levels by increasing insulin production to lower blood glucose levels. This fetal hyperinsulinemia can also accelerate growth and lead to hypoglycemia in the first few days following birth. Infants of diabetic p. 839p. 840mothers

can have **low birth weight** as a result of significant diabetes-related vascular complications in the mother, or preeclampsia.

VI. OBSTETRIC MANAGEMENT

A. Fetal growth: Maternal hyperglycemia is related to excessive birth weight in infants of diabetic mothers, and has been explained by the causal chain of fetal hyperglycemia, leading to fetal hyperinsulinemia, which subsequently causes excess growth and fat deposition. Strict glucose control in pregnancy has been associated with a reduction in **fetal macrosomia**, although prospective, controlled studies that examined this issue have largely been conducted in women with GDM. Likewise, there is an increased incidence of **intrauterine growth restriction** in some women with diabetes. Infants born to mothers with preexisting renal disease, hypertension, or cardiovascular disease may be more at risk as blood flow to the placenta may be compromised if these conditions are present. In addition to total fetal growth, the growth of the abdominal circumference can be a marker for growth abnormalities. Failure of the abdomen to grow appropriately signifies fetal undernutrition and poor fat deposition. Conversely, accelerated abdominal circumference growth has been used as a proxy for fetal hyperinsulinemia; that is, elevated fetal amniotic insulin levels, which have been associated with an increase in biochemical and somatic fetopathy. Accelerated abdominal growth (and amniotic fluid insulin levels) has been used as an indication for increased stringency of glucose control in diabetic patients, both pregestational and gestational. Thus, periodic assessment of the fetal growth pattern every 4 to 6 weeks in the third trimester can be useful to identify fetopathy in utero to modify management strategies and initiate close fetal surveillance if needed.

B. Fetal well-being: In addition to ultrasound studies of fetal growth, **antepartum fetal surveillance** is utilized, given the increased risk for stillbirth with poorly controlled diabetes in pregnancy. The gestational age to initiate surveillance depends on maternal and fetal risk factors and may vary among institutions. For most patients with pregestational diabetes, testing will begin at 32 to 34 weeks and may include nonstress testing (fetal heart rate monitoring) and assessment of the biophysical profile (ultrasound measurement of amniotic fluid volume, fetal movement, fetal tone, and fetal breathing). Testing is typically performed once or twice weekly. Earlier testing may be

appropriate for some patients, such as those with a prior stillborn fetus, those with renal or vascular disease, or when known fetal growth disturbances are present.

C. Delivery planning: A well-controlled diabetic patient can be managed expectantly until the 39th week of gestation. Generally, continuation of pregnancy after 40 weeks is not recommended. Delivery timing for a patient with poorly controlled diabetes is individualized and may occur before 39 weeks, given the significantly increased risk for stillbirth. Amniocentesis to assess for fetal lung maturity is sometimes utilized in these cases. The route of delivery should be determined by the usual obstetric indications. Current guidelines of the American College of Obstetrics and Gynecology state that given the increased risk for shoulder dystocia and fetal birth injury, cesarean delivery may be considered if the estimated fetal weight is greater than 4 500 g at the time of delivery in women with diabetes. Early induction of labor in pregnancies with a fetus with suspected macrosomia has not been found to reduce birth trauma and may increase the cesarean delivery rate.

D. Labor management: As patients are kept fasting, maternal blood glucose is usually easily kept within 80 to 110 mg/dL during labor by a simultaneous infusion of short-acting insulin (starting at a dose of 0.5 to 1.0 U/hour, titrated up as necessary to maintain control) and a low-carbohydrate intravenous solution such as 5% dextrose or lactated Ringer's solution. Women with type 1 diabetes who have demonstrated competence in self-management with an insulin pump may be allowed to wear it during induction of labor with a 20% reduction in basal rate to account for increased muscular activity (uterine contractions). The need for insulin in patients with type 2 diabetes in general is more variable. In the immediate postpartum period, there is a marked increase in insulin sensitivity because of both rapid reduction of circulating placental hormones and slower return to the normal pituitary GH-IGF-1 axis. Patients, especially those with type 1 diabetes, are at high risk for hypoglycemia p. 840p. 841during this period, which may last from several hours to several weeks. This period requires a continued close monitoring of glucose and a reduction in insulin dosing to 1/3 to 1/2 of the

preconception total daily dose.

E. Diabetic women should be encouraged to breast-feed their infants: Maternal insulin (either endogenous or exogenous) is secreted in breast milk but is destroyed by neonatal gastric enzymes. Maternal oral agents such as metformin or glyburide are also secreted in breast milk, but in low levels such that hypoglycemia in the infant is not thought to be a major risk. The quality of breast milk is not affected by diabetes, and breastfeeding appears to reduce the risk of childhood allergies, obesity, and later diabetes. Finally, breastfeeding may assist women with postpartum weight loss, which can be particularly important in obese women with type 2 diabetes.

F. Contraception and preconception planning: After delivery, healthcare providers should begin discussing the timing of a future pregnancy, if desired by the woman. If a woman and her partner would like to use a method other than barrier contraception, data indicate that many contraceptive methods are safe in women with diabetes. These include low-dose combination or progestin-only pills, injectable Depo-Provera, vaginal rings, subdermal implants, and intrauterine devices. The progesterone-only methods are safer for women who are smokers or who have micro- or macrovascular complications of diabetes. These methods of hormonal contraception do not generally alter glycemic control or lipid levels.

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Management of Diabetes Mellitus in the Perioperative Period

Rajesh Garg

I. INTRODUCTION

Patients with diabetes mellitus often require a surgical procedure because of their high risk of developing conditions like cardiovascular disease, infections, and some types of cancer. For example, 20% to 30% of all patients undergoing a cardiac or vascular surgery have a diagnosis of diabetes. Moreover, patients with diabetes mellitus may require an elective surgery, for example, hip or knee replacement. There is an interaction between the surgical procedure and diabetes control and *vice versa*. Whereas high blood glucose levels increase the risk of surgical complication, the stress of surgery tends to raise the blood glucose levels. Many patients, even those without diabetes, become hyperglycemic during the perioperative period because of the stress of illness, surgery, or medications. Perioperative hyperglycemia, with or without diabetes, is an independent predictor of prolonged hospitalization, admission to an intensive care unit (ICU), postsurgical infections, thrombotic complications, and renal insufficiency, and is associated with increased resource utilization and high hospitalization costs. Similarly, hypoglycemia is associated with a very significant increase in mortality and morbidity among hospitalized patients. Therefore, perioperative management of diabetes is considered exceedingly important to reduce the risk of surgical complications. This chapter discusses available data and a reasonable approach to manage patients with diabetes undergoing a surgical procedure.

II. PATHOPHYSIOLOGICAL CHANGES IN DIABETES AFFECTING SURGICAL OUTCOMES

Hyperglycemia induces multiple pathophysiological changes that may affect the healing process after surgery.

A. Increased inflammatory response

Patients with diabetes mellitus have increased inflammation and oxidative stress at baseline as demonstrated by high levels of circulating proinflammatory cytokines and markers of oxidative stress. Hyperglycemia without diabetes is also known to induce a proinflammatory state. Therefore, the presence of diabetes as well as nondiabetic hyperglycemia adds to the inflammatory stress induced by surgery. Whereas some level of inflammatory response is desirable and required for healing, an exaggerated response can be detrimental to the healing process. Thus, patients with diabetes are prone to a severe inflammatory response after surgery. Moreover, if an infection occurs after surgery, it may exacerbate the inflammatory response that may make the healing process more difficult. Studies have shown that hyperglycemia contributes to exaggerated inflammatory response to endotoxin that reverses on normalization of blood glucose levels with insulin infusion. Studies also suggest an independent effect of insulin on suppressing inflammation and oxidative stress.

B. Impaired neutrophil phagocytic response

Neutrophil activity is required not only for preventing infections but also for wound healing after surgery. There is impaired phagocytosis by neutrophils in the presence of high blood glucose levels, which gets corrected upon normalization of glucose levels. In a study of patients with type 2 diabetes, it was demonstrated that neutrophils' ability for phagocytosis was impaired during poor diabetes control and improved remarkably when glycemic control improved after treatment with glyburide for 3 months. In patients undergoing cardiac surgery, neutrophil phagocytic p. 843p. 844activity is impaired, but it can be improved by maintaining good glycemic control with insulin infusion.

C. Endothelial dysfunction

Multiple studies have shown an impairment of endothelial function in patients with diabetes and in the presence of nondiabetic hyperglycemia. The endothelium controls microcirculation by producing nitric oxide. It also controls bleeding by interacting with clotting factors. Thus, impaired endothelial function in diabetes may affect the healing process after surgery.

D. Underlying microvascular and macrovascular complication of diabetes

In addition to the acute effects of hyperglycemia, many patients with diabetes have underlying vascular disease that may affect circulation to healing tissues. Moreover, the primary disease that led to surgery may be more severe in patients with diabetes. For example, atherosclerotic coronary artery disease or peripheral vascular disease is often more severe and complicated in patients with diabetes than in those without diabetes. The presence of baseline nephropathy in patients with long-standing diabetes may make the fluid electrolyte management more challenging. Moreover, patients with diabetes are at high risk of acute kidney injury after surgery because of already compromised renal blood flow, and acute kidney injury itself is an independent risk factor for poor clinical outcomes. Acute kidney injury may also be related to radiological contrast dyes that may be given during the planning process for surgery. The presence of neuropathy can also interfere with the healing process and increase the chances of pressure ulcers after surgery.

III. CLINICAL EVIDENCE SHOWING POOR SURGICAL OUTCOMES IN PATIENTS WITH DIABETES

Much of the clinical data showing poor surgical outcomes among patients with diabetes is based on observational studies. In a recent meta-analysis, patients with diabetes had an increased risk of surgical site infections. Hyperglycemia in the perioperative period is a direct determinant of postoperative infections. Other clinical outcomes in patients with diabetes undergoing surgery include an increased risk of renal failure, acute MI or stroke in the postoperative period, an increased need for blood products, complications related to thromboembolism, and delayed wound healing. Patients with diabetes are also more likely to be admitted to an ICU and require longer ventilator support after major surgery. The length of hospital stay is about 20% longer in patients with diabetes than in those without diabetes. Not only are these complications seen more often in patients with diabetes but also the risk of complications is directly related to blood glucose levels in the perioperative period. Therefore, good glycemic control in the perioperative period may help reduce the risk of complications.

Unfortunately, very few interventional studies have been conducted to evaluate the impact of glycemic control on surgical outcomes. A study in a surgical ICU showed markedly improved clinical outcomes with tight glycemic control. Although further studies on tight glycemic control in

nonsurgical ICU settings showed disappointing results, data in surgical patients are still relevant. A recent study in the non-ICU setting showed benefits of good glycemic control in surgery patients by reducing the risk of complications. Moreover, studies conducted by Furnary and colleagues in cardiac surgery patients showed remarkable reduction in sternal wound infections, reaching levels of those seen in nondiabetic patients, after the implementation of strategies for good glycemic control in cardiac surgery patients in the perioperative period. Blood glucose levels were maintained below 200 mg/dL using insulin **infusion for 72 hours after surgery** in these cases. Subsequent studies also showed benefits in mortality and hospitalization costs with the use of insulin infusion post cardiac surgery. As a result of these data, many cardiac surgery centers use intravenous (IV) insulin infusion protocols to maintain adequate glycemic control postoperatively. Thus, postoperative glycemic control is considered a standard of care at most of the academic institutes.

However, intraoperative insulin infusion studies have consistently failed to show benefits. A study by Gandhi et al. in patients undergoing cardiac surgery showed no benefits and potential harm of tight intraoperative glycemic control when all patients received tight glycemic control postoperatively. Similarly, there are insufficient data on p. 844p. 845the benefits of preoperative diabetes control before elective surgery. A few studies have shown high hemoglobin A_{1c} (HbA_{1c}) to be a predictor of increased mortality in the months and years after cardiovascular surgery. A logical explanation for this increased mortality is more severe cardiac disease in association with poorly controlled diabetes rather than an effect of blood glucose on surgery itself. However, increased mortality and risk of complications have also been shown in patients undergoing noncardiac surgery. In a retrospective study of patients undergoing major noncardiac surgical procedures, we found that **preoperative elevated HbA_{1c} >8% was associated with longer hospital stay**. Thus, current data support a moderate level of glycemic control at all stages of surgery.

IV. MANAGEMENT APPROACH TO A DIABETIC PATIENT UNDERGOING SURGERY

Ideally, the management of diabetes should begin at the time of referral to

a surgeon and should continue well after discharge from the hospital. However, in many cases, the opportunity to intervene may not be present in the early stages of surgical planning. For example, in case of urgent or semiurgent surgery, there may be no time to manage diabetes before the surgical procedure. However, once surgery has been performed, there is no excuse to ignore diabetes management.

A. Preoperative period

Evaluation and treatment of diabetes should start at the time the surgery is being planned. If possible, a complete diabetes workup should be performed in the primary care office. This workup should include the evaluation of current diabetes control, current diabetes treatment, the risk of hypoglycemia, and the presence of complications. However, many surgeries are planned in the surgical outpatient clinics and patients are often sent for a preoperative evaluation that is performed by their primary care providers or by a preoperative anesthesia team. Most studies show poor attention to diabetes at all levels of care in the preoperative period. Using measurement of HbA_{1c} as an indicator that diabetes was addressed as a problem, we found that only about one third of diabetic patients scheduled for a major elective surgery at a tertiary care hospital received any attention to diabetes preoperatively. Once a program was implemented to improve the management of patients with poorly controlled diabetes in the preoperative period, the proportion of patients getting an HbA_{1c} increased to over 90%. Thus, the involvement of a multispecialty diabetes care team early rather than late in the process of surgery planning may help provide adequate management of diabetes in the preoperative period.

HbA_{1c} should be obtained in the surgeon's office or at the time of the preoperative evaluation visit unless a test result is available prior to surgery. HbA_{1c} is not only an indicator of long-term glycemic control but also predicts perioperative blood glucose levels. Thus, it helps identify patients who may need specialist care after admission to the hospital. However, no intervention studies are currently available to show that lowering HbA_{1c} reduces surgical complications. Anecdotally, some surgeons have been trying to achieve an HbA_{1c} <7% before surgery, whereas others do not set an upper limit, relying only on the perioperative glycemic control. Evidence from

observational data suggests that an HbA_{1c} ≤8% is a reasonable preoperative goal. Therefore, in a patient with diabetes who requires an elective surgery, all attempts should be made to **bring down HbA_{1c} to** Ä**8% before scheduling surgery**. However, it is hard to set an absolute HbA_{1c} criterion for cancelation of surgery because some patients may not be able to achieve the goal of an acceptable HbA_{1c} level for the surgery. Moreover, for many patients requiring surgery, lowering HbA_{1c} may not be an appropriate goal of treatment because of the need to wait for several weeks or months before HbA_{1c} can change. Goal of treatment in patients who fail to achieve an HbA_{1c} ≤8% in a reasonable time period (6 months) or where surgery cannot be delayed should be adequate blood glucose control before the day of surgery. Because the current evidence suggests poor clinical outcomes with blood glucose levels ≥200 mg/dL perioperatively, one should try to **achieve a blood glucose level** <**200 mg/dL before surgery**.

Referral of patients with poorly controlled diabetes to a diabetes care team may be helpful because aggressive treatment with very close follow-up is needed in p. 845p. 846the preoperative period. Insulin may be started or insulin doses may be adjusted, sometimes requiring daily dose adjustments. However, as mentioned above, blood glucose levels up to 200 mg/dL on the day of surgery are acceptable and an elective surgery should not generally be canceled unless blood glucose is >200 mg/dL. For patients with blood glucose >200 mg/dL, surgery should be rescheduled if it can be safely done. If surgery cannot be rescheduled, IV insulin infusion should be used to bring down the blood glucose level before surgery.

Another main component of preoperative evaluation and treatment is medication planning for the day before and day of surgery. Some patients may need special diet in preparation for surgery. Dose of oral agents and/or insulin should be adjusted individually for that diet. For example, if a patient is instructed to consume only clear liquids for bowel preparation, basal insulin should be continued, whereas short-acting insulin should be decreased to 25% to 50% of the usual dose. Insulin secretagogues may need to be stopped to prevent hypoglycemia. All oral agents and nutritional insulin coverage should be held on the day of surgery. Basal insulin may be given in full dose

the night before the surgery. However, if a patient takes basal insulin in the morning, only half the usual dose should be given on the morning of surgery.

B. Intraoperative period

Management of diabetes during the intraoperative period falls within the purview of anesthesia. A patient with a good preoperative diabetes treatment plan can go through surgery without any special treatment during the surgery. However, blood glucose should be tested before inducing anesthesia. If blood glucose is >200 mg/dL, consider rescheduling surgery or starting an insulin drip. Patients with type 1 diabetes or insulin-treated type 2 diabetes may be electively started on insulin drip during surgery, especially if the surgery is expected to last for several hours. Otherwise, in a T2DM patient or T1DM patient who received adequate basal insulin coverage, blood glucose may be monitored every hour in the operating room and insulin drip started only if blood glucose is higher than 200 mg/dL.

Very tight glycemic control in the intraoperative period has not been shown to add to the benefits of postoperative glycemic control. Therefore, a **glycemic goal of 80 to 200 mg/dL during the intraoperative period is quite adequate**. If the stress of surgery raises blood glucose levels above 200 mg/dL, insulin infusion should be started in the operating room. For any hypoglycemia, IV glucose should be given.

C. Postoperative period

Postoperative treatment of hyperglycemia depends on the severity of illness. In general, glycemic goals for **patients in the ICU are 140 to 180 mg/dL** and on the general floors 80 to 180 mg/dL. Patients should be treated with insulin infusion if admitted to the ICU and with basal-bolus insulin therapy if admitted to the general floors. It is customary to **continue insulin infusion for up to 72 hours after cardiac surgery**. This is based on data generated by Furnary and colleagues, as described above. Noncardiac surgery patients admitted to the ICU are also candidates for insulin infusion. Patients receiving steroids or agents for hemodynamic support are also likely to respond better to insulin infusion.

Data on glucose control in the **non-ICU** setting are very scanty. Only one randomized controlled trial **compared tight glycemic control using basal-bolus insulin versus sliding scale insulin**. Both groups were treated to a target blood glucose level of

100 to 140 mg/dL before meals. There was a significant difference in glucose levels with **better glycemic control achieved in the basal-bolus insulin** group, and the primary outcome of this study that included a composite of complications was also better in the basal-bolus insulin therapy group. A significant difference in composite outcomes that included wound infection, pneumonia, bacteremia, and respiratory and acute renal failure was present between the two groups. **The main difference was seen in the rate of postoperative infection**. Therefore, most patients should receive a basal-bolus insulin therapy in the postoperative period. However, the exact insulin regimens may vary according to the nutritional needs of an individual patient, as presented in Table 64-1. It is important to adjust the insulin doses daily to treat hyperglycemia and to avoid hypoglycemia.

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TABLE 64-1 Basal-Bolus Insulin Therapy for Postoperative Care

Feeding	Basal	Bolus
Regular food intake	Glargine or intermediate-acting (NPH) or detemir once or twice daily	Rapid-acting insulin before meals + correction doses
Continuous tube feedings	Glargine or NPH or detemir once or twice daily	Regular insulin every 6 hr for nutritional and correction coverage
Bolus tube feedings	Glargine or NPH or detemir once or twice daily	Rapid-acting insulin with each bolus feeding to cover the bolus feeding and to correct for hyperglycemia
Parenteral nutrition	Add regular insulin to parenteral nutrition	Regular insulin every 6 hr to correct for hyperglycemia

1. Avoiding hypoglycemia

Avoiding hypoglycemia is as important as the treatment of hyperglycemia. Patients after surgery may be more prone to hypoglycemia because of poor nutritional intake, steroid doses being tapered off, renal or liver failure, nervous system disorders, and cognitive disability. Whenever insulin is ordered, a hypoglycemia protocol should also be ordered. See Table 64-2 for a typical hypoglycemia protocol.

2. **Insulin pump**
   Well-controlled patients on an insulin pump can be allowed to continue their pump through all stages of surgery. However, such patients should be proficient at the use of insulin pump and the staff should be vigilant to the possibility of pump failure. Blood glucose should be monitored at least every 4 hours while the patient is under anesthesia. In case of pump failure, an insulin drip should be promptly started. If the patient or staff is not comfortable with continuing insulin pump during surgery, it may be best to switch to basal-bolus insulin on the morning of surgery. Pump may be restarted at any stage after the surgery, mostly when the patient is able to eat and manage his or her own pump.
3. Noninsulin antidiabetic agents are not preferred for use in the hospital. However, noninsulin agents may be appropriate in some patients after surgery. In general, a p. 847p. 848patient who is able to take regular meals, is admitted to the general floor, not planned for any further procedures, and had adequate glycemic control on noninsulin agents before surgery may be a candidate for these agents after surgery. DPP4 inhibitors have been tried in this setting and are reported to be safe and effective.

TABLE 64-2 Treatment of Hypoglycemia in the Postoperative Period

Bedside blood glucose (BBG) <70 mg/dL:
- If the patient is not symptomatic, repeat the test to confirm before treating. If the patient is symptomatic, treat immediately.

If the patient is able to take orally:
- Give 4 oz of juice, nondiet soda or 8 oz of nonfat milk.
- Check BBG every 15 min and repeat treatment if BBG is below 70 mg/dL.
- When BBG is above 70 mg/dL, give snack or meal.

If unable to take orally and an IV line is available:
- Give 50 mL of 50% Dextrose (1 ampoule = 25 g) stat (can be pushed over 2 min).
- Check BBG every 15 min and repeat IV dextrose, or switch to oral treatment if BBG is below 70 mg/dL. Keep repeating the cycle until BBG is above 70 mg/dL.

If unable to take orally and no IV line is available:
- Give Glucagon HCl 1 mg IM.
- Check BBG every 15 min and repeat any of the above treatments if BBG is below 70 mg/dL till you see a BBG >70 mg/dL.

TABLE 64-3 Discharge Instructions for Antidiabetic Medications

Preoperative HbA_{1c} (%)	
<7	Continue the preadmission antidiabetic treatment regimen unless the clinical situation has changed.
7–8	Modify the preadmission antidiabetic regimen, but try avoiding new medications.
>8	Change the preadmission antidiabetic regimen by adding new medications or start basal insulin. If insulin is started, try to keep the regimen as simple as possible.
All patients should be instructed to follow with their diabetes care providers within 1 month or sooner.	

V. DISCHARGE PLANNING

Discharge planning is an important part of the postoperative diabetes management. Patients keep recovering from surgery for a few weeks to months after discharge. During this period, poor diabetes control may complicate their recovery process. Diabetes treatment may need adjustments depending on the type of surgical procedure, postoperative complications, need for rehabilitation, etc. Therefore, the diabetes team should be involved in discharge planning, and discharge instructions should be individualized according to patient needs. General guidelines for discharge instructions regarding antidiabetic medications are presented in Table 64-3.

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65 Diabetes Mellitus: Recent Developments and Clinical Implications

Roy G. Handelsman and Yehuda Handelsman

I. INTRODUCTION

This chapter focuses on the contemporary approach to managing diabetes on the basis of the past 10 years of development. It will address state-of-the-art technological development, including glucose monitoring and new systems for delivering medications—specifically insulin. Continuous glucose monitoring (CGM) devices have become small, accurate, and available to communicate through the cloud. Insulin pumps are smaller and have significantly improved communication abilities. With these advancements, the closed-loop insulin pump has become a reality. Meanwhile, on the medication front, several new classes have been developed, offering an effective and safe way to manage diabetes.

II. TECHNOLOGY

Two significant rulings from the Food and Drug Administration (FDA) in late 2016 signify the future, now present, of technological development in diabetes. First, the approval of the hybrid closed loop system, Medtronic's MiniMed 670G system, underscores the confidence placed by the FDA on these systems, leading the way to the future with nearly 10 more similar systems in different stages of development. Second, the approval of Dexcom's G5 CGM allows patients to act on its glucose values without the need to confirm it with fingersticks and glucose-monitoring meters.

A. CGM

1. **G5 CGM:** The DexCom G5 is the first CGM that can be used to make treatment decisions without the need to confirm with a fingerstick test. The G5 CGM is a small sensor inserted below the skin that continuously measures glucose levels, with real-time results sent wirelessly every 5 minutes to a compatible mobile device. The G5 will require a fingerstick every 12 hours for

calibration, but not for treatment decision. The FDA approval confirms the accuracy of the G5 CGM to be at least as good as that of glucose meters.

2. **The Freestyle Libre Pro** (Fig. 65-1), approved in late 2016 for clinicians' use, is a small glucose sensor to be worn on the back of the upper arm for up to 14 days. It measures glucose levels every 15 minutes, requiring no patient interaction nor fingerpricks to calibrate the device. The FreeStyle Libre, a small CGM designed for patients' use, utilizes the same sensor as that of the Pro and communicates with a handheld device to view the data in real time. The patient version has already been in use in Europe and was just approved in September, 2017 in the United States.

B. The closed-loop pumps—automatic insulin delivery

1. Medtronic's **MiniMed 670G hybrid closed loop system** (Fig. 65-2), featuring the Guardian Sensor 3, was approved by the FDA in 2016 and is the world's first pump/sensor system to be able to dose insulin on its own. The MiniMed 670G system adjusts basal insulin by itself with the patient controlling the bolus insulin per meals. Medtronic's pivotal study of the MiniMed 670G system demonstrated a 0.5% reduction in A_{1c} from a low baseline of 7.4% and with fewer episodes of hypoglycemia.
2. Tandem launched the **t:slim X2** pump incorporating a low-glucose suspend algorithm using the Dexcom G5 CGM. The t:slim X2 also enables users to receive software updates directly to their pumps while at home, which also allows for receiving improved algorithms without the need for new hardware. Their predictive low-glucose suspend device is expected in 2018.

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Figure 65-1. The Freestyle Libre Pro.

3. Bigfoot Biomedical is planning a **disposable pump** with a reusable, Bluetooth-enabled controller, together with Dexcom CGM, and includes a glucose control algorithm and utilizes a smartphone app. It is planning to offer automated insulin delivery as a monthly service.
4. Insulet, the makers of the **OmniPod patch pump**, has committed to **Automatic Insulin Delivery**, developing Horizon AP—a hybrid closed-loop system with Bluetooth communicating directly into the pod, working with an Android phone.
5. The **Bionic Pancreas** (Fig. 65-3) differs from the rest of the Automatic Insulin delivery systems (closed-loop pump) by introducing glucagon. This insulin and glucagon bihormonal approach offers a "natural" physiologic pathway, allowing the insulin pump to offer an active mechanism to minimize hypoglycemia.

C. Future noninvasive glucose monitors: Diabetes patients may soon be able to monitor their blood sugar with **contact lenses** on the basis of a developed transparent sensor. The sensor uses a nanostructured transistor that can detect subtle glucose changes in physiologic buffer solutions, such as the tear fluid in the eyes. **A laser**

sensor to measure blood sugar levels without penetrating the skin of people with diabetes is also under development. The device has a piece of silica glass with ions that shine, or fluoresce, when a low-power laser light hits them. With the user's finger on the glass, the fluorescence varies in relation to the concentration of glucose in the blood. Two devices are planned for development, a small finger-touch device and a wearable version for continuous monitoring.

D. Improvements in insulin delivery

1. **Memory pen:** Insulin pens that remember the last dose come in handy when patients cannot remember how much insulin they took —or how long ago. Novo Nordisk's NovoPen Echo reusable insulin pen with memory function (Fig. 65-4) records the last insulin dose and how much time has passed since the administration of injection.

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Figure 65-2. MiniMed 670G hybrid closed loop system.

2. **Smart insulin pen devices** with built-in Bluetooth features enable patients to track their doses, send alerts and reminders, and

transfer the insulin data to a smartphone. In addition, a smartphone app has been developed that is compatible with other Bluetooth devices, sharing the data for the most complete picture of blood sugar level. Smart insulin pens also help in transferring the insulin data wirelessly to be made visible to physicians, for those patients who do not want to, or cannot, use a smartphone.

3. **Needles:** Great strides have been achieved in developing needles to reduce pain without jeopardizing delivery.

   Hollow microneedles: Becton Dickinson (BD) has developed a perpendicular 1 mm injection into the intradermal space (as opposed to subcutaneous). This allows for more rapid uptake and reduces the pain, anxiety, and fear of injections.

   Ultrafine and ultra-beveled needles—33 gauge with a steeper angle in bevel to minimize pain at injection site (Fig. 65-5).

E. Medications

The main cause of morbidity and mortality in diabetes is cardiovascular disease (CVD). Most people with type 2 diabetes (T2D) have hypertension and lipid disorders. The contemporary approach to management is, therefore, addressing all CV risk factors: lipids, typically with statins; and blood pressure, generally with medications from the angiotensin-converting enzyme (ACE) or angiotensin II receptor blocker (ARB) family. Controlling glucose showed positive results on CV endpoints, but typically only 10 to 20 years later, as was shown in the 10-year follow-up to the United Kingdom Prospective Diabetes Study (a 5-year study in newly diagnosed T2D patients) and in the 20-year follow-up to the Diabetes Control and Complications Trial (the study in people with type 1 diabetes [T1D]). Giant strides have been made in the matter of treating glucose intolerance in the past decade. Medications now address p. 852p. 853the multifaceted pathophysiology of this disorder, as depicted by the “Ominous Octet” described by Ralph DeFronzo (Fig. 65-6). Medications have been introduced that are effective, do not cause hypoglycemia, and often reduce blood pressure and weight, as well as improve lipids.

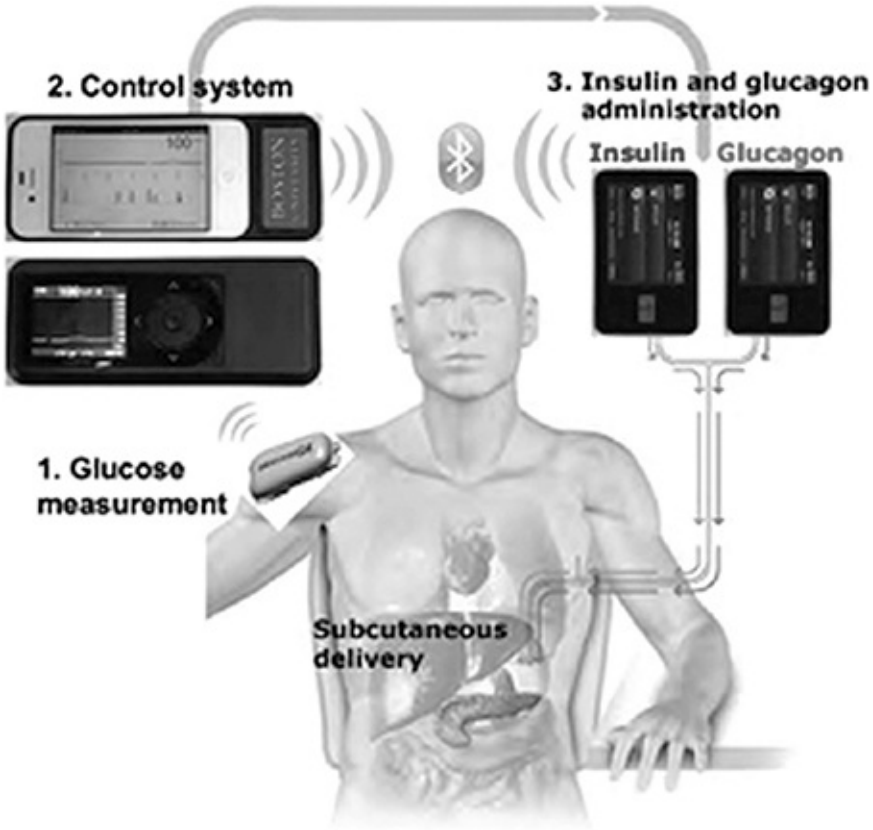

Figure 65-3. Components of bihormonal bionic pancreas.

Figure 65-4. NovoPen Echo reusable insulin pen with memory function.

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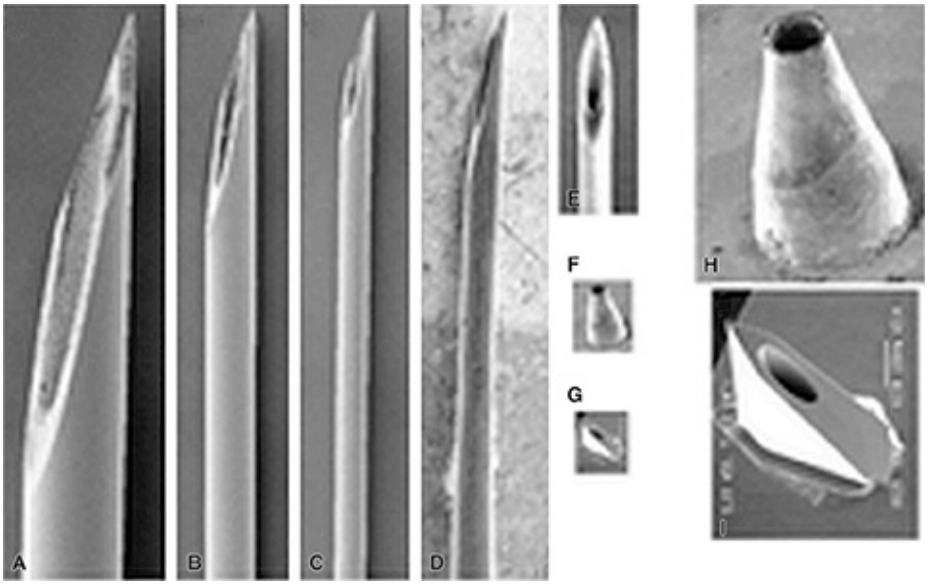

Figure 65-5. Ultra fine and ultra-beveled needles to minimize pain at injection sites.

1. In recent years, we witnessed an incredible development of medications primarily for people not only with T2D, but also with T1D. As a result, we now have **11 classes of noninsulin medications** to control hyperglycemia (Table 65-1).
2. Combination medications are increasing their presence in the market, addressing different pathophysiology components, making it easier for patients to adhere to treatment plans and often with reduced copays.

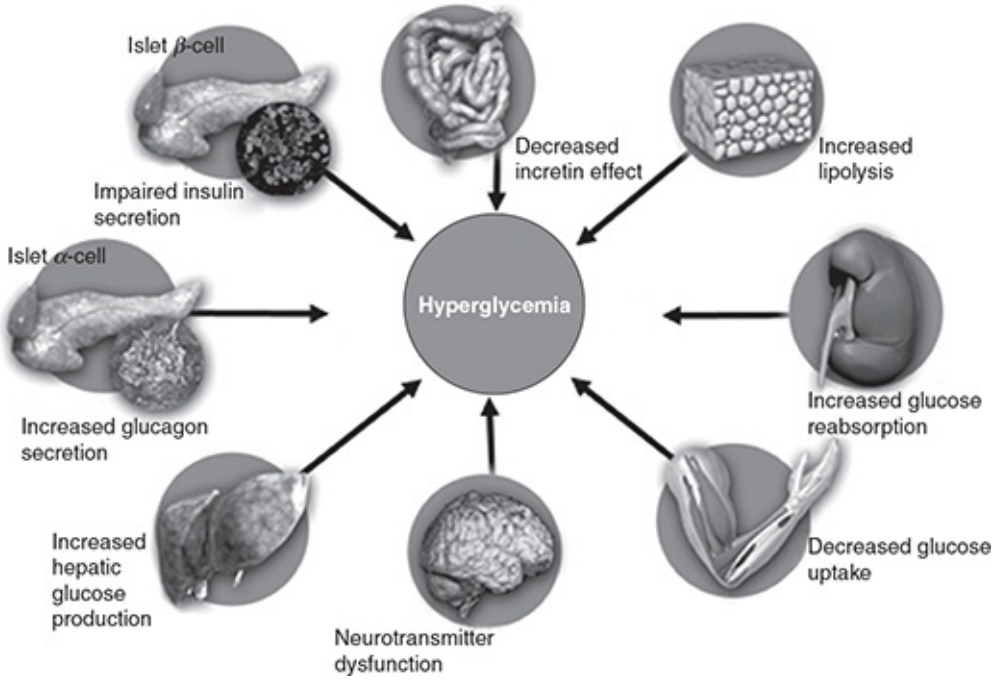

Figure 65-6. Main pathophysiologic defects in T2D: "The ominous octet."

TABLE 65-1 Noninsulin Agents Available for Treatment of Type 2 Diabetes

Class	Primary mechanism of action	Agent	Available as
α-Glucosidase inhibitors	• Delay carbohydrate absorption from intestine	Acarbose Miglitol	Precose or generic Glyset
Amylin analog	• Decreases glucagon secretion • Slows gastric emptying • Increases satiety	Pramlintide	Symlin
Biguanide	• Decreases HGP • Increases glucose uptake in muscle	Metformin	Glucophage or generic
Bile acid sequestrant	• Decreases HGP? • Increases incretin levels?	Colesevelam	WelChol
DPP4 inhibitors	• Increase glucose-dependent insulin secretion • Decrease glucagon secretion	Alogliptin Linagliptin Saxagliptin Sitagliptin	Nesina Tradjenta Onglyza Januvia
Dopamine-2 agonist	• Activates dopaminergic receptors	Bromocriptine	Cycloset
Glinides	• Increase insulin secretion	Nateglinide Repaglinide	Starlix or generic Prandin
GLP1-receptor	• Increase glucose-	Exenatide	Byetta

agonists	dependent insulin secretion • Decrease glucagon secretion • Slow gastric emptying • Increase satiety	Exenatide QW	Bydureon
		Liraglutide	Victoza
		Albiglutide	Tanzeum
		Dulaglutide	Trulicity
		Lixisenatide	Adlyxin
SGLT2 inhibitor	• Increases urinary excretion of glucose	Dapagliflozin	Farxiga/Forxiga
		Canagliflozin	Invokana
		Empagliflozin	Jardiance
		Ipragliflozin	Suglat
Sulfonylureas	• Increase insulin secretion	Glimepiride	Amaryl or generic
		Glipizide	Glucotrol or generic
		Glyburide	Diabeta, Glynase, Micronase, or generic
Thiazolidinediones	• Increase glucose uptake in muscle and fat • Decrease HGP	Pioglitazone	Actos
		Rosiglitazone	Avandia

DPP4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide-1; HGP, hepatic glucose production; SGLT2, sodium glucose co-transporter-2.

3. Multiple insulin products are now available as well, from very short- and ultra-rapid-acting insulin to very long-acting, flat insulin (Table 65-2).
4. Just, or soon-to-be, approved by the FDA are ultrarapid short-acting insulin—rapid novo; basal insulin coformulated with glucagon-like peptide-1 receptor agonists (GLP1RAs): Xultophy (iDegLira—degludec insulin and liraglutide) and Soliqua (iGlarLixi—glargine insulin and Lixisenatide); and an implantable small cylinder with a 6-month supply of the GLP1RA exenatide, ITCA 650 (Fig. 65-7). The FDA has approved the first biosimilar/follow-up biologic insulin glargine, Basaglar, with several more similar products expected to be approved soon. In late-stage development, there is a new form of metformin set to be active only in the distal ileum in order to reduce the side effects produced by the metformin-associated gut.

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TABLE 65-2 Insulin Available for the Treatment of Type 2 Diabetes

Class	Primary mechanism of action	Agent	Available as
Basal	• Increases glucose uptake • Decreases HGP	Detemir U100	Levemir
		Glargine U100	Lantus
		Degludec U100 and U200	Tresiba
		Glargine U300	Toujeo
		Neutral protamine Hagedorn (NPH)	Generic
Prandial		Inhaled insulin	Afrezza
		Aspart	NovoLog, Fiasp
		Glulisine	Apidra
		Lispro U100 and U200	Humalog U100, U200
		Regular human	Humulin, generic
		Regular U500	Humulin 500 and Pen
Premixed		Biphasic aspart 70/30	NovoMix
		Biphasic lispro 75/25 50/50	Humalog Mix

F. Integrated treatment of T2D—the new way to balance

In the past, the treatment method was sequential: the patient was prescribed one drug until it failed and then another one until this also failed, and so on. Today, there is a paradigm shift in treatment led by the American Association of Clinical Endocrinologists (AACE): the comprehensive DM management algorithm (Fig. 65-8). Instead of waiting for treatment failures, it is now recommended to start with combination therapy in addition to lifestyle modification from the onset. This approach is based on patient baseline characteristics, specifically A_{1c}. This new method promotes success with early and sustained control.

Figure 65-7. ITCA 650: 6 months continuous subcutaneous delivery of exenatide.

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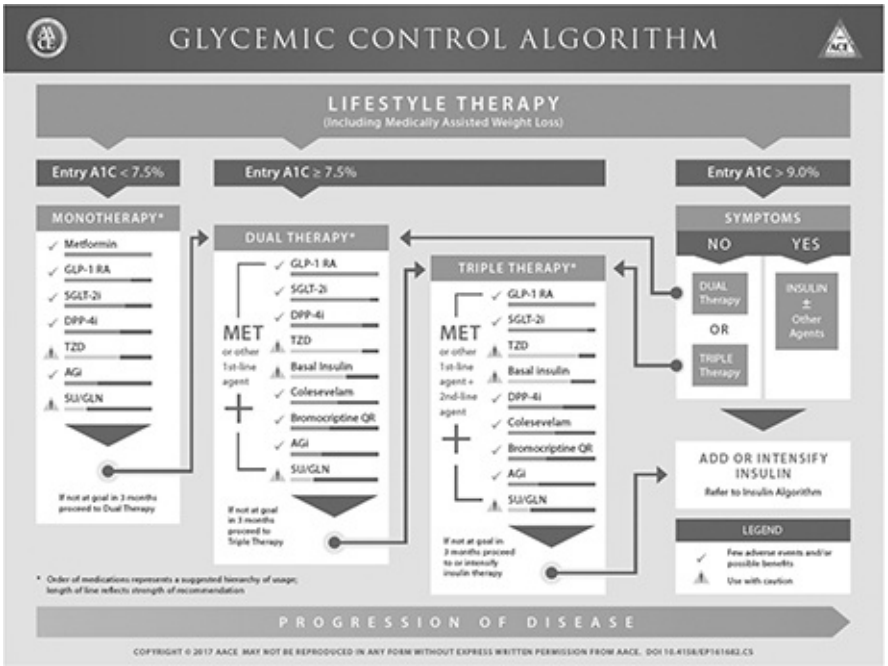

Figure 65-8. AACE/ACE comprehensive T2D management algorithm.

1. Traditionally, following metformin, the first drug of choice was Sulfonylurea (SU). Although the drug initially has a reasonable effect in reducing glucose, this effect is fast waning with a rapid

loss of control. SUs carry a high risk for hypoglycemia, are responsible for many patient visits to the emergency room, and have increased morbidity and mortality. As a result, the AACE developed its management recommendation focusing on safety first and then efficacy, especially choosing drugs with low hypoglycemia risk. The resulting AACE recommendation, following metformin, is to choose drugs from the incretin family, for example, GLP1RA and dipeptidyl peptidase-4 (DPP4) inhibitors, as well as sodium-glucose cotransporter-2 inhibitors (SGLT2i).

2. Another important feature of today's treatment approach is to reduce other CV risk factors, beyond lowering blood glucose levels, especially weight and blood pressure. Effective treatment classes that address such risks include GLP1RA and SGLT2i. These drugs are effective in lowering glucose levels without hypoglycemia and have a significant effect on reducing weight and blood pressure.

G. Incretin-based therapy

Today's selection of varied, safe, and effective drugs is impressive. Incretin-based therapy includes **GLP1RA** that acts as the intestinal hormone GLP1, which, beyond its glucose control, is also effective in controlling satiety, weight, and blood pressure. Another group from the incretin family is the **DPP4 inhibitors**. Whereas these drugs are not as potent as the GLP1 analogs, they are safe to use with fewer side effects. The DPP4 inhibitor is a good option for people with diabetes who refuse to take injections.

1. GLP1RAs

GLP1 is a hormone synthesized in the ileum in response to food intake. In patients with diabetes, the efficacy of GLP1 is reduced. GLP1 and Gastric inhibitory polypeptide (GIP), another intestinal hormone, regulate glucose by improving insulin production and quality. GLP1 also reduces glucagon and liver glucose output. GLP1 receptor agonists have several systemic effects, including reducing central appetite, slowing down gastric emptying, increasing weight loss, reducing blood pressure, and improving dyslipidemia. The half-life of natural GLP1 is very short because it is deactivated within 2 to 3 minutes by the enzyme DPP4. The

856p. 857discovery of the role of GLP1 led to the development of GLP1 receptor agonists with extended half-lives. It is the pharmacologic dose of GLP1RAs that beyond glycemic control, affects satiety, causes weight loss, and lowers blood pressure. GLP1RAs have also been reported to be associated with cardioprotective effects.

There are several GLP1RAs available, both short- and long-acting. The first one on the market was **exenatide (Byetta)**, a naturally occurring peptide, from the Gila monster lizard, administered twice daily. Exenatide was then developed as a once-weekly injection (Bydureon) with better efficacy. Liraglutide (Victoza) is a modification of human GLP-1 with 24 hours' efficacy and is, therefore, administered once daily. GLP1RAs are approved as monotherapy and in combination with oral diabetic agents and with insulin. The majority of adverse effects are gastrointestinal, the most frequent of which are nausea, vomiting, and diarrhea. Of note, the long-acting GLP1RAs were associated in preclinical trials with the development of medullary thyroid cancer in rats and mice. This phenomenon was not observed in humans. This finding was not observed with short-acting GLP1RAs such as Byetta.

Several more GLP1RAs have been approved. A short-acting formulation, lixisenatide (Adlyxin), is similar to exenatide; however, it is approved for once-daily use. Both dulaglutide (Trulicity) and albiglutide (Tanzeum) are approved for once-weekly use. In summary, because of its efficacy and safety, low rate of hypoglycemia, association with weight loss, as well as positive effects on CV risk factors, this class of drugs is a favorite among experts of diabetes management. There is also particular excitement for the combination of insulin and GLP1RAs as a promising management strategy.

2. ***DPP4 inhibitors***

The enzyme DPP4 deactivates the incretins, GLP1 and GIP, within 2 to 3 minutes. The pharmacologic inhibition of DPP4 increases the half-life of endogenous GLP1 to 24 hours, preserving their glucose-lowering effect. DPP4 inhibitors result in a decrease in A_{1c} of approximately 0.5% to 0.7%. Currently available DPP4

inhibitors include sitagliptin, saxagliptin, linagliptin, and alogliptin. These drugs are quite similar in their efficacy and safety. CV outcome studies with DPP4 inhibitors have suggested that these agents are not associated with an increase in CV risk. In summary, DPP4 inhibitors have become a reliable treatment option despite their modest effect on glucose reduction.

H. SGLT2i

An even newer treatment class is the **SGLT2i**, which offer a totally new mode of action inhibiting glucose reabsorption from the kidneys. This new class has an impressive effect on lowering glucose levels with no risk of hypoglycemia while offering significant weight loss and remarkable blood pressure reduction.

The SGLT in the kidney is the primary mechanism by which glucose is reabsorbed. Of the two available SGLTs in the kidney, SGLT2 and SGLT1 (the main transporter in the intestines), the SGLT2 is responsible for the majority (90%) of glucose reabsorption in the body. This led to the introduction of a new class of antihyperglycemic medications, the SGLT2i. They reduce renal reabsorption of filtered glucose and increase urinary glucose excretion. Three drugs are currently approved in the United States: dapagliflozin (Farxiga), canagliflozin (Invokana), and empagliflozin (Jiardance), with a fourth one, ertugliflozin, in development and soon to be submitted to the FDA for approval. Several other SLGT2i are approved in Japan. Unlike most approved noninsulin antidiabetic drugs, the glucose-lowering effect of SGLT2 is independent of insulin secretion or reduction of liver glucose output. Therefore, they **do not pose a hypoglycemia risk** and are effective in all types of patients, including those with insulin dependence. However, the drugs are still not approved for T1D, in which they have recently been studied in phase 3. The glucose-lowering effect of these drugs ranges between 0.7% and 1% of A_{1c} as monotherapy and in combination. Of note, the glucose-lowering effect of SGLT2i depends on kidney function and is reduced in patients with kidney disease. Beyond lowering plasma glucose, these drugs have a significant effect on **reducing blood pressure** by an average of 5 p. 857p. 858to 6 mmHg and a weight reduction of 6 to 10 lb. The main side effects of SGLT inhibitors are urinary mycotic infection (primarily in females and

uncircumcised males), increased urination, thirst, and occasional dizziness, as well as increased production of ketones which can raise the risk of diabetic ketoacidosis. Diabetes is a chronic disease, and patients are exposed to risks of end-organ damage, namely the kidneys, eyes, feet, and the brain. One of the most common and dire problems in diabetes is kidney damage. Given that SGLT2 inhibitors' mode of action is in the kidneys, when they first came to the market, clinicians were reluctant to use them, fearing kidney damage. However, newer data showed that these drugs **may actually improve kidney function**.

I. Combination of SGLT2i and incretin-based therapy

There has been a lot of excitement among experts in combining incretin-based therapy with SGLT2i because of their complementary, noncompeting, mechanism of action in which the incretin-based treatment impacts glucose-dependent insulin secretion and liver glucose output, whereas the SGLT2i reduces the kidney's glucose reabsorption. The studies combining DPP4i and SGLT2i showed varied results with a combined A_{1c} reduction of 0.6% to 1.1% and a minimal side-effect profile somewhat short of expectations. Then, a recently published study, DURATION-8, combining dapagliflozin (Farxiga) and exenatide QW (Bydureon) in addition to metformin, impressed the experts, producing a combined A_{1c} reduction of 2.1% as well as weight and blood pressure reductions.

J. New information on older drugs

1. Metformin

Metformin is the preferred first-line therapy for treatment of T2D, alone and in combinations with other drugs—SUs, thiazolidinediones (TZDs), *α*-glucosidase inhibitors (AGIs), the glinides, DPP4 inhibitors, GLP1 analogs, colesevelam, and/or insulin—concurrently with lifestyle modification. Metformin is believed to suppress hepatic glucose production; hence, it does not cause hypoglycemia and generally no weight gain. The FDA allows starting metformin with a lower estimated glomerular filtration rate (eGFR) (creatinine clearance) of >45 mL/minute and to continue its use until eGFR is ≥30 mL/minute.

2. TZDs

TZDs act mainly on PPAR-*γ*, causing increase in fat cells, reducing

peripheral insulin resistance, improving insulin-dependent glucose disposal, reducing hepatic glucose output, and may help preserve *β* cells function. TZDs reduce CV risk factors, including inflammation, blood pressure, urinary microalbumin, improve endothelial function, and have positive effects on lipids. Yet, a correlation with a beneficial effect on CV events has not been consistently demonstrated. The two available TZDs are **rosiglitazone** and **pioglitazone**. Both may cause increases in bone fractures, weight gain, edema, and congestive heart failure. Rosiglitazone was also implicated in causing CVD and pioglitazone in causing bladder cancer. Thus, their use in the United States was nearly eliminated. However, on the basis of a prospective study, RECORD, the FDA cleared rosiglitazone from causing CVD, whereas a 10-year study addressing pioglitazone and bladder cancer did not support such risk, though the FDA is yet to address it. Another CV outcome trial, IRIS, evaluated pioglitazone in people with cardiometabolic conditions and prediabetes who had strokes. In this study, pioglitazone reduced fatal and nonfatal stroke and myocardial infarction (MI) by 24% ($p = 0.007$) compared with placebo. It also significantly reduced progression to diabetes by 52%. Of note, the FDA did not approve any antihypoglycemic drug for prediabetes. This good news for the class, combined with the impressive reduction of A_{1c} by 0.7% to 1%, without causing hypoglycemia and the fact that the drugs are generic now, indicates that the class is likely to witness a revival.

3. **`-glucosidase inhibitors (AGIs)**

AGIs were approved many years ago; however because of significant, although nonserious, side effects, such as abdominal pain, bloating, flatulence, and diarrhea, its use in the United States and globally has been limited. Not being absorbed, p. 858p. 859they do not cause hypoglycemia, and with early studies results (STOP-NIDDM) also showing reduction in CV outcome, it led to a recent resurgence in interest in the class in some countries, particularly in China, and making experts in the United States take a second look at the class.

K. Contemporary insulin products

Insulin is used with all patients who have T1D; however, up to 30% of people with T2D currently also use insulin alone or in combinations with oral medications. In recent years, insulin analogs have been dominating the market over humulin (human-like) insulin. These include the fast-acting analogs—lispro, aspart, and apidra, and the long-acting analogs—detemir, glargine, and glargine U300, as well as the ultralong degludec. The efficacy of analog insulin seems similar to that of human insulin; however, it has typically shown less hypoglycemia. The fast onset of action of the rapid insulin makes it easier for the patient to inject shortly before a meal and still reduce postprandial hyperglycemia. Their shorter duration reduces the risk for hypoglycemia. Generally, the fast-acting analogs are used with basal insulin, hence the basal-bolus strategy to manage patients with insulin-requiring diabetes. The use of premixed formulations containing a rapid-acting and long-acting insulin, that is, insulin lispro 75/25 and biphasic insulin aspart 70/30, has been discouraged. Although these preparations are easier to administer, they do not mimic normal physiology, have less dosing flexibility, and induce more hypoglycemia.

Several new insulin formulations were introduced in recent years. They include longer-acting basal insulin, concentrated insulin, ultra-rapid-acting inhaled insulin, and, pending FDA approval, ultra-rapid-acting injectable insulin (Fig. 65-9).

1. **Toujeo-insulin glargine U300:** This concentrated insulin has a reduced rate of absorption; is flatter, has more prolonged pharmacokinetic and pharmacodynamic profiles; less variability; a half-life of approximately 23 hours, duration ≤36 hours, and a steady state of 4 days. Studies showed that it has an A_{1c} reduction similar to that of Glargine U100 and perhaps less nocturnal hypoglycemia.
2. **Degludec insulin:** This is an ultra-long-acting insulin; duration of action >42 hours, half-life of approximately 25 hours, and steady state of 3 to 4 days. It is available in pen, in both a U100 and a concentrated U200, delivering up to 160 units of basal insulin in one injection. Because of its long action, the drug can be taken at any time during the day, allowing people who happen to forget, to take it at a later time. This is referred to as flexible dosing. In a series of recent studies called SWITCH trials,

degludec insulin proved to have less hypoglycemia than that of insulin glargine in both T1D and T2D patients and is awaiting an appropriate FDA indication.

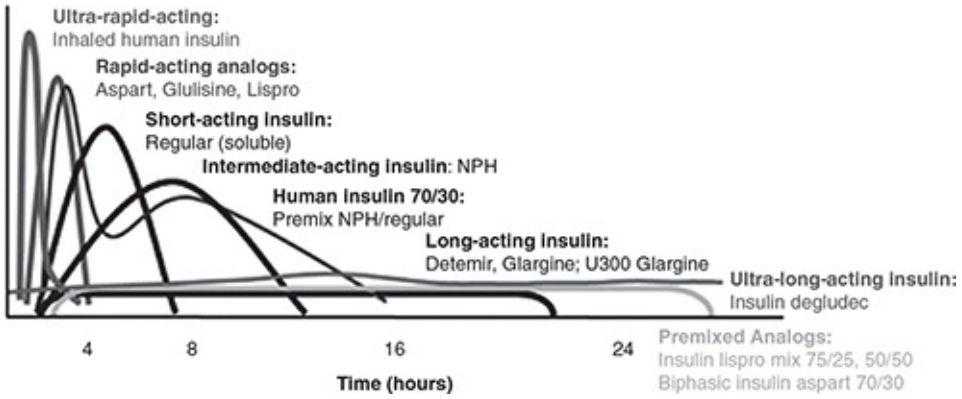

Figure 65-9. Types of insulin. NPH, neutral protamine Hagedorn (Adapted from Hirsch I. Insulin analogues. *N Engl J Med* 2005;352:174–183.)

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3. **Concentrated insulin: Insulin Lispro U200** has the same properties and action profile as those of lispro U100; however, it allows the patient to administer large doses of insulin per meal with half the volume, allowing for less pain, yet preserving its original properties. Lispro U200 is delivered with a pen, which makes it easy for patients to just dial the needed units without the need to calculate. **Insulin Humulin regular U500:** This insulin has been around for many years; however, it was quite difficult to use, especially creating issues for patients to calculate the needed dose. It has now been approved in a pen delivery system that allows users to just dial the number of units that they need.
4. **Inhaled Technosphere insulin (Afrezza):** In 2014, the FDA approved ultra-rapid-acting insulin, human inhalation powder for prandial glycemic control in adults with T1D and T2D (Fig. 65-10). Inhalable insulin is rapid-acting and should be administered at the start of each meal. It is effective in reducing postprandial glucose and, because of its fast in-and-out action, typically demonstrates less hypoglycemia. In patients with T1D, inhalable insulin should be used in combination with long-acting insulin. A black box warning cautions against use in patients with chronic

lung disease, such as asthma or chronic obstructive pulmonary disease. The use of inhalable insulin can cause acute bronchospasm in these patients; thus, pulmonary function test is required before initiating the drug.

L. Insulin and GLP1RAs combinations

In December 2016, the FDA approved two new injectable medications with a fixed coformulation of GLP1RA and basal insulin, Xultophy and Soliqua.

1. **iDegLira (Xultophy)** is a fixed coformulation of the long-acting insulin degludec with the long-acting liraglutide for once daily subcutaneous injection. It is supplied as a 3 mL prefilled pen containing 100 U/3.6 mg insulin degludec/liraglutide per mL. The proportion of patients reaching target HbA_{1c} was higher with Xultophy than with insulin degludec or liraglutide alone. Adverse effects are typical of the component drugs, with a lower incidence of gastrointestinal effects but less weight loss than liraglutide alone.
2. **iGlarLixi (Soliqua)**, once known as LixiLan, is a fixed-ratio coformulation of the long-acting insulin glargine and the short-acting GLP1RA, lixisenatide. The combination has more A_{1c} reduction and fewer episodes of hypoglycemia than the individual components.

   The FDA approved both drugs to patients who are already on either basal insulin or GLP1RA, making it suitable for late disease. However, many experts believe that these drugs would be best as the first injection, offering an “improved basal insulin” that would address both fasting and prandial glucose. However, until relevant studies will support this approach, it is considered off-label.

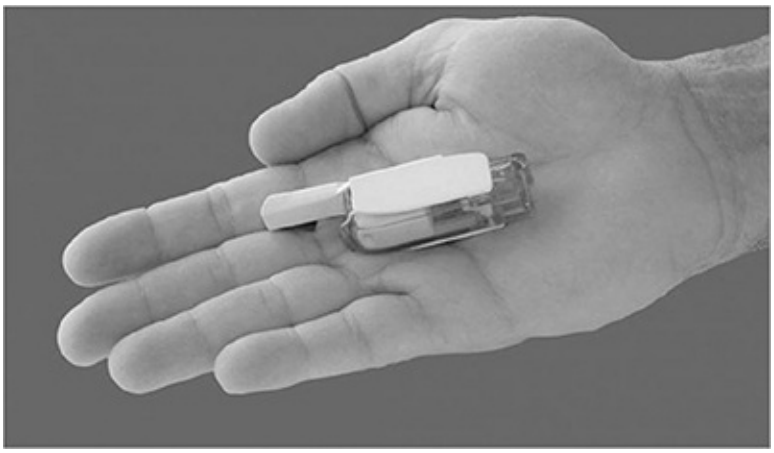

Figure 65-10. Technosphere inhaled insulin (Afrezza).

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M. Cardiovascular outcome trials (CVOT)

Following the 2007 meta-analysis implicating rosiglitazone with increased risk for CV death as well as other reports implicating various other diabetes medications for seemingly increasing CV risk, in **2008, the FDA started to demand CV safety trials for all new medications for diabetes** (Fig. 65-11). Some of the companies designed their trials to also be able to show superiority if noninferiority (safety) was met.

1. The **EMPA-REG CVOT** with the SGLT2i, Empagliflozin, studied people with DM and established CVD and showed a superior effect in reducing the primary endpoint (three points major adverse cardiac events (MACE): CV death, nonfatal MI, and nonfatal strokes) by 14% (p = 0.038). Whereas the reduction in the CV events were nonsignificant, the driving result was **38% significant reduction of CV death**. All-cause mortality was reduced significantly by 32%. It is important to note that these results were on top of good usual care where most patients (>80%) were on statins, ACE inhibitors as well as β-blockers, and typically two to three antihyperglycemic medications, including 45% on insulin. Another important outcome of the study was improvement in kidney function. For the first time ever for antihyperglycemic drugs, the FDA, in December 2016, **approved empaglflozin an indication to reduce CV death** in people with DM and prior CV events.

2. **LEADER** is a CVOT with the GLP1RA, liraglutide, which was studied in patients with T2D with high risk for, or established, CVD. The study showed a significant p. 861p. 862 13% decrease in the primary composite outcome of nonfatal MI, nonfatal strokes, and CV death. Interestingly, here too, the results were driven just by the significant **reduction of CV death by 22%**. An important finding was a significant **improvement in kidney function**. As GLP1RA carry warnings on the potential deleterious effect on the kidney, these results have special importance in not only reassuring GLP1RA's safety but also underscoring the beneficial effect on the kidney. In August 2017, the FDA approved liraglutide an indication to reduce major CV events, including death, in people with DM and established CVD.

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo	placebo	placebo	sulfonylurea	placebo
N	16,500	5,400	14,000	6,000	8,300
	NEUTRAL	NEUTRAL	NEUTRAL		
Results	2013	2013	June 2015	2017	2017

Study	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND	FREEDOM
GLP1-RA	liraglutide	lixisenatide	semaglutide	exenatide LR	dulaglutide	ITCA-650
Comparator	POSITIVE	NEUTRAL	POSITIVE	placebo	Placebo	NEUTRAL
N	16,500	14,000	6,000	5,400	8,300	4000+
Results	2016	2015	2016	2018	2019	2015

Study	EMPA-REG	CANVAS	DECLARE	NCT01986881
SGLT-2-i	empaglifozin	canagliflozin	dapagliflozin	ertugliflozin
	POSITIVE			
Comparator	placebo	placebo	placebo	placebo
N	7300	4300	22,200	3900
Results	Sept 2015	2017	2019	2020

Figure 65-11. CV outcome studies with GLP1RA confirmed safety from the CVD point of view: ELIXA (Lixisenetide), FREEDOM (Exenatide ITCA-650) as well as LEADER (Liraglutide) and SUSTAIN-6 (Semaglutide—once weekly, pending FDA approval). Two of the trials also proved superior in reducing CV morbidity (SUSTAIN-6) and mortality (LEADER). The long-term outcome clinical trials with DPP4i, SAVOR (saxagliptin), EXAMINE (alogliptin), and TECOS (sitagliptin) demonstrated safety, showing no increased risk of CVD yet no superiority in reducing CVD. The SGLT2i CVOT EMPA-REG (empagliflozin) was first to show a superior effect by an

antihyperglycemic agent in reducing CV mortality. Two long-acting basal insulin analog studies, ORIGIN with glargine insulin (Lantus) and DEVOTE with degludec insulin (Tresiba), confirmed CV safety. Large Noninsulin CVOTs in T2DM. CVD, cardiovascular disease; CVOT, cardiovascular outcome trial; DPP4i, dipeptidyl peptidase-4 inhibitors; FDA, Food and Drug Associations; GLP1RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter-2 inhibitors; T2DM, type 2 diabetes mellitus.

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3. **SUSTAIN-6** studied the once-weekly GLP1RA, semaglutide, which received FDA approval in December 2017. Although the study was designed to show noninferiority only for safety, it ended up demonstrating a 26% risk reduction for its primary composite endpoint of nonfatal stroke, MI, and CV death (p = 0.02). The results were driven mainly by a significant **39% reduction in the risk of nonfatal stroke** (p = 0.04).

In conclusion, the importance of these CVOT results to the field far outweighed the individual drug benefits. For many years since 2007, the management of hyperglycemia was gripped by the fear that these medications may cause heart disease. But these results restored confidence in the matter of diabetes management, allowing patients to have better control of their condition, thus improving their morbidity and mortality. In fact, currently the discourse has changed to the extent that not only is it accepted that the drugs are safe, it is now expected that they would have a positive effect on CV outcome. With the indication of empagliflozin to reduce CV death in DM and the similar indication for liraglutide, as well as other drugs from the SGLT2i family, we are witnessing a revolution in the present and future management of diabetes.

III. SUMMARY

In summary, the present and the near future offer an excellent opportunity to improve the life of people with diabetes. Because T2D is a heterogeneous disease, patient-centered, individualized care and goal-setting is appropriate. Interactions between glycemic imbalance and CV risk factors lead to micro- and macrovascular complications that result in retinopathy leading to blindness, kidney disease, amputation, and CVD. Addressing all CV risk factors (including hyperglycemia, hypertension, and dyslipidemia) is important in the reduction of micro- and

macrovascular complications. The new indication for empagliflozin, the antihyperglycemic medication, to reduce CV death has opened new dimensions in the future management of diabetes especially as other drugs from the SGLT2i and the GLP1RA families are following through with similar indications. The technological advances incorporating state-of-the-art science with wireless and Bluetooth capabilities are offering simple and easy glucose monitoring. The soon-to-be available complete closed-loop artificial and bionic pancreas will allow patients, primarily with T1D, to achieve their desired goals easily and safely.

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66 Artificial Pancreas

Kathleen H. Ang and Stuart A. Weinzimer

I. INTRODUCTION

Continuous subcutaneous insulin infusion pumps have been utilized in the care of patients with type 1 diabetes for decades, and within the last decade, the use of continuous glucose monitors (CGMs) has evolved from an experimental "niche" device to a mainstay of management for many adults and children. However, despite these technological advancements, most patients with type 1 diabetes do not meet recommended glycemic targets, have unacceptably high rates of hypoglycemia, and also suffer from the daily burden of diabetes care. In order to reduce this burden and improve glycemic control, closed-loop automated insulin delivery, or "artificial pancreas" (AP) systems, has been developed. These AP systems rely on a control algorithm that allows for automatic modulation of insulin delivery rates from the pump on the basis of the continuous stream of glycemic data from the CGM, designed to improve glucose control and reduce user intervention (Fig. 66-1). The first closed-loop hospital studies were conducted in the 1970s using large in-hospital devices. The development of small, portable, accurate, and user-friendly glucose monitoring and insulin infusion devices with wireless connectivity has enabled studies to be conducted in ambulatory and home environments. The current era of AP testing includes both small short-term feasibility and safety testing of new systems, and longer term, larger randomized-controlled efficacy trials designed to lead to approval of the Food and Drug Association (FDA).

II. TERMS AND DEFINITIONS

A. Nomenclature: AP, automated insulin delivery system, bionic pancreas, and closed-loop system have all been used as terms for these devices, somewhat interchangeably. There are no standardized definitions of these individual terms, but the FDA considers an "artificial pancreas device system" a device to "reduce or increase insulin infusion . . . to automate the process of maintaining blood glucose concentrations at or near a specified target or range."

B. Types of systems: AP systems may have varying degrees of automation, and have different types of control algorithms, ranging from simple on/off control of pump basal rates to more complicated systems that reduce or augment insulin delivery on the basis of current glucose level, the glucose rate of change, the content and timing of meals and exercise, and other inputs such as heart rate. Control algorithms may be characterized as “control to target,” in which the system aims to correct the glucose level to a specific number, or “control to range,” in which the goal of the algorithm is to maintain the glucose level within a prespecified zone of acceptable glucose values.

C. Hybrid versus fully automated systems: Most systems in development today are “hybrid” in nature, which means that automation is not complete: some manual user input is necessary for routine insulin delivery. The most common example of a hybrid system is one that requires the wearer to manually “announce” to the system an impending meal; the user might have to enter into the system the exact carbohydrate content of the meal, or just the general size of the meal (small, medium, large). Exercise might be handled similarly: the user might have to toggle an “exercise on/off” button to alert the system to the start and conclusion of physical activity. In contrast, a fully automated system would be expected to handle the challenges of meals and exercise without external inputs.

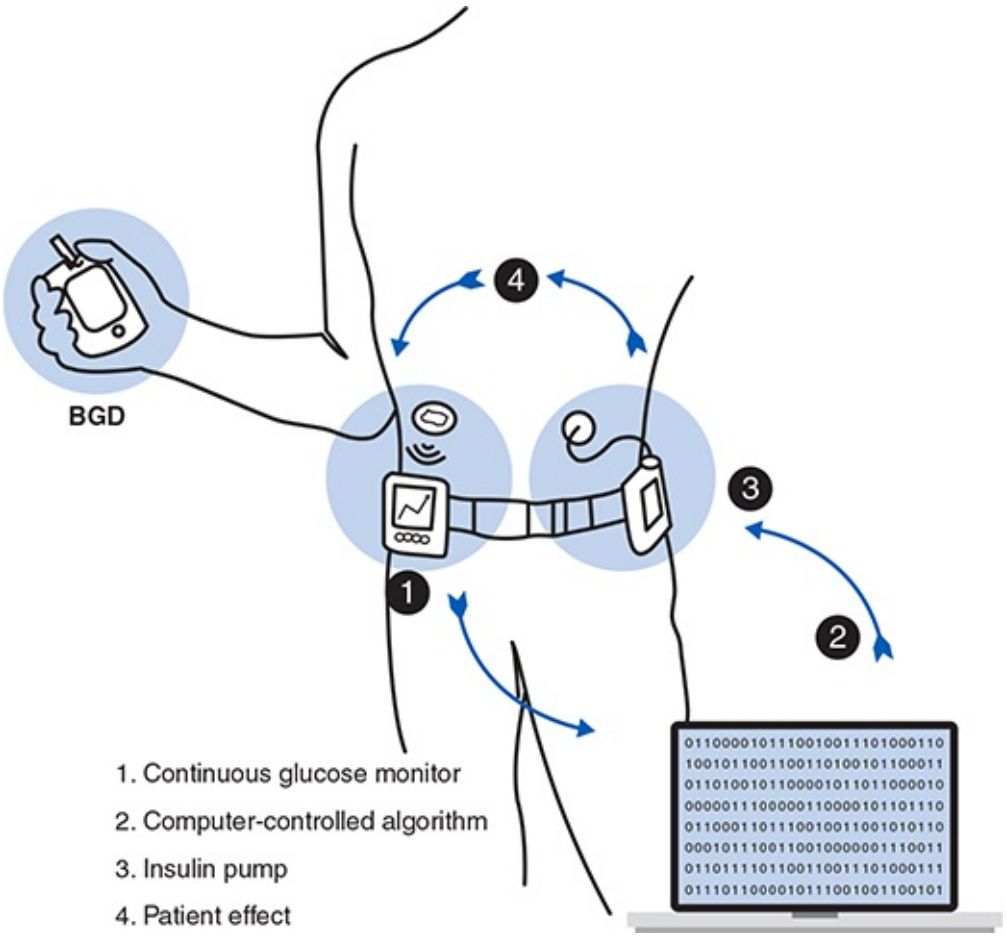

Figure 66-1. A schematic diagram of the parts of an AP device system: the continuous glucose monitor (CGM) (1) provides information to the controller (2), which determines the appropriate amount of insulin to be delivered by the insulin pump (3). The process is iterative: the administered insulin dose results in a new glucose level, and the process repeats at frequent intervals (4). The system also includes a blood glucose device (BGD), for calibration of the CGM. (From FDA: Guidance for Industry and Food and Drug Administration Staff: The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) applications for AP device systems, November 9, 2012: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/C

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D. Single-hormone versus dual-hormone: Whereas most AP systems are constructed as insulin-only types, some systems incorporate an additional hormone, usually **glucagon**, **infused via a second pump** under separate algorithmic control. Other hormones besides glucagon, such as **incretins, are under study as well**.

III. SYSTEM COMPONENTS

A. Insulin pumps: These devices are responsible for the delivery of

insulin (and other hormones) on a continuous basis. In standard “open-loop” configuration, pumps can be programmed to deliver “basal” insulin doses in a continuous fashion; rates may be constant, or vary over time, typically in 30-minute increments. Pumps can also deliver “bolus” doses of insulin, either to correct hyperglycemia or to account for ingested carbohydrates. In an automated insulin delivery system, the basal insulin delivery is typically adjusted up or down, in 5- to 15-minute increments, on the basis of the blood glucose level or trend, determined by the continuous glucose p. 866p. 867sensor and the controller algorithm. Almost all insulin pumps used in AP systems are **external devices**, carried by the user on or close to the body, and deliver insulin into the subcutaneous compartment through a percutaneous insertion that must be changed every few days. However, **surgically implanted systems**, in which the pump is inserted into a subcutaneous pocket, with the catheter tip protruding into the peritoneal space, have also been evaluated. The potential advantages of such a design (more rapid insulin pharmacokinetic and pharmacodynamics profiles, elimination of the need for frequent site changes, absorption problems because of scar tissue) must be weighed against the disadvantages (infection risk, inconvenience of pump refills and catheter occlusion). Regardless of the type of pump, closed-loop systems may or may not require manual entry of meal and/or exercise information for routine operation.

B. CGMs: CGMs, or “sensors,” are devices that measure ambient glucose levels, on a continuous basis, throughout their functional life span. All of the sensors in use today are electrochemical-type ones: platinum electrodes impregnated with an enzyme layer that oxidizes glucose to generate a small electric current proportional to the glucose concentration in the interstitial fluid of the subcutaneous compartment. These devices are consumables, not unlike glucose test strips, but are inserted percutaneously and then discarded after their period of use, typically 5 to 7 days, although newer sensors in development may allow longer periods of use. The sensor data are transmitted to a receiver device on a regular basis, typically every 5 minutes, allowing for “real-time” visualization of glucose levels both numerically and graphically. Depending on the system, the receiver may be a stand-alone device, a smartphone, or an insulin pump. Audible or vibratory alerts for actual or predicted high or low glucose levels may be set and

adjusted by the user. All of the sensors available today require intermittent calibration against capillary glucose levels to maintain accuracy, and even with optimal calibration conditions, sensor accuracy is inferior to capillary glucose testing (although improving). As with insulin pumps, sensors are currently used in "open-loop" diabetes management in many children and adults with type 1 diabetes and have been shown in multiple studies to be an effective intervention to improve A_{1c} levels and reduce hypoglycemia. In closed-loop systems, sensors serve as the afferent arm, providing the data stream to the controller algorithm to adjust insulin pump delivery.

C. **Controller:** Representing the "brain" of the AP system, the controller provides the connectivity for all of the system components and contains the algorithms required for processing the continuous stream of glucose data, calculating the required insulin doses, and commanding the pump to deliver. Depending on the AP system, the controller may either be a stand-alone device, usually within a smartphone, or housed within the insulin pump itself. The algorithms for closed-loop control that determine insulin delivery vary greatly in their approach and complexity. A nonexhaustive sample of approaches is as follows:

1. **Insulin suspension systems** toggle insulin delivery on or off on the basis of the prevailing glucose conditions, such as current low glucose level (threshold suspend) or predicted low glucose level within a predetermined time horizon (predictive suspend).
2. **Proportional-integral-derivative** systems are "reactive" algorithms that respond to the current blood glucose level and the glucose trend. The proportional component takes into account the deviation from a blood glucose set point; the derivative component responds to the rate of change of the glucose from the previous glucose value; and the integral component responds to longer term deviations from the set point. These types of algorithms may be adapted to account for other variables, such as insulin delivery and action characteristics.
3. **Model predictive control** systems represent a more complex approach that uses mathematical models of physiologic systems to "predict" the appropriate insulin delivery required to meet the prevailing conditions. These systems are designed to account not only for the glucose levels and rates of change, but also for insulin

pharmacokinetics and pharmacodynamics, carbohydrate absorption, exercise, and other variables.

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4. **Fuzzy logic** systems are designed to account for clinician expertise and human individualization in the models.
5. **Other aspects of controllers:** In an AP system, regardless of the algorithm utilized to determine insulin delivery, the controller should also specify safety parameters under which closed-loop control can continue or should be terminated, at which point the system reverts to an open-loop status (e.g., if communication fails between components or the system suspects a sensor or pump malfunction).

IV. TYPES OF AP SYSTEMS

A. Low-glucose (threshold) suspend: This type of system represents the most basic level of feedback control: suspension of basal insulin in response to a low sensor glucose level. The controller has essentially **two choices**: run the preprogrammed basal rates (typical open-loop control) or suspend insulin delivery entirely. When the sensor crosses a predefined threshold glucose level, the system alarms, and if no user response is made, the system goes into a suspend mode for 2 hours; the suspension can be terminated at any time, resuming normal insulin delivery, and even without a response, the system resumes normal basal insulin delivery after 2 hours of suspension. Threshold suspend systems are designed primarily for safety: to reduce exposure to hypoglycemia, particularly at night, when audible or vibratory alarms may not be noticed during sleep, and when patients are at highest risk for severe hypoglycemia. This system is commercially available (**Medtronic Veo, 530G, and 630G systems**), and has been shown in a large clinical trial of 247 subjects to reduce exposure to hypoglycemia by 31% and nocturnal hypoglycemia by 38% without deteriorating glycemic control.

B. Predictive low-glucose suspend: The next incremental advancement from threshold suspend systems are ones in which **hypoglycemic excursions can be predicted and prevented, rather than just mitigated**. Like threshold-suspend systems, these are “toggle on/off” systems: the controller has two options: continue the preprogrammed basal insulin delivery or suspend insulin delivery

entirely. But unlike threshold systems, predictive systems attempt to predict a hypoglycemic occurrence before it occurs, and suspend insulin ahead of time; in addition, the period of suspension is variable, turning insulin back on in response to the prevailing glucose levels, not just for a given duration of time. Studies of a predictive system used at nighttime only demonstrated the effectiveness of this approach in reducing nocturnal hypoglycemia by up to 80% in adults with type 1 diabetes and at least 50% in children with type 1 diabetes as young as 4 years of age. At the time of this writing, a predictive low-glucose management system is commercially available as a stand-alone system as the Medtronic 640G and as an option in the Medtronic 670G. Clinical trials of predictive suspend systems have demonstrated safety and effectivness in reducing hypoglycemia exposure.

C. **Unihormonal AP systems** including insulin only comprise the majority of AP systems in development. The major difference between these AP systems and the suspension systems described above is that these **not only reduce insulin delivery in advance of low glucose levels but also augment insulin delivery for actual or predicted hyperglycemia**. They are designed not only for safety (hypoglycemia minimization) but also for efficacy (hyperglycemia minimization and improvement of overall glycemic control). Generally, these systems are “hybrid” in nature, requiring users to input meal information such as the timing and carbohydrate content, but control algorithms provide additional layers of automation “underneath” and adjust basal insulin upward or downward as needed. Studies of single-hormone AP systems have progressed from inpatient proof-of-concept studies, through short-duration studies in semisupervised outpatient environments such as a hotel setting, to longer trials in the home environment. Using this stepwise approach, multiple groups utilizing different algorithmic approaches and pump/sensor combinations have demonstrated beneficial effects of an AP system in two principal areas: **(1) reducing hypoglycemia exposure and (2) improving overall glucose control** (mean glucose levels). Most recently, the ability to conduct studies of up to 3 months in duration has allowed for the demonstration of p. 868p. 869reduction in A_{1c} levels with the use of an AP

system. Importantly, clinical trials have shown benefit in both adult and pediatric populations, and most recently, in pregnancies complicated by type 1 diabetes. At the time of this publication, one hybrid closed-loop system is commercially available (Medtronic 670G), and other systems are in development.

D. Bihormonal AP systems include not only **insulin**, but also a second hormone, usually **glucagon, delivered from a second pump** and under separate algorithmic control. The rationale for the addition of glucagon to the system lies in the fact that glucagon is a critically important regulator of glucose homeostasis in nondiabetic individuals, and that an insulin-only system may be insufficient for optimal control, especially in an AP system, in which insulin is delivered nonphysiologically, in the subcutaneous compartment. In a bihormonal system with glucagon, it would theoretically be possible to deliver insulin more aggressively at mealtimes and during hyperglycemia, because hypoglycemia caused by insulin overshoot would be prevented by the judicious delivery of glucagon during downward glucose excursions. A glucagon-containing system would be particularly **advantageous during exercise**, when hypoglycemia occurs commonly even with the complete suspension of insulin. Initial short-term studies of bihormonal systems with insulin and glucagon have shown promise, improving average glucose levels and reducing hypoglycemia in both adult and pediatric cohorts, although the requirement for freshly preparing the glucagon powder every day for use in the insulin pump currently precludes its large-scale commercial use; efforts are currently underway to develop liquid stable glucagon for use in such systems. **Other hormones considered** for use in a bihormonal system include the **amylin analog pramlintide** and the **incretin mimetics exenatide and liraglutide**. Proof-of-concept studies of systems utilizing these combinations have shown beneficial effects on reducing both postprandial glycemic excursions and insulin requirements.

V. FUTURE DIRECTIONS

A. Improvements in “human factors” to make systems smaller and easier to use

B. Improvements in algorithms to allow for full automation without meal or exercise announcement

C. Incorporation of other inputs (e.g., heart rate or accelerometry data) to

enable improved performance during exercise

D. Acceleration in insulin pharmacokinetic and pharmacodynamics properties, either by novel insulins or by novel delivery techniques, to improve AP system performance

E. Use of liquid-stable glucagon preparations for application in bihormonal systems

F. Use of other adjunctive medical therapies with AP systems.

G. Development of practical guidelines for clinicians incorporating these systems into clinical practice.

VI. SUMMARY

The AP holds great promise as a means to improve glycemic control, while reducing the burden of care for people with type 1 diabetes. Through the integration of continuous glucose sensor data into complex algorithms, insulin (and other hormones) can be delivered in an automated fashion with minimal reliance on patient participation. Closed-loop systems have been shown to increase time in target glycemic range, decrease hypoglycemic exposure, and improve benchmarks such as A_{1c} levels; and have been shown to be safe in a wide range of patient populations. The next generation of AP devices will continue to improve performance, user satisfaction, and translation into a commercial device available for everyone with type 1 diabetes.

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67 Glycated Proteins in the Diagnosis and Management of Type I and Type II Diabetes Mellitus

Norman Lavin

I. INTRODUCTION

Glycation occurs continuously over the lifetime of a protein. Hemoglobin A_{1c} (HbA1c), which is formed by the condensation of glucose with select amino acid residues in hemoglobin, reflects the average blood glucose value over a period of 60 to 90 days. Other glycated proteins include fructosamine, glycated albumin, and advanced glycation end products (AGEs). HbA_{1c} can be measured by immunoassays, high-performance liquid chromatography (the two most commonly used methods), affinity chromatography, capillary electrophoresis, and enzymatic assays.

HbA_{1c} levels between 5.7% and 6.4% indicate prediabetes and an increased risk to develop full-blown diabetes. Levels of 6.5% or higher indicate the presence of this disease. I recommend that people with diabetes have this test performed every 3 months.

II. INTERFERENCE

A. Chronic renal failure (CRF). Blood cell survival is reduced in this disorder, decreasing the HbA_{1c}. Furthermore, some patients with CRF are treated with erythropoietin to stimulate erythropoiesis with subsequent increase in the number of young red blood cells (RBCs), which further reduces the HbA_{1c}. The HbA_{1c}, therefore, in patients with diabetes and concurrent CRF may not accurately indicate glycemic control.

B. Iron deficiency. This disorder elevates the level of HbA_{1c} independently of glucose and hemoglobin levels. However, once treatment is initiated with iron supplementation, HbA_{1c} concentrations

decrease significantly as a result of the production of immature cells. In addition, other hemoglobin modifications occur because of various middle molecules that accumulate in chronic kidney disease (CKD), such as AGEs, which may bind to hemoglobin and cause more potential interference.

C. Erythrocyte life span. Lower than expected levels of HbA_{1c} are found in people with shortened RBC life spans, such as with glucose-6-phosphate-dehydrogenase deficiency, sickle cell disease, or any other condition causing premature RBC death. For example, if a physician has a patient where the HbA_{1c} is 7.0% with a normal RBC life of 120 days, and later it is 10 days shorter, then the corresponding HbA_{1c} would be 6.4%, whereas if it were 10 days longer, then the HbA_{1c} would be 7.6%. Therefore, the HbA_{1c} value would not accurately reflect average blood glucose concentration. This would be true in hemolytic anemia or in severe beta thalassemia.

D. Variable glycation. Individuals may have different glycation rates, but the concept of variable glycation remains to be validated.

E. Factors that interfere with measurement. Improvements in analytic methods have eliminated many types of interference from some factors, including aspirin, bilirubin, and triglycerides. It is still possible that there are other drugs or other factors that interfere significantly in current HbA_{1c} assays.

F. Hemoglobin variants. These include hemoglobin AS, hemoglobin AC, hemoglobin AD, and hemoglobin AE, which, if present, makes the measurement of HbA_{1c} impossible, particularly if the patient has hemoglobin SC disease because A is absent.

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G. Other abnormalities. Additional entities that can affect the results of the HbA_{1c} include supplements (vitamins C and E), high cholesterol levels, kidney disease, and liver disease.

III. GLYCATED SERUM PROTEINS

Alternate glycated plasma proteins include fructosamine and glycated albumin, which are also formed nonenzymatically when proteins react with glucose in a manner similar to the formation of HbA_{1c}. The turnover of plasma proteins, however, is much shorter than hemoglobin (half-life

of 2 to 3 weeks). Thus, the degree of glycated plasma proteins provides an index of glycemia over a shorter period of time.

A. Fructosamine

Fructosamine is the generic name for plasma protein ketoamine. All glycated serum proteins are fructosamines, and because albumin is the most abundant serum protein, the measurement of fructosamine is thought to largely reflect the concentration of glycated albumin. Fructosamine is thought to be not valid when serum albumin is <30 g/L. It can be used in the diagnosis of gestational diabetes mellitus (GDM) because hyperglycemia develops relatively quickly with the onset of GDM, and red cell turnover may be altered in pregnancy, precluding the use of HbA_{1c}. However, the measurement of fructosamine is not currently a standard to screen for GDM.

Moreover, fructosamine is influenced by the concentration of low-molecular weight substances, such as urea and uric acid. It also has a potential role in end-stage renal disease, certain types of anemia, and transfusion.

B. Glycated albumin

Similar to that of fructosamine, glycated albumin provides a short-term index of glycemic control and is not influenced by albumin concentration. In addition, glycated albumin is not affected by RBC life span or erythropoietin administration and other limitations affecting HbA_{1c} and fructosamine values.

Albumin accounts for over 80% of total glycated serum protein. There are factors that influence albumin metabolism, including the nephrotic syndrome, cirrhosis, thyroid disease, hyperuricemia, hypertriglyceridemia, and smoking. Protein levels may also be altered with liver, thyroid, and renal disease. Glycated albumin is **used as a screening test for diabetes among blood donors in Japan**. There are also some recent data that it is a better test than HbA_{1c} for diabetes screening in nonobese patients.

C. AGEs

Glycation of proteins may link hyperglycemia and the complications of diabetes. More than 20 AGEs have been identified, which do not return to normal even when hyperglycemia is corrected. Therefore, there is accumulation over the life span of the protein. Thus far, AGEs have not been measured by most clinicians.

The formation and accumulation of AGEs has been implicated in

the progression of many age-related diseases, such as Alzheimer's disease, cardiovascular disease, stroke, cataracts, reduced muscle function, arthritis, nephropathy, and neuropathy. The mechanism by which AGEs induce damage is through a process called cross-linking, which causes intracellular damage and apoptosis.

Although not completely proven, AGEs may contribute to microvascular and cardiovascular complications of diabetes. As an interesting theory, it is possible that AGE-burden may explain why only a subset of patients with poor glycemic control develop complications.

Methods for measuring specific AGEs have been developed, many of which use immunoassays, yielding variable results. Isotope dilution analysis, liquid chromatography–mass spectrometry (LC–MS/MS) is a promising technique. Presently, isotope-labeled standards are not commercially available for the full range of analytes, preventing assay standardization.

D. RAGE

AGEs can activate a receptor, which is nicknamed RAGE, inducting intracellular signaling that results in the production of proinflammatory cytokines and increased oxidative stress.

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Inhibitors of the formation of RAGE, such as aminoguanidine, prevented microvascular complications of diabetes in animal models, but was not shown in human trials. One study showed that patients receiving metformin treatment for type II diabetes had lower AGE levels than a control group not receiving metformin.

E. Can glycated albumin provide better positive predictive value than HbA_{1c} in the incidence of diabetic nephropathy?

The global incidence of diabetes mellitus is rising exponentially, and diabetic nephropathy is now the predominant cause of CKD. Studies have demonstrated that in the early stages of diabetic nephropathy, good glycemic control delays the onset and progression of albuminuria.

It is estimated that at least 35% of patients receiving dialysis are patients with poorly controlled diabetes. In order to obtain adequate control, clinicians rely on HbA_{1c}. However, obtaining these readings is not always an adequate measure for glycemic control in patients with

diabetes who suffer from other diseases that affect RBCs and hemoglobin. Some studies show that glycated albumin and glycated albumin to HbA_{1c} ratio can provide a stronger predicting value than HbA_{1c} alone. The role of HbA_{1c} in patients with end-stage renal disease can be affected by variable erythrocyte fluctuations. Glycated albumin to HbA_{1c} ratios can be a good predictor of glycemic control in the presence of diabetic nephropathy because of its close relationship between glucose levels after meals and pancreatic beta cell secretory function. However, some will disagree with these conclusions.

IV. MEASURING GLYCEMIC CONTROL

A. Glycated hemoglobin. Good correlations exist between plasma glucose concentrations and HbA_{1c} measurements in populations with type I and type II diabetes and normal kidney function.

B. Kidney disease. Several features present in chronic renal disease have a significant impact on HbA_{1c} concentrations, and values may be falsely low or high. Besides glucose, HbA_{1c} is influenced by other factors, including the life span of the RBCs, recombinant human erythropoietin, the uremic environment, and blood transfusions. RBC life span is reduced in patients with chronic renal disease. The subsequent increased rate of hemoglobin turnover leads to decreased exposure time to ambient glucose, which, in turn, lowers the extent of nonenzymatic binding of glucose to hemoglobin. This results in reduced value for HbA_{1c}. Therefore, in these patients with kidney disease and a shortened RBC life span, lower HbA_{1c} levels are observed than would be expected from measured glucose control.

V. GLUCOSE CENTRIC FOCUS

Some diabetologists say that making treatment decisions solely on the basis of a HbA_{1c}–centric focus could lead to wrong decisions. They suggest that we move from a HbA_{1c}–centric focus to a glucose-centric focus for diabetes management. The continuous glucose monitoring (CGM) provides real-time glucose data that have a role in the management of type I and type II patients.

VI. THE AMBULATORY GLUCOSE PROFILE

The ambulatory glucose profile (AGP) provides 2 weeks of metric

subglycemic ranges. The patient gets a visual representation of how times and ranges can affect treatment, and the patient can learn about glucose variability, hypoglycemia, and hyperglycemia. The AGP is an important tool to help clinicians interpret data collected from a CGM system; these glucose data are used in addition to HbA_{1c} to individualize therapy.

VII. FUTURE DIRECTIONS

It is clear that HbA_{1c} is an extremely useful tool in diagnosing prediabetes and diabetes mellitus, both type I and type II. As mentioned above, there are other potentially p. 873p. 874useful additional or adjunct measures of glycated serum proteins and AGEs that have emerged.

AGEs have the potential to identify a subset of patients who develop cardiovascular and microvascular complications independent of HbA_{1c}. Further research needs to be done to use AGE-related measures to improve the prediction of risk for diabetes complications, as well as to develop risk-reduction therapies on the basis of these pathways.

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68 Inhaled Insulin

Maamoun F. Salam and Janet B. McGill*

I. GENERAL PRINCIPLES

Inhaled insulin has been developed as an alternative to conventional subcutaneous rapid-acting insulin analogs (RAAs) for preprandial administration. All patients with type 1 diabetes mellitus (T1DM) and many patients with type 2 diabetes mellitus (T2DM) require prandial insulin to cover caloric intake and for correction doses to treat out-of-range hyperglycemia. RAAs are absorbed more quickly than regular human insulin, but none are able to match gastric emptying and peak postprandial glucoses when given shortly before meals. The delayed onset of action and prolonged effects can contribute to hyperglycemia after eating and hypoglycemia before the next meal. Inhaled insulin has been shown to have more rapid absorption than the currently available RAAs when administered subcutaneously and faster decline in serum insulin levels. These characteristics allow inhaled insulin to match the timing of the physiologic postprandial glucose excursion. Reduced rates of postprandial hypoglycemia with similar glycemic control compared with RAAs, and less weight gain may be beneficial for some patients.

Pulmonary drug delivery has been used for both local effects of drugs and for systemic absorption. Pulmonary delivery takes advantage of alveolar anatomy, which features large surface area (50 to 140 m^2), thin membranes with permeability to macromolecules, substantial blood perfusion, reduced mucociliary clearance, minimal enzymatic degradation, neutral pH, and the avoidance of first-pass metabolism. For drugs like insulin, this also means eliminating the need for frequent injections, injection-site problems, and the social distress of injecting oneself in public areas.

Two insulin inhalation systems have been approved by the Food and Drug Administration (FDA) for the management of T1DM and T2DM in adults; however, only one is currently available.

II. THE FIRST SYSTEM (trade name Exubera) consisted of human insulin powder formulation, which was dispensed into a designated chamber of

the inhaler device before administration. This system was approved by the FDA in January 2006; however, it has not been available for several years because of the manufacturer's decision to cease manufacturing.

III. THE SECOND SYSTEM (trade name Afrezza) comprises inhaled Technosphere insulin (ITI), which is composed of a dry powder formulation of recombinant human insulin and fumaryl diketopiperazine (FDKP), an inert excipient, and a dedicated inhaler. The ITI microparticles are formed by the adsorption of insulin electrostatically onto the acid-induced assembly of FDKP molecules to produce appropriate particle size for deep lung absorption across alveolar membranes. When inhaled, these microparticles reach the deep lung where they dissolve rapidly because of the physiologic pH, allowing absorption of insulin and FDKP into the systemic circulation. FDKP is excreted unchanged in the urine. ITI is inhaled through a breath-activated inhaler that is roughly the size and shape of a whistle. The amount of ITI delivered to the lung will depend on the dose administered and individual patient factors. This system, including the combination of ITI and dedicated inhaler, received FDA approval in 2014. The remainder of p. 875p. 876this chapter will comment mainly on the **ITI system, because it is the only product currently available for use**.

A. ITI bioavailability, absorption, distribution, and elimination (Fig. 68-1)

ITI is administered shortly before or immediately after a meal. ITI reaches its peak concentration in 12 to 15 minutes and peak effect in about 53 minutes. ITI action lasts about 120 to 180 minutes which is shorter than that of insulin lispro (180 to 240 minutes). The relative bioavailability of ITI when compared with regular subcutaneous (SC) insulin is 21% to 30% (Table 68-1). However, insulin concentrations from ITI p. 876p. 877p. 877p. 878inhalation closely match endogenous postprandial insulin concentrations in healthy subjects. Intrapatient variability in the pharmacodynamics and pharmacokinetic properties of ITI is low and similar to (or less than) subcutaneous insulin injection.

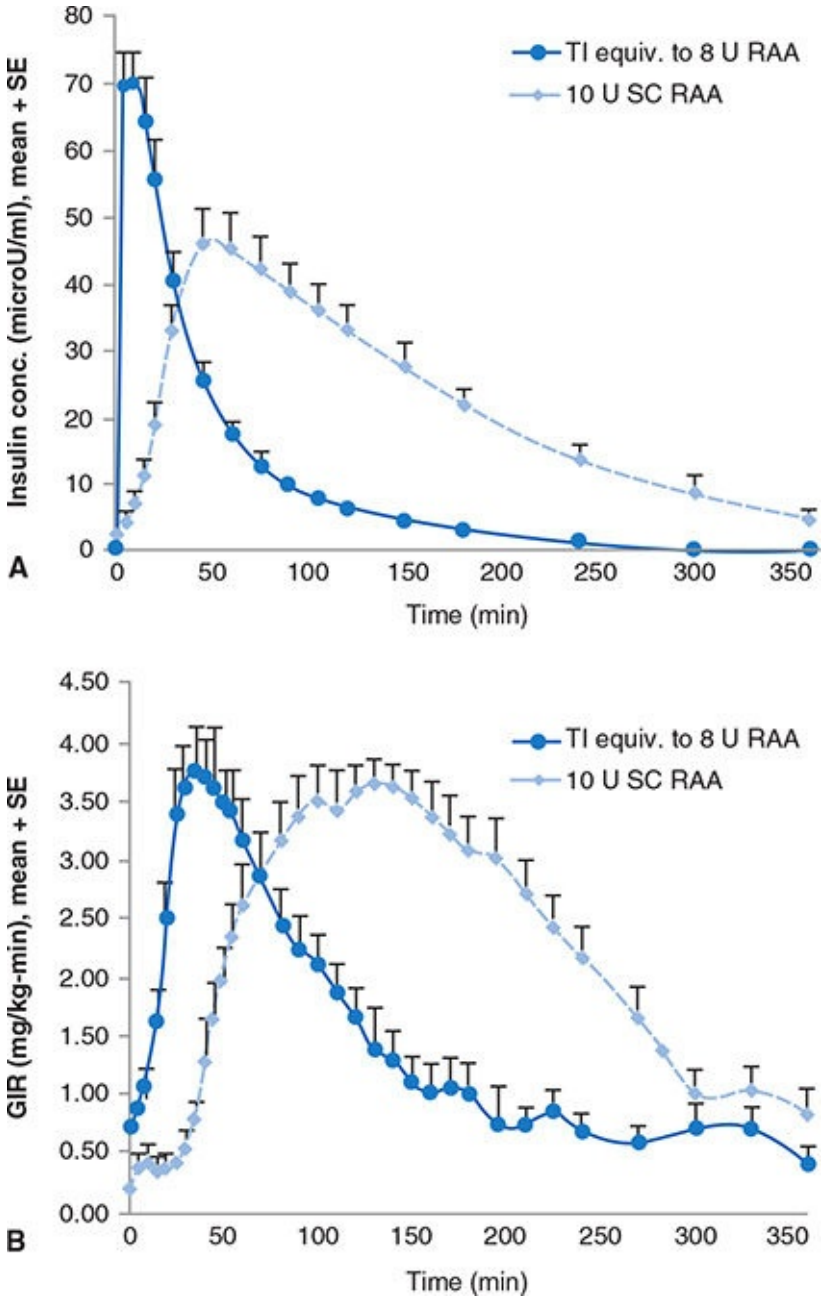

Figure 68-1. The pharmacokinetic and pharmacodynamics profile of ITI versus an RAA. **(A)** Insulin concentration (microU/mL), mean + SE. **(B)** Glucose infusion rate (mg/kg-min), mean + SE. ITI, inhaled Technosphere insulin; SC RAA, subcutaneous rapid-acting insulin analog. (From Boss AH, Petrucci R, Lorber D. Coverage of prandial insulin requirements by means of an ultra-rapid-acting inhaled insulin. *J Diabetes Sci Technol* 2012;6:773–779.)

TABLE 68-1 **Summary for Important Pharmacodynamics and Pharmacokinetics Parameters for the Inhaled and Subcutaneous (SC) Rapid and Regular Insulins**

Insulin product	Time of administration in relation to meal	Onset time	T_{max} (min)	Peak effect (min)	Duration of action (min)	Bioavailability	Elimination half-life (min)
Afrezza	At or immediately after a meal	Shorter than insulin lispro	12–15	About 53	120–180 (Shorter than insulin Lispro)	21%–30% compared with regular SC insulin	28–39 (dose dependent)
Exubera	Within 10 min before a meal	10–20 min	38–78	120	About 360 min	8%–11% compared with regular SC insulin	NA
SC regular insulin	30–60 min before a meal	30 min	48–120	150–300	240–720 (may increase with increasing dose)	55%–77%	90
Insulin lispro	Within 15 min before or immediately after a meal	15–30 min	30–90	30–150	≤300	55%–77%	About 60
Insulin glulisine	Within 15 min before or within 20 min after starting a meal	12–30 min	36–120	96–168	180–240	About 70%	42
Insulin aspart	Within 5–10 min before a meal	12–18 min	40–50	60–180	180–300	Similar to regular insulin	81

From Al-Tabakha MM. Future prospect of insulin inhalation for diabetic patients. The case of Afrezza versus Exubera. *J Control Release* 2015;215:25–38.

TABLE 68-2 Summary of Inhaled Technosphere Insulin Clinical Trials

Trial	Bode/diabetes care/2015		Rosenstock/diabetes care/2015	
Design	T1D/24 wk/open label/noninferiority		T2D/24 wk/double blinded/superiority	
Intervention	Aspart + basal	TIGen2 + basal	OAD + TI	OAD + Pbo
Number of participants	170	174	177	176
Baseline A_{1c}	7.92	7.94	8.25	8.27
Change in A_{1c}	−0.40	−0.21	−0.82	−0.42
Change in FPG	+10.15	−25.27	−11.2	−3.8
Change in weight	−0.39	+0.93	+0.49	−1.13
Hypoglycemic events rate	13.97	9.8	1.16	0.50

FPG, fasting plasma glucose; OAD, oral antidiabetic; Pbo, technosphere placebo; TI, technosphere insulin; T1D, type 1 diabetes; T2D, type 2 diabetes.

B. Clinical trials (Table 68-2). Numerous clinical trials investigated the safety and efficacy of ITI in T1D and T2D patient populations. The formulation of ITI remained the same, but the inhaler was modified after the initial set of studies, so only the most recent Phase 3 clinical trials, which used the marketed inhaler, will be discussed.

1. ITI in T1DM. Patients with inadequately controlled T1DM

participated in a 24-week, open-label, active-controlled study to evaluate the glucose-lowering effect of mealtime ITI used in combination with a basal insulin. After a 4-week basal insulin optimization period, 344 patients were randomized to ITI (n = 174) or insulin aspart (n = 170), each administered before every meal and significant snack. Basal and mealtime insulin doses were titrated to glycemic goals for the first 12 weeks and kept stable for the last 12 weeks of the study.

a. **Effect on HbA_{1c}.** At Week 24, treatment with basal insulin and mealtime ITI provided a mean reduction in HbA_{1c} that met the prespecified noninferiority margin of 0.4%. ITI provided less HbA_{1c} reduction than insulin aspart, and the difference was statistically significant. More subjects in the insulin aspart group achieved the HbA_{1c} target of ≤7%. This observation is most likely due to higher glucose levels in the late postprandial period 2 to 5 hours post inhalation.
b. **Effect on** fasting plasma glucose **(FPG).** There was a significantly greater change from baseline in FPG in the ITI group (−25.3 mg/dL vs. +10.2 mg/dL in the insulin aspart group; p = 0.001). This may have been due to higher doses of basal insulin in the ITI group.
c. **Effect on weight.** ITI patients had a small weight loss (–0.4 kg) compared with a gain (+0.9 kg) for aspart patients (p = 0.0102).
d. **Effect on hypoglycemia.** ITI patients had a **lower hypoglycemia** event rate than patients taking insulin aspart (9.8 vs. 14.0 events/patient-month, $p < 0.0001$). Importantly, the timing of the hypoglycemia events with ITI paralleled the rapid kinetics of the drug. Hypoglycemia event rates within 2 hours post meal were similar between ITI and insulin aspart, but were two to three times higher in the insulin aspart group at 2 to 5 hours after meals (Fig. 68-2).

2. **ITI in T2DM.** Insulin naïve patients with inadequately controlled T2DM on optimal or maximally tolerated doses of metformin only, or two or more oral antidiabetic (OAD) agents participated in a 24-week, placebo-controlled, double-blind study. p. 878p.

879 After a 6-week run-in period, 353 patients were randomized to ITI (n = 177) or an inhaled Technosphere placebo powder without insulin (n = 176). Insulin doses were titrated for the first 12 weeks and kept stable for the last 12 weeks of the study. OAD doses were kept stable.

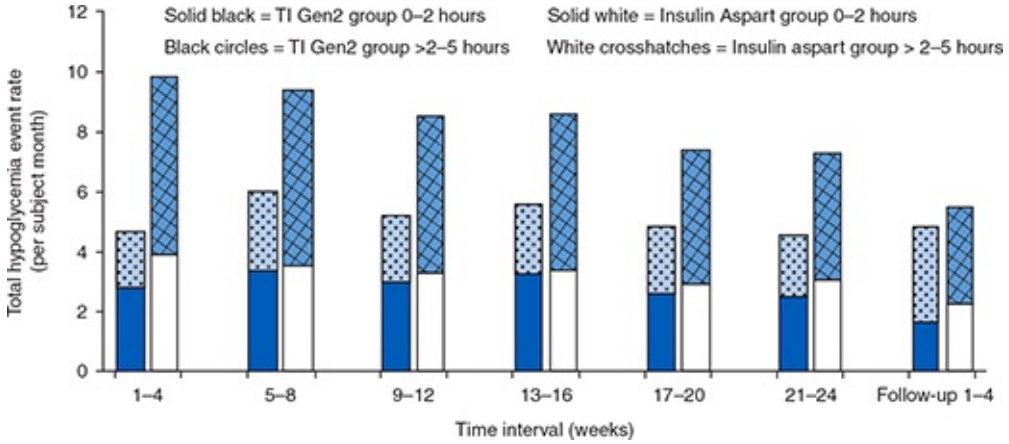

Figure 68-2. Total hypoglycemia event rates 0 to 2 and >2 to 5 hours after a meal throughout the Affinity 1 Study. (From Bode BW, McGill JB, Lorber DL, et al; Affinity 1 Study Group. Inhaled Technosphere insulin compared with injected prandial insulin in type 1 diabetes: a randomized 24-week trial. *Diabetes Care* 2015;38:2266–2273.)

a. Effect on HbA_{1c}. At Week 24, treatment with ITI plus OADs provided a mean reduction in HbA_{1c} that was statistically significantly greater than the HbA_{1c} reduction observed in the placebo group (–0.82% vs. –0.42%; treatment difference –0.40% [95% CI, –0.57 to –0.23]; $p < 0.0001$). A significantly greater proportion of patients treated with ITI achieved A_{1c} ≤7.0% (38% vs. 19%; $p = 0.0005$). A unique feature of this insulin trial was the adoption of a double-blind, placebo-controlled design. Interestingly, subjects in the inhaled placebo group who continued their OADs also showed a meaningful HbA_{1c} reduction during the course of the study. Such a response could be due to the introduction of close monitoring and regular medical supervision during the trial in this insulin naïve population with T2DM who may have had limited glucose monitoring and previous low treatment compliance. Knowledge of their true glycemic status during the study and the perception

of receiving additional inhaled medicine may have prompted some participants to make more effective lifestyle changes including better treatment adherence, improved eating habits, and exercise, a hypothesis supported by the weight loss observed in the TP group.

b. **Effect on FPG.** Mean FPG was similarly reduced in both groups.
c. **Effect on weight.** There was a modest mean weight increase of 0.5 kg in the ITI group versus a mean loss of 1.1 kg in the TP group. Over the 24-week treatment period, mean change from baseline in body weight favored TP (treatment group difference of –1.6 kg, $p < 0.0001$).
d. **Effect on hypoglycemia.** The incidence and event rate of all and severe hypoglycemia were higher in the ITI group than in the TP group. The incidence of all hypoglycemia in the ITI and TP groups was 67.8% versus 30.7%, respectively ($p < 0.0001$), and the incidence of severe hypoglycemia was 5.7% versus 1.7% ($p = 0.0943$).

C. Safety and side effects. The safety profile of ITI was similar to comparators in clinical trials with the exception of pulmonary effect. The most common adverse reactions associated with ITI (2% or greater incidence) are **hypoglycemia, cough, and throat pain or irritation**.

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1. **Hypoglycemia** is the most common adverse reaction associated with all insulin products, including ITI. Patients with T1DM had less hypoglycemia when taking ITI compared with those taking an RAA. However, patients in the T2DM clinical trial had more frequent hypoglycemia, though at low overall rate. Patients should be counseled on hypoglycemia symptoms, risks, complications, and management.
2. **Cough** was reported in more patients taking ITI than RAAs in the T1DM clinical trial, but at similar rates to those taking TP in the T2DM clinical trial. It was usually characterized as mild, transient, and occurring within minutes of administration.
3. **Acute bronchospasm** in patients with chronic lung disease has been observed following ITI dosing in patients with asthma and patients with chronic obstructive pulmonary disease (COPD).

Because of this risk, ITI is **contraindicated in patients with chronic lung disease**.

4. **Decline in pulmonary function** was associated with ITI use. In clinical trials that excluded patients with chronic lung disease and lasting up to 2 years, ITI-treated patients experienced a small (40 mL [95% CI, −80, −1]) but greater forced expiratory volume in one second (FEV_1) decline than comparator-treated patients did. The FEV_1 decline was noted within the first 3 months, and persisted for the entire duration of therapy (up to 2 years of observation). The annual rate of FEV_1 decline did not appear to worsen with increased duration of use, and resolved after treatment discontinuation. The **long-term effect of ITI use for more than 2 years on FEV_1 has not been established**, and there is insufficient data to comment on reversal of the effect on FEV_1 after long-term use and subsequent discontinuation of ITI.
5. **Other potential adverse events are** hypersensitivity reactions, hypokalemia, fluid retention and heart failure with concomitant use of the proliferator–activated receptors (PPAR)-γ agonists, and lung cancer. **Lung cancer** was observed in two participants who were exposed to ITI in clinical trials, whereas no cases were observed in comparators. In both cases, a prior history of heavy tobacco use was identified as a risk factor for lung cancer. Two additional cases of squamous cell lung cancer occurred in nonsmokers exposed to ITI and were reported by investigators after the completion of clinical trials. These data are insufficient to determine whether ITI has an effect on lung or respiratory tract tumors. As with all other medication prescribing, the decision to recommend the use of ITI to an individual patient should be based on risk–benefit estimation.

D. Contraindications. ITI is contraindicated in all patients during episodes of hypoglycemia, and in those patients with chronic **lung disease** such as asthma or COPD because of the risk of bronchospasm. ITI is contraindicated in patients with hypersensitivity to regular human insulin or any of the ITI excipients.

E. Dosing and administration. ITI must be used with long-acting insulin in patients with T1DM. It is not recommended for the treatment of diabetic ketoacidosis or for patients who smoke or who have recently stopped smoking (within the last 6 months). ITI is

administered using a single inhalation cartridge, at the beginning of a meal via oral inhalation. Currently available single-use cartridges contain 4, 8, or 12 U. In patients requiring a higher dose of ITI or whose blood glucose control is not achieved with the maximum ITI dose, a second dose must be considered after the meal, or the use of subcutaneous mealtime insulin must be continued.

F. Monitoring. Prescribing physicians should be aware of the limitations of use and they should perform a detailed medical history, physical examination, and spirometry (FEV_1) in all patients prior to starting ITI. **Pulmonary function testing** (PFT) should be assessed at baseline, after the first 6 months of therapy and annually thereafter, even in the absence of pulmonary symptoms. In the presence of pulmonary symptoms, more frequent monitoring of PFT should be considered. A decline in FEV_1 of 20% or more from baseline should prompt the consideration of discontinuing ITI use. No dose adjustment is necessary for subjects who have a upper respiratory infection and are able to appropriately inhale ITI.

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IV. CONCLUSION

Inhaled insulin has been tested and approved for use as preprandial insulin in patients with T1DM and T2DM. Patients with T1DM will need to use basal insulin in addition to ITI. Patients with T2DM can use ITI with other oral medications or with basal insulin as needed. ITI has been shown to have a more rapid onset of action and shorter duration of action than the currently available RAAs, and thus patients may have less postprandial hypoglycemia. The testing of pulmonary function before and at intervals during therapy with ITI is required. ITI should not be used in patients who are current smokers, and who have asthma or COPD or lung cancer. ITI has not been approved for use in children or in women who are pregnant. As with any new or different pharmaceutical, patients should be carefully selected and counseled about the appropriate use and safety concerns of ITI.

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69

The Application of Stem Cells in Diabetes Mellitus

Arye Lavin

I. INTRODUCTION

A. Diabetes

Diabetes mellitus type 1 is characterized by an insulin deficiency caused by an autoimmune attack of the insulin-producing β cells mediated by T-cells in the pancreas. Diabetes is a very serious disease affecting a widespread, numerous, and diverse group of people. In the United states alone, there are 29.1 million cases of diabetes (1.29 million of that being type 1), making up a significant 9.3% of the population. The absence of insulin yields unregulated blood sugar levels, and if left untreated, can result in many serious complications such as ketoacidosis, nonketotic hyperosmolar comas, chronic kidney failure, cardiovascular disease, eye damage, foot ulcers, and stroke. Diabetes is a chronic condition with no current known cures. Tedious injections of insulin and scrutinizing the management of diet and exercise are the only ways to treat and live with this disease. Clearly, research into better treatments and developing a cure is of major interest to the scientific and diabetic community. With the recent advancements in stem cell biology and regenerative medicine, a major push to use these newfound techniques to develop cures is underway.

B. Stem cell research background

Stem cell research has been accelerating at an exciting pace. Its aim, to develop new cell therapies, has created a push to make novel discoveries as well as to evolve and adapt existing techniques. It can be safely said that stem cell research holds huge promise in matters of identifying drug targets, testing potential therapeutics, testing toxicity, understanding the prevention and treatment of birth defects, and studying cell differentiation, tissue, and cell transplantation. There is also the overwhelming potential for the use of stem cells in regenerative medicine. This potential is of extreme interest to those seeking a cure for diabetes because with the regeneration of the

damaged cells of the pancreas, the β cells would be able to produce insulin and therefore properly regulate the level of blood sugar.

II. STEM CELLS

A. Definition

Stem cells are distinguished from other cell types of the body by two important characteristics:

1. the ability to self-renew or divide many times to produce more stem cells and
2. the ability to undergo differentiation or specialization to give rise to other types of tissues or organ specific cells with special function.

Assuming these two characteristics, cells deemed stem cells can then be classified into three broad categories on the basis of their developmental/differentiation capacity:

a. A **totipotent** stem cell can give rise to all the cells that can potentially develop into a new "individual" on its own.
b. A **pluripotent** stem cell can give rise to all types of cells from all three germ layers of the body (ectoderm, mesoderm, and endoderm).
c. A **multipotent** stem cell can give rise to only some of the cell types of the body, and some, not all, of the three germ layers.

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The term "stemness" has been coined to define an essential characteristic of a stem cell that distinguishes it from differentiated cells. All of these three types of stem cells have a degree of stemness, but only pluripotent stem cells contain the ability to differentiate into any type of cell in the body.

Pluripotent stem cells come in several different forms and therefore have multiple origins. The most common are (1) **Embryonic Stem Cells (ES cells)** come from the embryo, specifically the inner cell mass of the blastocyst stage. (2) **Induced pluripotent Stem Cells (iPS cells)** are a very exciting innovation in the stem cell world, as their origins are adult somatic cells, so an embryo is not even needed. iPS cells are simply adult somatic cells that have been reprogrammed or "induced" to enter an ES cell–like state. This occurs through an introduction of certain factors (proteins, transcription factors, etc.)

that maintain the "stemness" of the ES cells. Some examples include *Oct4*, *Sox2*, *Klf4*, and *c-Myc*. Because of this relationship, iPS cells and ES cells are almost identical. (3) **Epiblast-derived Stem Cells (EpiSCs)** are, as the name implies, derived from the isolation and cultivation of the epiblast (one of two distinct layers arising from the inner cell mass that will eventually give rise to the germ layers). **Embryonic Germ cells (EG cells)** are derived from the primordial germ cells found in the gonadal ridge (gives rise to the testis or ovaries) of the late embryo.

Adult Stem Cells, also known as tissue specific stem cells, are multipotent. They are a rare minority found in most tissues as they comprise less than 1 in 10 000 of all cells. Their multipotency comes from their limited ability to give rise to only a few types of differentiated cells, and usually in a tissue-specific manner. The problem with these types of cells in the advancement of research is that they are very difficult to propagate and expand in substantial numbers outside of the body; therefore, their therapeutic potential is currently curtailed.

B. Characterization and biochemistry

Stem cells are characterized in four ways:

1. Morphology
2. Expression of stem cell markers
3. In vitro self-renewal assay
4. In vivo differentiation assay.

Essentially, if a cell looks like a stem cell, contains the correct biochemical markers, and can be shown to properly self-renew as well as differentiate, then it is a stem cell. The morphology of stem cells is different for different species. For example, mouse ES and iPS cells form dome-shaped, refractile colonies, whereas human ES cells, iPS cells, and EpiSCs form a flat colony morphology. The key determining feature of a stem cell is the expression of its stem cell markers. Different types of stem cells possess different markers, but the majority will include some combination of the following:

Alkaline phosphatase (AP), SSEA-1, Oct4, Nanog, Sox2, Rex1, Klf2, and Klf4

These markers either help maintain the self-renewal of stem cells or, when prompted, help initiate the differentiation process to whatever target in the body is needed. As an example, SOX2 is a

transcription factor found throughout many pathways in the body, but it plays an integral part in stem cell self-renewal.

Finally, the formation of teratomas and chimeras in vitro or in an animal model will prove a cell's characterization as a stem cell. Teratomas contain all three germ layers and can be formed by injecting ES cells into a variety of locations in the body. The formation of these teratomas, followed by a histologic analysis, will allow for a confirmation of the cell's differentiation potential and therefore the pluripotency of that starting cell. Chimera formation is used in a similar manner. A chimera is a single organism composed of cells from different zygotes. A common way to produce them is by the combination of ES cells and a diploid embryo. Because gene targeting can occur with stem cells, this allows for the two types of cells to come together and form a functioning organism. The ability to form chimeras has essentially become the golden standard for determining the pluripotency of stem cells.

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C. Pancreatic stem cells

1. Pancreas cell types

Most of the pancreas consists of the exocrine pancreas that is involved in digestion and various forms of secretion. This is composed of pancreatic acinar cells as well as duct cells. The endocrine pancreas is involved in hormone release that regulates the glucose levels in the blood stream. This part of the pancreas comprises four major cell types that are organized into compact islets, so that they can secrete hormones into the blood stream. These cells are α, β, δ, and PP cells. α and β cells produce insulin and glucagon, respectively, and they regulate blood glucose levels. δ and PP cells (pancreatic polypeptide–producing cells) produce somatostatin and pancreatic polypeptide which modulate the secretory properties of the α and β cells. β cells form a strong majority of the islet cell population as they account for 60% to 70%. At high blood glucose levels, insulin is released by β cells to cause cells to take in glucose from the blood. At low blood glucose levels, glucagon is released by α cells to cause the liver to release glucose into the blood. Both pathways achieve normal blood glucose levels.

2. Stem cell development, types, and functions

The development of the pancreas and its cell types occurs early in the developing embryo (within the first 7 weeks). Starting from ES cells, several markers and molecules initiate the differentiation at each of the steps in the following pathway:

ES cells → Mesendoderm → Endoderm → Anterior Definitive Endoderm (ADE) → For/midgut → Pancreas → endocrine cells → α, β, δ, or PP cells.

The molecules activin/nodal, Wnt, FGF, RA, hedgehog, and Notch are all hugely involved in this process.

Looking specifically at β cells, the generation of β cells can also be completed in two other ways. The first is from the differentiation of acinar tissue cells that come from the exocrine part of the pancreas. So, this method would involve taking the cells from the part of the pathway that distinguishes the exocrine from the endocrine. This can be done by the transduction of three master regulatory transcription factors into the acinar tissue cells. These factors are *Pdx1, neurogenin 3 (Ngn3),* and *Mafa*. The other method is via the transdifferentiation of β cells from α cells. This can be done simply through the overexpression of one transcription factor, *Pax4*. To summarize, there appears to be four ways to produce β cells (Fig. 69-1):

a. Replication of preexisting β cells
b. Differentiation of stem cells and their progenitors (starting with ES cells and moving down the pathway)
c. Differentiation of stem cells/progenitors from the acinar tissue and other parts of the exocrine system
d. α cell transdifferentiation to β cells.

III. CURRENT/FUTURE STEM CELL APPLICATION IN DIABETES

Currently, it is possible to supply insulin-producing cells via pancreas transplants to patients with diabetes. However, the source for these cells is cadaver donors, and the number of these donors is extremely inadequate compared with the number of people afflicted with diabetes. Herein lies the reason for a new source of β cells and insulin-producing cells to be found if a viable cure or treatment is able to be reached. The previously mentioned methods to create β cells are all currently being researched with much success when figuring out how to include these cells into the damaged pancreas. Specifically, there has been a demonstrated generation

of functional human pancreatic β cells in vitro. By introducing certain soluble inductive signals including small molecules and proteins, researchers have been able to start with human ES cells or iPS cells and induce β cells to form, ones that are capable of insulin release. Transplantation of these stem cell β cells into diabetic mice yielded treated mice with normal fasting blood glucose levels.

Another method of achieving this result is the transplantation of an ES cell–based device into a diabetic patient. The first clinical trial of this started in 2014, so the success rate is yet to be determined, but the promise is there. *Encaptra* is a drug delivery p. 884p. 885system that consists of ES cells like pancreatic progenitor cells. The device contains a semi-permeable cell containment barrier that allows insulin, amylin, glucagon, and other pancreatic outputs to be released. This method uses the concept of **β-cell encapsulation**.

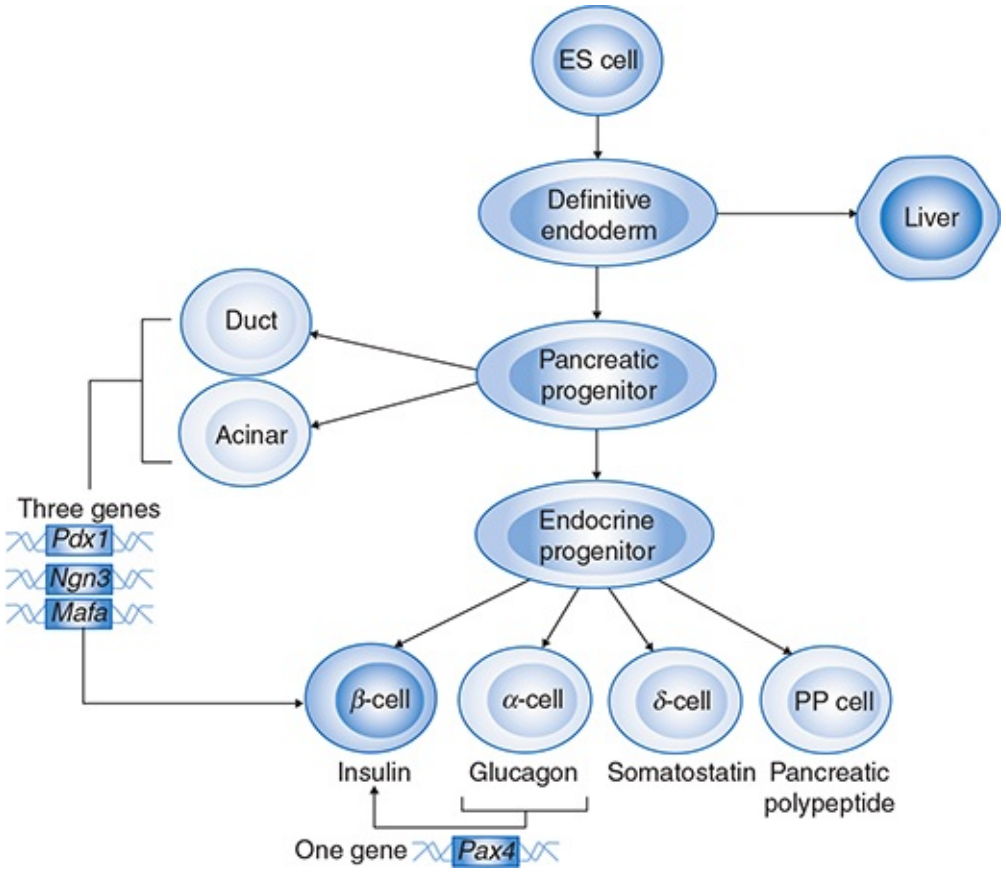

Figure 69-1. Differentiation of embryonic stem cells. (From Vetere, Amerdeo. Burns, Sean M. Wagner, Bridget K. Targeting the pancreatic β cell to treat diabetes. *Nat Rev Drug Discov*

2014;13:278–289.)

Researchers have also shown an ability to generate functional insulin-producing tissue from adult human liver cells. By using pancreatic and duodenal homeobox genes as well as other soluble factors, they were able to induce a comprehensive developmental shift of adult human liver cells into functional insulin-producing cells. Essentially, this method induces a pluripotent stem cell to form from the adult liver cell and then to finally develop into the necessary β cells. When transplanted under the renal capsule of diabetic, immunodeficient mice, these cells produced insulin which corrected hyperglycemia for prolonged periods of time.

IV. CONCLUSION

The future of stem cells in the treatment of diabetes is very promising. By either creating the ability to have the patient be able to regenerate functioning β cells and be able to self-sustain the regeneration of these cells or utilizing stem cell techniques to tissue-engineer a new functioning pancreas, the future of stem cell research will inevitably make diabetes a disease of the past.

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SECTION 10

Sex Hormone Treatments

70

The Care of Gender-nonconforming and Transgender Youth

Johanna Olson-Kennedy

I. GENERAL CONSIDERATIONS

Transgender individuals are those who experience a difference between their internal gender identity and their assigned sex at birth. Many transgender people experience *gender dysphoria*, the persistent physical, emotional, and/or psychological distress about this incongruence. The last decade has seen an exceptional number of children and youth presenting with gender dysphoria at gender-specific clinics and centers around the United States, Canada, and Europe. In addition to the scarcity of training in the care of children and youth with gender dysphoria in formal educational settings, there is also a paucity of research in this area of medicine. The existing dearth of scientific research contributes to a lack of consensus about the approach to the care of children and adolescents with gender dysphoria among medical and mental health professionals. Although this research and informational gap is being addressed across disciplines, access to timely and appropriate care remains the biggest obstacle facing transgender youth and their families.

Gender Dysphoria is described in the Diagnostic and Statistical Manual of Mental Disorders, version 5 (DSM-5), and replaces the previous clinical entity, “Gender Identity Disorder.” In the past, gender

incongruence has been assigned psychopathologic clinical diagnostic codes. Gender nonconformity and transgender identity should not be considered or categorized as psychopathologic, but the distress that results from the incongruence may often lead to functional problems that might benefit from the attention of a multidisciplinary team of professionals in collaboration with the youth and their parents or caregivers.

For prepubertal children who are gender-nonconforming or transgender, medical intervention is neither necessary nor appropriate. For these children, parents, guardians, family members, and professionals should focus on creating a safe, nurturing, and healthy environment. This may include supporting a "social transition" in which a child changes their gender expression, and presents themselves to the world around them in a manner that is more consistent with their asserted gender of identity. Social transition might include different clothing, hairstyle, pronouns, or name. Social transition has become more common, and recent evidence indicates that the mental health of transgender children socially transitioned and supported in their asserted gender is equivalent to that of the general childhood population. Social transition for children

p. 887p. 888can be logistically complicated and is best facilitated by a support team that includes the family, medical providers, mental health therapists, and possibly lawyers. Mental health therapists can play a significant role in the education of parents and other family members about transgender and gender-nonconforming (TGNC) children, and their need for support and love.

A. Creating a safe office environment

Creating a culturally competent and sensitive space for **TGNC** children and youth is critical to providing appropriate care. Medical professionals should be aware that the language of gender is dynamic, particularly among TGNC children and youth, and best approached by asking each individual how he or she identifies himself or herself before assuming a gender identity, pronoun, or name. It is not unusual for TGNC adolescents and young adults to identify simply as "boy/man" or "girl/woman." Additionally, there are many TGNC youth who identify as **"nonbinary,"** outside of the traditional paradigm of the two gender model, who may have completely different terminology to describe their gender.

TGNC children and adolescents should be asked about the name and pronouns that are most accurate, and those should be used at their

office visits. Inquiring about each young person's identity, name, and pronoun preference can help engender trust between provider and patient.

B. Prevalence

There are no census data describing the numbers of TGNC children and adolescents in the United States, but recent estimates of adult transgender experience indicate a prevalence rate of 0.6%. Because obtaining prevalence information is difficult, a two-step process that includes assigned sex at birth, with a follow-up question about gender identity is recommended.

C. Medical intervention

Many transgender individuals pursue a phenotypic gender transition utilizing hormones and/or surgery to more closely align their bodies with their gender. The approach to care for transgender youth is dependent on the age and sexual development of youth at presentation, the presence of a social support system, medical condition, and the individual desires of the youth. Primary modalities for medical intervention among youth include the suppression of the hypothalamic–pituitary–gonadal (HPG) axis in order to halt the endogenous puberty process, and/or the use of cross-sex hormones to induce female or male secondary sex characteristics that more closely match one's gender identity.

1. Puberty suppression

The onset of endogenous puberty for many gender-nonconforming youth can be extremely difficult. Gender dysphoria commonly emerges for the first time during the onset of puberty in response to the development of permanent and undesired secondary sex characteristics. Although this is the likely cause of the distress, gender dysphoria may present in other ways, including declining academic and social functioning, behavioral problems, impulse control problems, drug use, social isolation, and disordered eating. Clinicians should note that the symptoms of gender dysphoria often closely resemble those of depression, anxiety, and other mood disorders.

Temporarily suspending endogenous puberty in TGNC adolescents utilizing gonadotropin-releasing hormone agonists (GnRHas) was introduced by the Gender Identity Clinic in Amsterdam. Suppressing or delaying endogenous puberty in TGNC youth provides an opportunity to bypass the development

of secondary sexual characteristics and to potentially avoid the need for future surgeries. Suppression of puberty also allows an opportunity to explore gender without having to experience the anxiety of an impending undesired developmental process. An additional advantage of puberty blockers is to give parents and families an increased opportunity to integrate what might be a relatively recent disclosure and develop skills to support their child's authentic self.

The most effective mechanism to suspend sexual development is to temporarily suppress the HPG axis with **GnRH agonists** (triptorelin, histrelin, goserelin, and leuprolide). GnRH agonists were developed decades ago for the treatment of p. 888p. 889precocious puberty, endometriosis, prostate cancer, and other medical conditions managed by deactivating the HPG axis. Three to four weeks following the administration of GnRH agonists, the gonads stop producing sex hormones and the patients are returned to a prepubertal physiologic state. Regression of secondary sexual characteristics may occur if medication administration occurs in early pubertal development. Puberty suppression with GnRH agonists is considered a reversible intervention. Children administered GnRHas for precocious puberty suppression resume endogenous puberty within 6 to 12 months of discontinuing GnRHas. Little is known about the growth trajectory of TGNC youth undergoing puberty suppression, but studies are currently being undertaken to understand this element of GnRH analog use in this population. Using GnRH agonists for prolonged periods of time results in the accrual of bone mineral density continuing at, or returning to, a prepubertal rate during the duration of medication administration. Data from the Netherlands indicate that in the first cohort of youth treated with puberty blockers, bone mineral density stayed about the same over the first 2 years of treatment, and increased appropriately when cross-sex hormones were added to the regimen. Long-term impact of GnRH analogs on bone density is unknown, although studies are currently being undertaken to better understand this aspect of care as well.

2. **Timing of puberty suppression**

The Endocrine Society's Clinical Practice Guideline: "Endocrine Treatment of Transsexual Persons," published in 2009 recommends initiating puberty suppression at the earliest stages of puberty, Tanner 2 or 3, regardless of chronologic age. There is a role for using GnRH agonists in youth who are in the later stages of pubertal development, either for induction of amenorrhea or to halt ongoing development of undesired secondary sex characteristics. The World Professional Association of Transgender Health Standards of Care version 7 also recommends suppression of puberty in its earliest stages for gender dysphoric youth. Mental health professionals or medical providers experienced in the care of TGNC youth can make a diagnosis of gender dysphoria and assess the utility of GnRH agonists in clinical settings.

3. Dosing/types of GnRH agonists

The most commonly used GnRH agonists in the United States are leuprolide and histrelin. Leuprolide comes in the form of an injectable GnRH agonist, and ranges from daily subcutaneous dosing to every 4-month dosing. Additionally, leuprolide is available as a subcutaneous implant. Histrelin is administered via a small implantable rod that is inserted into the inside of the upper arm positioned between the triceps and the biceps muscle. The histrelin implant adequately suppresses the HPG axis. The implant can be placed easily in an outpatient office or surgical suite, and does not require sedation. The implant is effective for over a year, and can be removed and replaced again when necessary in the same visit.

4. Impact of blocking puberty

There are limited data published outlining the impact of GnRH agonist use in gender-nonconforming youth. Early results from the Netherlands describing a cohort of 70 gender dysphoric youth undergoing puberty suppression showed a decrease in overall psychological functioning, improvement in behavioral and emotional problems, as well as a decrease in depressive symptoms.

Early data examining the effect of GnRH agonist use in youth with gender dysphoria on executive function demonstrated no differences between treated and control groups. Ongoing studies are being undertaken to more completely understand the impact of GnRH agonists on bone health and cognitive and psychosocial development.

D. Follow-up and monitoring of youth on GnRH agonists

The Endocrine Society Clinical Guidelines recommend continuing youth with gender dysphoria on GnRH agonists with the addition of cross-sex hormones when appropriate. Although the guidelines make a broad recommendation to initiate cross-sex hormones at around the age of 16 years, many centers around the United States initiate hormone administration in patients younger than age 16. Although p. 889p. 890there is a **lack of consensus regarding an "ideal" age to start hormones**, the developmental trajectory for each youth is different, requiring that multiple factors beyond chronologic age be considered in the decision-making process. The Endocrine Society Clinical Guidelines outline recommendations for monitoring of laboratory values, anthropometric measures, and bone density while youth are undergoing pubertal suppression.

1. **Cross-sex/gender-affirming hormone therapy**

   Adolescents and young adults can be prescribed cross-sex hormones to induce secondary sexual characteristics that more closely match their internal gender identity. Those youth who are ready to initiate their phenotypic gender transition with masculinizing or feminizing hormones already receiving GnRH agonists for puberty suppression have more opportunity to experience puberty with exogenous hormones that more closely approximate those of their cisgender (nontransgender) peers. Because there is no need to use exogenous sex hormones to suppress endogenous secretion of sex hormones, an escalating dose of either testosterone (for transgender males) or estradiol (for transgender females) is effective at inducing secondary sex characteristics.

2. **Transgender males**

   Induction of masculine features in transgender males is most commonly achieved with the testosterone esthers (cypionate or enanthate). Testosterone can be administered as an injection or topically via gel, compounded cream, or patch. The injectable testosterone esthers are suspended in oil, and can be injected either subcutaneously or intramuscularly. Subcutaneous dosing is done weekly in order to keep levels more sustained. Intramuscular

injections can be done every other week or weekly to avoid feelings of lethargy and irritability that are common on day 11 to 13 of a 2-week cycle. Optimal dosing escalation schedules are not currently available and likely vary depending on the chronologic age of the youth seeking care, as well as developmental stage and height.

One example of such a schedule in a younger adolescent might be starting with 10 mg SC weekly for 8 weeks, increasing to 20 mg SC weekly. Testosterone levels should be assessed after 3 months and dosing adjusted in 10 mg intervals accordingly. Providers may decide to escalate dosing in a manner that corresponds to Tanner stages by checking total testosterone levels and adjusting dosing accordingly. Other providers use a more standardized approach. Most patients achieve a normal male range of total testosterone and good clinical results at 50 mg of testosterone delivered subcutaneously each week, although higher doses are often needed in patients with higher body mass indices.

For those youth who are not on concurrent GnRH agonists, dosing can start at 25 mg SC each week increasing to 50 mg a week after 8 weeks if tolerated. Youth can learn to self-inject into the subcutaneous space in the flank or thigh, switching sides each week. Not uncommonly, induration in the area of injection occurs, which can be minimized if the area is massaged substantially after injection.

Intramuscular dosing of testosterone weekly or biweekly with an escalating schedule is similar; 25 mg IM each week for 4 to 8 weeks and then increasing to 50 mg IM each week is one example of a titrating regimen for those on concurrent GnRH agonists. Dosing can be adjusted in 20 mg increments as guided by total testosterone levels and clinical response. Most patients do well on 50 to 100 mg IM each week or between 100 and 200 mg every 2 weeks.

For those youth who are not being administered simultaneous GnRH agonists, intramuscular dosing can start at 50 to 100 mg IM every 14 days, and titrate to a likely final dose of 200 mg IM every other week.

a. Monitoring and effects of testosterone use

Monitoring for safety of testosterone is described in the Endocrine Society guidelines.

Physiologic changes that are expected to occur from testosterone administration are an increase in hemoglobin, blood pressure, total and low-density lipoprotein cholesterol, and weight. Other side effects of testosterone include acne, thinning of the hair, coarsening of the skin, and prominence of veins. p. 890p. 891Desirable effects of testosterone are increased libido, deepening of the voice, development of male pattern body and facial hair, clitoral growth, and increased muscle mass. Of these, deepening of the voice, clitoral growth, and development of male pattern facial and body hair are permanent, and would continue even if testosterone were discontinued. Although there are transgender men who have discontinued testosterone use, resumed ovulation, and carried and birthed their own children, it is unclear when in the course of testosterone treatment fertility is no longer an option. Harvesting eggs is expensive and difficult, and is not commonly done, but should be discussed with patients interested in preserving reproductive tissue for future use. In youth who begin treatment in Tanner stage 2 or 3, viable reproductive tissue will not have developed, and will likely not be suitable for harvesting. It is unknown if patients who have their endogenous puberty suppressed before maturation of follicles occur and who go on to testosterone would be able to develop mature eggs suitable for harvesting if they discontinued testosterone use at a later point in life.

3. Transgender females

In order to induce feminizing features in transgender females, 17-β estradiol is used. Estradiol also helps suppress the production of testosterone. Youth on simultaneous GnRH agonists have their endogenous testosterone secretion suppressed, so would not need adjunctive antiandrogen therapy. Estrogen is not adequate to fully suppress testosterone production without the concurrent use of either a GnRH agonist or an antiandrogen such as aldactone. Aldactone was originally developed as an antihypertensive diuretic, but was found to have antiandrogenic properties. It blocks the testosterone receptors at terminal sites, slowing down male pattern body hair growth, reducing spontaneous erections, and mildly decreasing circulating testosterone. A potential estrogen

titration cycle might be:

a. **Transdermal:** twice weekly patches (6.25 μg [achieved by cutting a 25-μg patch]) with gradual increase to the recommended adult dose of 100 or 200 μg twice weekly patches
b. **Oral/sublingual:** daily (0.25 mg with gradual increase to a full adult dose of 6 to 8 mg/day)
c. **Parenteral IM (synthetic esters of 17β-estradiol):** estradiol valerate (5 to 20 mg up to 30 to 40 mg/2 week) or estradiol cypionate (2 to 10 mg/week).

If aldactone is being used for peripheral testosterone blockade, it should be started at 50 to 100 mg/day and increased to 200 mg/day as tolerated. Aldactone can cause hypotension, hyperkalemia, and dizziness. Care should be taken (slower escalation or lower dosing) in very thin patients or those with baseline hypotension.

The use of progesterone to facilitate feminizing features is controversial; clinical experience has shown that bioidentical micronized progesterone is better tolerated than the synthetic progestagens. Dosing of micronized progesterone should be 100 to 200 mg daily; added onto the hormone regimen after 6 months of estradiol.

In those youth being treated simultaneously with GnRH agonists, feminization usually occurs adequately with smaller doses than for those using an antiandrogen in the regimen. Monitoring for safety of estradiol is outlined in the Endocrine Society guidelines. Dosing adjustments should be made according to clinical response, laboratory values (suppression of endogenous testosterone levels), and safety.

Very little information documenting the medical side effects of cross-sex hormone use in transgender adolescents is available. Physiologic changes that can occur with the use of estradiol are an elevation in the transaminases, blood pressure, weight, and prolactin. Desirable side effects of feminizing hormones are breast development, softening of the skin, fat distribution in the hip and chest area, and softening of the facial features. Of these changes, breast development is the only known permanent change. Rare side effects may include venous thromboembolic events, liver damage, prolactinoma, p.

891p. 892and gallstones. All youth should be counseled about the likely loss of fertility, and if male pubertal development has progressed to the later Tanner stages, sperm banking should be discussed as an option for those interested in future biologic offspring.

II. CONCLUSION

Transgender youth and young adults should be treated with the same dignity and respect as any other youth or young adult. The use of accurate names and pronouns, as well as the use of specific names for body parts that feel most comfortable, should be solicited and subsequently honored. Medical and mental health professionals should model nonjudgmental and compassionate communication with youth in front of parents, caregivers, and other family members. The needs of youth with gender dysphoria should be taken seriously, as the sequelae of untreated gender dysphoria can be life-threatening. Because there is such a strong correlation between parental support and well-being of transgender youth, parents and caregivers who are struggling to understand and accept their transgender children should be referred to local support groups, family gender conferences, and appropriate literature.

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Hormone Therapy in Transgender Adults

Steven C. Myers and Joshua D. Safer

I. INTRODUCTION

Transgender individuals have gender identities that differ from the sex designated at birth based on external genitalia. Studies estimate that 0.3% to 0.5% of adults or 900 000 individuals are transgender in the United States. Transgender individuals have limited access to healthcare because of both a lack of adequate insurance and a lack of knowledgeable providers. To begin to educate providers, both the World Professional Association for Transgender Health (WPATH) and the Endocrine Society created transgender care guidelines for broad use by physicians in multiple specialties.

II. EVIDENCE THAT GENDER IDENTITY IS NOT REVERSIBLE

Although modest, research supports the hypothesis that gender identity is biologically rooted. Some specific evidence for gender identity being fixed includes the literature regarding 46 XY children with congenital anomalies who were raised as girls. Historically, the medical establishment considered gender identity to be malleable and with change easily exerted by outside forces. The logic followed that for babies born with certain congenital anomalies, the most straightforward surgery should be chosen independent of chromosome status because gender identity could be influenced to match the assigned gender.

However, careful analysis of actual outcomes of these individuals (who would be predicted to have gender identities matching chromosomes most of the time) revealed otherwise. One study of genetically male children with cloacal exstrophy, in which 14 children were assigned female at birth, found all 8 of the children who were aware of their XY chromosome pattern identified as male. This included four children who reported male gender identity even prior to learning about their chromosomal status. Additionally, two children assigned as male continued to identify as male. In a larger study of 46-XY children with

penile agenesis, cloacal exstrophy, and penile ablation, where 72 children were assigned female at birth, investigators found 15 children identified as male and 10 of the children who continued to identify as female reported significant gender dysphoria. In this study, all of the children assigned male at birth continued to identify as male, except one male child who reported gender dysphoria. These studies give us the unique perspective of individuals whose gender was determined for them, in opposition of their biology. Despite the fact that these individuals were raised and socialized as female, a significant portion identify as male. The data suggest that gender identity cannot be manipulated externally but rather is a durable biologic entity.

Additional evidence for the biologic nature of gender identity comes from studies of the brains of transgender individuals that suggest a physical manifestation of gender identity. A post-mortem study of six transgender women (male-to-female, monitoring for transgender women [MTF]) found that the size of the bed nucleus of the stria terminalis (BST) in the hypothalamus was within the female range. Examination of an MTF individual who did not undergo hormonal treatment also showed BST staining within the female range, and examination of one transgender man (female-to-male, monitoring for transgender men [FTM]) revealed a BST within the male range. These differences in BST staining were independent of sexual orientation and sex hormone treatment.

MRI studies of living patients have also found anatomical differences that are associated with gender identity. One study found transwomen who had not begun hormone therapy (HT) had a significantly larger, more “feminized” volume of regional p. 893p. 894gray matter in the right putamen. Another study of transmen who had also not begun HT found evidence of subcortical gray matter “masculinization” in the right putamen. In a similar study of transwomen who had not yet begun HT, subjects were found to have thicker cortices in a number of regions across the lateral and medial cortical surfaces than their age-matched control males.

Diffuse tensor imaging studies showed that hormonally untreated transwomen exhibited white matter microstructure intermediate between males and females, and untreated transmen exhibited white matter microstructure more similar to males than females. A PET study

examining anterior hypothalamus activation while subjects smelled the progesterone derivative 4,16-androstadiene-3-one found similar activation in female controls and transwomen who had not begun HT. 4,16-Androstadiene-3-one has been reported to activate the hypothalamic networks in a sexually dimorphic manner.

Although these studies are small and there has not been a sexually dimorphic function attributed to these areas of the brain in humans, the studies are consistent with an organic nature to gender identity. Although research to support the organic nature of gender identity is modest, there is no convincing literature that demonstrates an ability to externally change a person's gender identity. Attempts to change gender identity rely on pressure to conform to sex norms, which only results in poor psychosocial outcomes.

III. HORMONAL TREATMENT FOR TRANSGENDER INDIVIDUALS

Both the WPATH and Endocrine Society guidelines for the treatment of transgender patients are examples of a move toward more evidence-based treatment guidelines. Both sets of guidelines give the same broad approach to HT for transgender patients: (a) androgens to virilize transgender men and (b) estrogens, in addition to antiandrogens, to reduce testosterone levels to the conventional female range for transgender women. In order to be conservative and avoid harm, most transgender hormone guidelines in the past suggested that transgender individuals undergo a "real-life test" living in the chosen gender prior to HT. Undergoing a "real-life test" was thought to ensure that patients would be prepared for the social transition to the desired gender. Because of the difficulty of living in a chosen gender without matching physical characteristics, the "real-life test" is impractical for many transgender individuals. It is no longer suggested that it be mandatory before the initiation of HT, but rather run in parallel.

Mental health support is key to a good transgender health program. Patients should be screened for confounding psychiatric issues and their psychological ability to undergo HT should be assessed. Although transgender individuals have a high incidence of psychological distress, it is often a result of social stigma and not of gender identity.

The following regimens are distilled from the WPATH and Endocrine Society guidelines, and are meant to be straightforward for most practitioners.

A. Transgender men (female-to-male)

The hormonal treatment for transgender men is very similar to hormone replacement therapy for hypogonadal males in general. In order to achieve maximum virilization, testosterone levels should be increased to be within the normal male physiologic range (300 to 1 000 ng/dL). Patients can anticipate cessation of menses, increased facial/body hair, male-pattern balding, increased acne, increased libido, increased muscle mass, clitoromegaly, and redistribution of fat within the first 3 to 12 months of testosterone therapy. Deepening of the voice may occur in many. The exact effects and time course of testosterone will vary from patient to patient.

When a patient begins hormone treatment, he can be started with half the dose used for a typical 70 kg man and then titrated quickly to achieve male physiologic serum levels (300 to 1 000 ng/dL). Testosterone can be administered orally, transdermally, or parenterally, although no oral products are available in the United States (Table 71-1). Testosterone enanthate or cypionate 50 to 200 mg weekly can be administered intramuscularly (i.m.) or subcutaneously (s.q.). IM testosterone can be administered every 2 weeks, but may result in periodicity in testosterone levels. Transdermal preparations such as testosterone gel (2.5 to 10 g/day) or testosterone patch (2.5 to 7.5 mg/day) will achieve the same virilizing effects as those of intramuscular testosterone (may cause skin irritation), but it may be harder to achieve desired levels with them. Oral testosterone undecanoate (160 to 240 mg/day) and p. 894p. 895testosterone undecanoate i.m. (1 000 mg every 12 weeks) have not been available in the United States.

TABLE 71-1 Monitoring for Transgender Men (FTM) on Hormone Therapy

(1) Monitor for virilizing and adverse effects every 3 mo for the first year and then every 6–12 mo.

(2) Monitor serum testosterone at follow-up visits with a practical target in the male range (300–1 000 ng/dL). Peak levels for patients taking parenteral testosterone can be measured 24–48 hr after injection. Trough levels can be measured immediately before injection.

(3) Monitor hematocrit and lipid profile before starting hormones and at follow-up visits.

(4) Do a bone mineral density (BMD) screening before starting hormones for patients at risk for osteoporosis. Otherwise, screening can start at age 60 or earlier if sex hormone levels

are consistently low.
(5) Screen FTM patients with cervixes or breasts.

Patients taking testosterone should be monitored for both virilizing and adverse effects every 3 months for the first year and then every 6 to 12 months (Table 71-1). At the aforementioned intervals, serum testosterone levels should be monitored until it stabilizes within the male range. Patients taking testosterone enanthate or cypionate IM can have testosterone peak levels measured 24 to 48 hours after injections and occasional trough levels measured immediately prior to injections. Patients taking testosterone transdermally can have levels sampled at any time after 1 week. Androgen-sensitive indices such as hematocrit (or hemoglobin) and lipid profile should also be monitored every 3 months for the first year and then every 6 to 12 months (Table 71-1). Adequate levels of sex hormones are required to maintain bone mass; thus, transgender men may be at risk for osteoporosis, and therefore, bone mineral density (BMD) should be measured before initiating testosterone. Otherwise, BMD screening can be initiated at age 60 or if testosterone levels are consistently low. Transgender men with cervixes or breast tissue should be screened accordingly.

Testosterone therapy should not be initiated in patients who are pregnant, have unstable coronary artery disease, or have untreated polycythemia (hematocrit at or above 55%). Testosterone therapy may unmask polycythemia and hyperlipidemia, which should be treated appropriately. It is unknown if testosterone therapy puts transgender men at an increased risk for uterine or ovarian cancer, so despite the absence of data, a **hysterectomy is often considered** as a preventive measure at some point. **Aromatase inhibitors play no role** for the hormone treatment of either transgender men or transgender women, although some transgender men use them for male-pattern balding just like nontransgender men.

B. Transgender women (male-to-female)

The hormonal treatment for transgender women is only slightly more complicated than the regimen for transgender men. In order to achieve maximum feminization, transgender women with testis **require an antiandrogen in addition to estrogen**. The goal in HT for transgender women is to decrease testosterone to the female range (30 to 100 ng/dL) without supraphysiologic levels of estradiol. Therefore,

estradiol levels for transgender women should be kept less than 200 pg/mL. Although the effects and time course of estrogen and antiandrogen therapy vary, patients can expect decreased facial/body hair, decreased libido, decreased spontaneous erections, decreased skin oiliness, decreased muscle mass, redistribution of fat, and breast development within the first 3 to 12 months. **Breast growth will usually peak after 2 years** of HT.

Incorporating an antiandrogen into the paradigm for transwomen allows for lower doses of estrogen (Table 71-2). **Spironolactone** is the most commonly prescribed and least costly antiandrogen used in the United States. It is an aldosterone receptor antagonist that has been shown to decrease mortality in patients with New York Heart Association Class 3 and greater congestive heart failure. Spironolactone also inhibits the secretion and activity of testosterone (although the mechanism is not known).

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TABLE 71-2 Monitoring for Transgender Women (MTF) on Hormone Therapy

(1) Monitor for feminizing and adverse effects every 3 mo for first year and then every 6–12 mo.
(2) Monitor serum testosterone and estradiol at follow-up visits with a practical target in the female range (testosterone 30–100 ng/dL; E2 < 200 pg/mL).
(3) Monitor prolactin and triglycerides before starting hormones and at follow-up visits.
(4) Monitor potassium levels if the patient is taking spironolactone.
(5) Obtain bone mineral density (BMD) screening before starting hormones for patients at risk for osteoporosis. Otherwise, start screening at age 60 or earlier if sex hormone levels are consistently low.
(6) Screen MTF patients for breast and prostate cancer appropriately.

Spironolactone can be administered in doses of 100 to 200 mg daily; up to 400 mg may be administered if tolerated. Doses can be divided, but patients should be aware that the weak diuretic properties of spironolactone may become more apparent at higher doses, making evening dosing less favored. Cyproterone acetate is often used in Europe, but is not available in the United States. Gonadotropin-releasing hormone (GnRH) agonists (3.75 mg subcutaneously monthly), such as leuprolide, inhibit the production of luteinizing

hormone and follicle-stimulating hormone and therefore testosterone, but are often expensive. Although GnRH agonists have been used to treat children with precocious puberty along with adolescent transgender individuals and appear well tolerated, there are no studies demonstrating safety with very long-term use.

Estrogen can be administered orally, transdermally, or parenterally (Table 71-2). Oral conjugated estrogens 2.5 to 7.5 mg and oral 17-beta estradiol 2 to 6 mg daily are popular because they are easy to use and readily available. Although some metabolites of conjugated estrogens may be missed on serum estradiol tests, the testing is still used as a rudimentary indicator that estradiol levels are below a supraphysiologic range (<200 pg/mL). Ethinyl estradiol has been associated with an increased risk of venous thromboembolism. Estradiol and spironolactone can be started at lower doses (e.g., 1/4 strength) and increased until serum testosterone levels are within the female range (30 to 100 ng/dL). Some propose that the hepatic first-pass for oral estrogen increases thrombosis risk and that a transdermal estradiol patch 0.1 to 0.4 mg twice weekly should be used in transgender women who are at increased risk for thromboembolic disease. Estradiol can be administered parenterally with estradiol valerate or cypionate 5 to 20 mg i.m. every 2 weeks or 2 to 10 mg i.m. every week, but levels are harder to monitor.

Transgender women on HT can be monitored for feminizing and adverse effects every 3 months for the first year and then every 6 to 12 months (Table 71-2). Serum testosterone and estradiol levels should be monitored until they stabilize within the female range (testosterone 30 to 100 ng/dL; estradiol < 200 pg/mL). Spironolactone is a potassium-sparing diuretic and can cause hyperkalemia in rare individuals, so it is vital to **monitor potassium for patients taking spironolactone**. Estrogen-sensitive indices such as prolactin and triglycerides should be monitored. Patients should be warned of the potential for venous thromboembolism and other cardiovascular impairments. Adequate levels of sex hormones are required to maintain bone mass; transgender women at risk for osteoporosis should have BMD measured before initiating HT. Otherwise, BMD screening should be initiated at age 60 or if sex hormone levels are consistently low. Transgender women should be screened for breast and prostate cancer appropriately.

Although it is thought that estrogens may increase the risk of

venous thromboembolic disease, hypertriglyceridemia, cardiovascular disease, hypertension, hyperprolactinemia, and prolactinoma, the degree of risk remains an area for future study.

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C. Children and adolescents

Treatment for transgender children and adolescents involves a puberty-delaying approach using puberty blockers in a fashion similar to the approach to precocious puberty. Studies have found that at least some of the time, younger children who identify as transgender do not become transgender adolescents. Because it is difficult to know if a child's gender identity will persist into adulthood, it is important to limit permanent treatment. In addition, children should not be treated medically until after puberty begins because reactions to early puberty often have diagnostic value. Puberty suppression via GnRH analogs can be started at Tanner stage 2 to 3. As puberty suppression is reversible, this provides time to determine if HT should be initiated. Unlike transgender children, transgender adolescents are likely to have persistent gender identities and become transgender adults. Puberty suppression might not only increase functioning but also reduce emotional and behavioral problems. Permanent surgeries should be deferred until patients are able to consent (e.g., at age 18).

IV. HORMONE TREATMENT SAFETY

Although there may be modest risk associated with HT, evidence has shown HT for transgender adults to be relatively safe and without the risk of adverse effects being significant. This being said, there are still things that should be monitored. Because of the fact that estrogens can be thrombogenic, a possible concern for transgender women is the development of thromboses and related complications. Thus, monitoring and addressing other cardiac risk factors like hypercholesterolemia, hypertension, and tobacco use is advised. In studies monitoring transgender women, data have indicated that the occurrence of venous thromboembolism appears linked with the presence of a hypercoaguable risk factor, including the no longer used, especially thrombogenic, ethinyl estradiol.

Estrogen is considered to increase triglycerides. Prolactin levels are also modestly increased in some women; however, it is not known if estrogen actually increases the risk of prolactinoma. Although there are

case reports of transgender women presenting with meningiomas, benign pituitary tumors, prolactinomas, and the occurrence of female predominant autoimmune conditions such as systemic lupus erythematosus, the data are too limited to draw conclusions.

For transgender men, the most prevalent risk factor is polycythemia; therefore, **monitoring of the hematocrit is mandatory for anyone on androgen therapy**. Studies have found no increase in rates of myocardial infarction, transient ischemic attack, or venous thromboembolism in transgender men when compared with male controls. Although current data on the effects of testosterone on female reproductive tissues are contradictory, the majority of studies suggest no elevated risk for hyperplasia among transgender men. Rather, tissue atrophy has been observed in the epithelium of both the cervix and the endometrium. The same study found maintenance of the corpus luteum in ovaries even after 1 year of HT.

Both transgender men and women have been shown to have an increase in insulin resistance, fasting glucose, and body fat redistribution. Adipocyte-derived hormone levels may play a role in these changes, as transgender women can have decreased leptin, and transgender men may have decreased adiponectin levels, both of which are associated with insulin resistance. Despite concern, data have not shown significant increases of cancer among hormonally treated transgender patients.

V. CONCLUSION

HT is the most effective treatment for transgender patients, and over the last few years, attention to transgender medical care has improved. Proof of its effectiveness and overall improvements is seen in the dramatic rise of transgender patients seeking medical care. Transgender patients are presenting to clinics for HT at younger ages and are less likely to acquire hormones from other sources. To keep up with the increased number of patients seeking treatment, it is vital to mainstream transgender care among medical providers, and data suggest that such change would not be difficult.

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Recently published transgender medical treatment guidelines provide a good foundation for making transgender patient care more generalized and accessible to all healthcare providers. However, a need remains for

more research to better define both benefits and risks of HT for transgender patients.

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72 How to Manage Men with Low Testosterone

Michael S. Irwig

I. GENERAL PRINCIPLES

The management of adult men with low testosterone has become commonplace because of the increased rates of measuring testosterone and the increased prevalence of medical conditions (i.e., obesity and diabetes) associated with lower levels of testosterone. The two major decisions that need to be made are whether the etiology is reversible or irreversible and whether the testosterone levels are unequivocally low versus low-normal or borderline. The diagnosis of low testosterone (also referred to as male hypogonadism) is based upon multiple low serum levels of testosterone in combination with consistent signs and/or symptoms. The diagnosis, however, can often be challenging because there is no clear agreement as to what level of testosterone is considered low, and most of the signs and symptoms are nonspecific.

Presenting complaints of low testosterone can be divided into sexual and nonsexual (Table 72-1). The sexual items are decreased libido, decreased spontaneous/AM erections, and erectile dysfunction. The nonsexual items are decreased energy, decreased muscle mass and strength, decrease in bone density, gynecomastia, hot flashes, feeling moody and headache, and/or visual field defect (if a pituitary tumor is present).

II. ETIOLOGY

Low testosterone in adults can be divided into the two major categories of primary and secondary. Primary relates to conditions that affect the testes themselves, whereas secondary relates to conditions that affect the hypothalamus and/or anterior pituitary gland. The vast majority of men with low testosterone will fall into the secondary category.

A. Primary

1. **Klinefelter syndrome** is the most common genetic cause of low testosterone. It is characterized by an extra X chromosome most

commonly resulting in a chromosomal analysis showing 47 XXY, although mosaicism is also possible. p. 900p. 901Men with Klinefelters often have small firm testes measuring <5 mL, sparse body hair, gynecomastia, and a female fat distribution. The clinical presentation varies widely. Some men with Klinefelters have normal testosterone levels and many go undiagnosed until later in life.

TABLE 72-1 Signs and Symptoms of Low Testosterone

Sexual
- Decreased libido
- Decreased spontaneous/AM erections
- Erectile dysfunction

Nonsexual
- Decreased energy
- Decreased muscle mass and strength
- Decrease in bone density
- Gynecomastia
- Hot flashes
- Depressed mood/depression

Headache and/or visual field defect (if pituitary tumor).

2. **HIV/AIDS** is often associated with low testosterone levels.
3. **Chemotherapy and/or radiation** for treatment of malignancy may result in damage to the germinal epithelium and to Leydig cells that produce testosterone.
4. **Postsurgical hypogonadism** follows surgical removal of the testes for treatment of testicular cancers that are often bilateral.
5. **Testicular torsion** is an uncommon urologic emergency in which damage occurs secondary to a disruption in the blood supply.
6. **Testicular trauma** is also uncommon and may be associated with cycling or other injuries.

B. Secondary

1. **Obesity** accounts for the majority of cases of secondary hypogonadism. The mechanisms are twofold. First, overweight and obesity are associated with lower levels of sex hormone–binding globulin (SHBG) which can result in low levels of total

testosterone. The free or bioavailable testosterones may be normal or low. In the large European Male Aging Study, mean total testosterone levels were 12% lower in men with overweight and 25% lower in men with obesity as compared to men with normal weight. Second, obesity is associated with increased aromatase activity in adipose tissue which leads to increased estrogen production which exerts negative feedback on the hypothalamus/pituitary gland.

2. **Diabetes and insulin resistance** are also linked to low testosterone and often occur in conjunction with overweight/obesity. Studies show a bidirectional relationship in which low testosterone is associated with increased insulin resistance as well.
3. **Medication-induced** low testosterone is most commonly found with opiates/narcotics and supraphysiologic doses of glucocorticoids. The mechanism is decreased production of gonadotropin-releasing hormone. The sexual symptoms associated with the opiates will often not resolve with testosterone replacement, however.
4. **Hypopituitarism** is a relatively uncommon condition that may be due to a lesion/tumor in the pituitary or hypothalamus or iatrogenic due to surgery or radiotherapy for a pituitary tumor. Large pituitary tumors may present with headache or visual field defects. Other causes include infiltrative diseases such as sarcoidosis, pituitary apoplexy, head trauma, or iron deposition in hemochromatosis.
5. **Acute illness** often results in low testosterone in proportion to the severity of the illness.

III. DIAGNOSIS

Given the nonspecific nature of many of the symptoms associated with low testosterone, it is sometimes unclear whom to screen. Often, patients request the tests themselves or have them done by their primary care physicians or other providers. In addition to the common complaints of low libido and erectile dysfunction, one should consider ordering a testosterone in a man with incomplete pubertal development, infertility, small testes, gynecomastia, or hot flashes. According to the European Male Aging Study, the three sexual symptoms (lower sexual desire, erectile dysfunction, and fewer morning erections) were more closely correlated to the diagnosis of male hypogonadism than the nonsexual

symptoms were. Nonetheless, the diagnosis relies more heavily upon serum testosterone concentrations, given the lack of specificity of the symptoms. In the European Male Aging Study, the authors proposed a definition of hypogonadism to include a total testosterone <320 ng/dL (11 nmol/L) in the presence of lower sexual desire, erectile dysfunction, and fewer morning erections. The challenge in diagnosing hypogonadism can be easily appreciated from the cross-sectional Boston Area Community Health Survey. In this study, 57% of men under age 50 with low testosterone levels lacked symptoms and 66% of men with symptoms lacked low total testosterone levels.

Obtaining a history should focus on the presence or absence of symptoms associated with hypogonadism, risk factors for primary and secondary hypogonadism, sleep duration, and a careful review of medications. The physical examination should include p. 901p. 902an assessment of testicular volumes, body mass index, and the presence or absence of acne and gynecomastia.

Figure 72-1 is an algorithm for how to assess for low testosterone in men with suggestive signs or symptoms.

A. How to assess testosterone concentrations

1. **Timing** of testosterone measurements is important, given the diurnal variation of the hormone due to the pulsatile release of luteinizing hormone (LH) from the anterior pituitary. For this reason, levels are typically checked between 7 and 10 A.M. This diurnal variability is less apparent in men over age 50. Given the intraindividual variability in testosterone, it is always important to confirm a low testosterone with a second measurement because approximately one third of repeat measurements are normal. When the second level is clearly normal, the patient can be reassured. When the second level is borderline, it is often helpful to obtain a third level and/or a different type of testosterone measurement such as free or bioavailable. One study also found that testosterone levels tended to be higher when fasting than when nonfasting.
2. **Many types of assays** are available to assess testosterone concentrations. Most endocrinologists start with a total testosterone because these assays are widely available and have been well studied. Liquid chromatography-mass spectrometry should be

ordered when possible because it is considered more accurate than the older radioimmunoassays. Free and bioavailable (free plus albumin-bound) testosterone is helpful when one suspects a low or elevated SHBG.

3. **Reference ranges** vary by assay, and the lower end of the reference range in one assay may be over 100 ng/dL (3.5 nmol/L) different from another assay. The reference ranges are generally established using standard deviations of the population sampled which is often lean men under age 40. The problem with this methodology is the arbitrary cut points that are assigned on the basis of a statistical p. 902p. 903value rather than a clinical outcome or symptom. Another major limitation is that the reference ranges fail to adjust for age. Given that testosterone levels decline with age, it is important to consider the age of the man being evaluated.

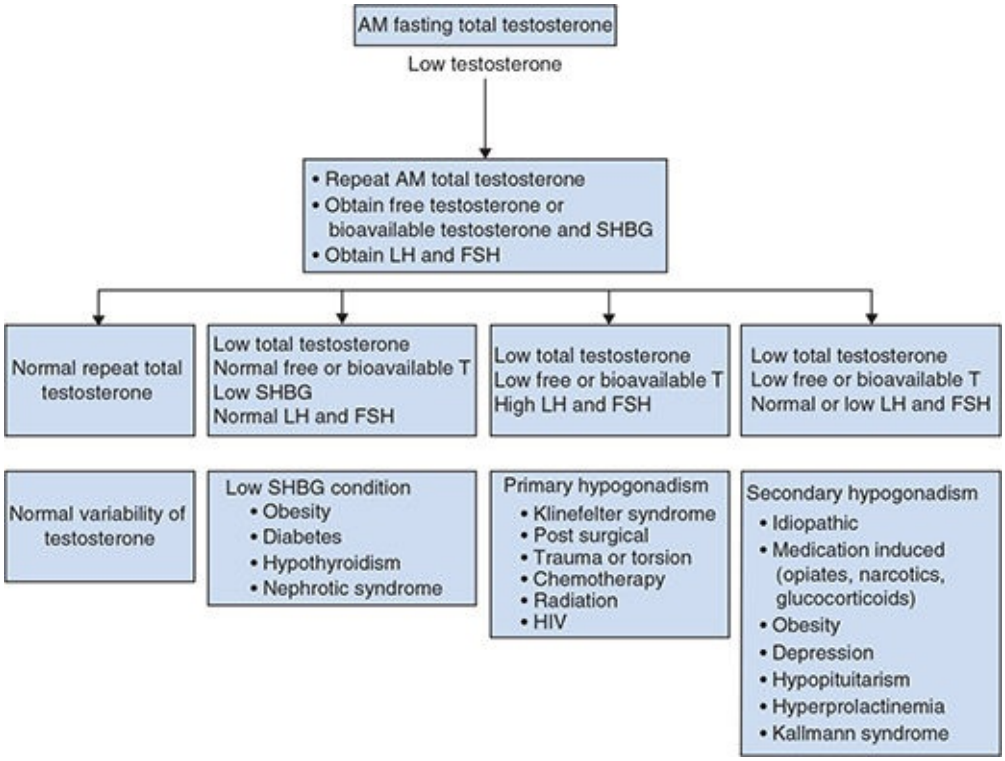

Figure 72-1. Testing men for low testosterone involves several testosterone measurements in addition to gonadotropins and other testing in selected circumstances. FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone–binding globulin; AM, morning; T, testosterone.

B. Other studies

1. **Gonadotropins (LH and follicle-stimulating hormone [FSH])** are used to distinguish between primary (hypergonadotropic) and secondary (hypogonadotropic) hypogonadism. Many of the causes of primary hypogonadism are apparent from the history, such as a history of radiation, chemotherapy, surgery, trauma, or torsion.
2. **Low SHBG** is often seen with obesity, diabetes, hypothyroidism, and nephrotic syndrome. **Elevated SHBG** is associated with aging, hyperthyroidism, hepatitis, HIV, and certain medications such as anticonvulsants.
3. **Chromosomal analysis (karyotype)** is used to screen for Klinefelter syndrome and certain rare genetic causes.
4. **Ferritin and iron levels** are elevated in hemochromatosis.
5. **Pituitary MRI** is rarely indicated but should be obtained if one suspects a pituitary tumor or hypopituitarism. A tumor may present with hyperprolactinemia, galactorrhea, headache, and/or visual field deficits. Hypopituitarism would present with symptoms of hypothyroidism, growth hormone deficiency, and/or adrenal insufficiency accompanied by low levels of free thyroxine, insulin-like growth factor 1, and/or AM cortisol.

C. Screening instruments

1. The abridged international index of erectile function is a five-question validated instrument that is used to screen for **erectile dysfunction**. It is also helpful in monitoring for improvement in erectile function in men on therapy because it provides a more objective assessment.
2. Multiple validated instruments are available to screen for **depressive symptoms/depression**. One study found that 56% of men referred for evaluation of borderline testosterone levels between 200 and 350 ng/dL (6.9 and 12 nmol/L) had depressive symptoms or known depression.
3. Multiple validated instruments are available to screen for **obstructive sleep apnea**, including the STOP-BANG Scoring Tool. Sleep apnea is quite common among men over age 50 who have hypertension, a neck circumference of over 17 inches, and those who report snoring loudly or daytime tiredness. The association between sleep apnea and lower testosterone concentrations is due to a combination of adiposity and decreased

sleep quality.

IV. TREATMENT

The decision to initiate testosterone therapy (Table 72-2) should be based upon a careful assessment of the patient's signs and symptoms, levels of testosterone obtained on at least two occasions, age, desire for fertility, and medical comorbidities. Therapy should be individualized on the basis of these factors, as opposed to simply looking at whether a man's testosterone levels fall within a "normal" reference range. For men with normal testosterone levels, off-label usage for antiaging purposes or to promote increased muscle mass or sexual desire should be discouraged because of potential adverse effects. Testosterone therapy should be offered when the potential benefits appear to outweigh the potential risks. Unfortunately, there has been no large, long-term randomized controlled trial (RCT) of testosterone therapy to evaluate whether it could impact cardiovascular events, stroke, fracture, or rates of prostate cancer. Testosterone therapy is often a chronic medication and is often expensive. For unclear cases, it is reasonable to offer a 3 to 6-month trial of testosterone to see if a man experiences symptomatic benefit. This information can guide whether to continue or discontinue the medication.

A. Goals of testosterone therapy for hypogonadism

1. **Improve sexual function** as it relates to libido and erectile function.
2. **Maintain bone health**
3. **Improve muscle mass and strength**
4. **Maintain a masculine body composition (fat and muscle)**
5. **Improve overall energy and sense of well-being**
6. In some trials, testosterone has been associated with **improvements in mood in those with depression.**

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TABLE 72-2 Testosterone Formulations

Formulation	Route	Dosing	Advantages	Disadvantages
Esters (enanthate or cypionate)	Intramuscular	100–200 mg every 2 wk (or half dose weekly)	• Lowest cost • Very effective at achieving target	• Peak and trough levels • Pain with injections • Increased rates

			levels	of erythrocytosis
Gels (1%)	Topical	25–100 mg daily	• Consistent T levels	• Expensive • Adverse effects if transferred to a woman or child
Patch	Topical	2.5–10 mg daily	• Consistent T levels	• Expensive • Skin irritation • Inadequate T levels
Axillary solution	Topical	30–120 mg daily	• Consistent T levels	• Expensive
Undecanoate	Intramuscular	750–1 000 mg every 10–14 wk	• Consistent T levels • Infrequent dosing	• Expensive • Large injection volume • Rare pulmonary oil microembolus
Undecanoate	Oral	40–80 mg 2–3 times daily with meals		• Inconsistent T levels
Pellets	Subcutaneous implants	150–450 mg every 3–6 mo	• Consistent T levels • Infrequent dosing	• Expensive • Need for incision and topical anesthesia • Bleeding • Infection • Less flexible dose titration
Buccal	Buccal	30 mg twice daily		• Expensive • Gum irritation • Taste alterations • Lack of adhesion
Nasal spray	Nasal	11 mg 3 times daily		• Expensive • Frequency dosing • Inadequate T levels
Certain formulations are not available in all countries.				

B. Are the sexual symptoms related to levels of testosterone?

Testosterone levels are often obtained in the evaluation of low libido and/or erectile dysfunction. According to the European Male Aging Study, increased rates of lower libido and erectile dysfunction are associated with total testosterone levels <230 ng/dL (8 nmol/L) and <245 ng/dL (8.5 nmol/L), respectively. Low libido in humans is poorly understood, but is thought to represent a complex interplay between excitatory and inhibitory pathways in various areas of the brain such as the amygdala, frontal cortex, hypothalamus, nucleus accumbens, and limbic p. 904p. 905systems. Rather than automatically attributing low libido to a low testosterone measurement, it is important to rule out other causes such as medications. Common offending medications include opiates and antidepressants. Likewise, low testosterone accounts only for a minority of cases of erectile dysfunction. Erectile dysfunction is largely a vascular condition in which there is a decrease in blood supply to the penis that is associated with aging. Other common causes of erectile dysfunction include diabetes, hypertension, hyperlipidemia, prostate surgery, and adverse effects of medications. Classes of medications associated with erectile dysfunction are anticholinergics, anticonvulsants, antidepressants, antihypertensives, antipsychotics, antispasmodics, barbiturates, benzodiazepines, diuretics, and nonsteroidal anti-inflammatory drugs.

C. Treating reversible causes of low testosterone often carries fewer risks and a greater potential in overall improvement in health than testosterone supplementation.

1. **Obesity** is inversely associated with testosterone levels. Men who are able to lose weight (even 5% to 10%) experience an increase in their endogenous testosterone levels in proportion to the degree of weight loss. Weight loss also has numerous additional benefits on other comorbidities such as diabetes, hypertension, and obstructive sleep apnea.
2. **Sleep duration** is associated with low testosterone levels. In one study, 1 week of sleep deprivation to 5 hours/night was associated with 10% to 15% lower daytime testosterone levels. It is, therefore, advisable to recommend that men with sleep deprivation increase their sleep duration to at least 7 hours/night.
3. **Obstructive sleep apnea** is a common cause of fatigue and low energy. Men with risk factors (age >50, hypertension, obesity, neck

circumference >17 inches) and snoring should be referred for a sleep study.

4. **Depression** is a common cause of low energy and low libido. Men suspected of depression on the basis of clinical symptoms or a positive score on a validated screening instrument should be referred to a mental health professional for evaluation.
5. **Medication side effects** can be associated with both low libido and erectile dysfunction. When safe to do so, it is reasonable to discontinue a medication for a month to see if the sexual symptom improves. It is often important to collaborate and discuss potential medication side effects with the prescriber of the medication who may suggest an alternate class of medication.
6. **Distinguishing between clearly low testosterone levels versus low-normal or borderline testosterone levels** has important clinical implications. There is broad agreement that men with unambiguous classical causes of hypogonadism (i.e., bilateral orchiectomy, chemotherapy, hypopituitarism, etc.) should be treated with testosterone. Levels of total testosterone <200 ng/dL (6.9 nmol/L) are associated with increased rates of osteoporosis and loss of lean-mass and muscle strength. In contrast, there is uncertainty over treating men with late-onset or low-normal total testosterone levels (230 to 350 ng/dL [8 to 12 nmol/L]) because the potential benefits are less established and the potential risks need to be taken into account.

D. Adverse effects of testosterone therapy

1. **Reversible infertility** is the most common adverse effect due to negative feedback resulting in a low FSH and a lack of stimulation of spermatogenesis. It can take up to 1 year for men to regain their baseline sperm concentration after discontinuing testosterone therapy. Men who are interested in fathering a child are instead treated with subcutaneous or intramuscular injections of human chorionic gonadotropin which acts like LH to stimulate endogenous testosterone production but not suppressing spermatogenesis.
2. **Erythrocytosis** may develop as a result of increased erythropoietin, bone marrow stimulation, and suppression of hepcidin. It is more common with the intramuscular esters that deliver supraphysiologic levels of testosterone for a few days after the injection. If the hematocrit reaches 52% to 54%, clinicians

should withhold therapy, reduce the dose, or change to a different formulation. Phlebotomy can be performed in extreme circumstances.

3. **Worsening of benign prostatic hypertrophy** may occur as testosterone is converted into the more potent androgen dihydrotestosterone in the prostate by 5α reductase. Dihydrotestosterone promotes growth of the prostate.

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4. **Acne** may occur with testosterone therapy, but usually does not require the use of topical or systemic acne medications. Skin irritation is quite common with the testosterone patch and is one of its major disadvantages.
5. **Prostate cancer** is a theoretical risk of testosterone therapy, but clinical guidelines suggest the routine measurement of prostate-specific antigen (PSA) and digital rectal examinations. If there is suspicion for prostate cancer (PSA > 4 ng/mL, increase in PSA >1.4 ng/mL within 12 months, or a palpable nodule), the patient should be referred to urology for further evaluation.
6. **Cardiovascular risks** of testosterone therapy is a controversial topic as studies show inconsistent and conflicting results. One RCT with elderly men with mobility limitations showed a 5.8-fold increase in cardiovascular events that were broadly defined. A retrospective health insurance database found that men over 65 who were given a testosterone prescription had a 2.2-fold higher incidence of myocardial infarction within 90 days of receiving the prescription. On the other hand, most systematic reviews failed to show any adverse cardiovascular effects of testosterone therapy. One RCT showed that testosterone therapy was not associated with changes in common carotid artery intima-media thickness or coronary artery calcium.

E. Contraindications to testosterone therapy

1. Prostate cancer (Some clinicians believe that it is reasonable to offer testosterone therapy to hypogonadal men with a history of low-stage prostate cancer if there is no evidence of cancer several years after treatment.)
2. Breast cancer
3. Hematocrit > 50%
4. Untreated severe obstructive sleep apnea

5. Severe lower urinary track symptoms
6. Poorly controlled heart failure.

Table 72-3 summarizes how men on testosterone therapy should be monitored. Testosterone levels are typically checked a few months after starting therapy and yearly if the levels are normal. For men under age 65, the 25% and 75% centiles for total testosterone are 372 and 594 ng/dL; for men over 65, the corresponding centiles are 294 and 484 ng/dL.

TABLE 72-3 Monitoring for Men on Testosterone Therapy

Assessment	Plan
Change in signs or symptoms	If no improvement after 3–6 mo consider discontinuing therapy
Testosterone level (for IM esters typically check mid-cycle)	Adjust dose if needed to target the level at the mid-normal for age
Hematocrit	If hematocrit is >52%–54% withhold therapy, reduce dose or change to a different formulation; phlebotomy in extreme circumstances
Prostate-specific antigen (PSA) and digital rectal examination	If there is a suspicion for prostate cancer (PSA > 4 ng/mL, increase in PSA >1.4 ng/mL within 12 mo or a palpable nodule) refer to urology for evaluation
Lower urinary tract symptoms	Discontinue therapy or reduce dose if symptoms significantly worsen; refer to urology for medical or surgical management

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73 The Use of Hormones in Female Sexual Dysfunction

Rosemary Basson

I. BACKGROUND

The etiology of women's sexual dysfunction is typically multifactorial, and the role of hormones in therapy is limited. Multiple studies confirm the major roles of mood and of the woman's feelings for her partner—both generally in the relationship and at the time of sexual engagement, in determining her sexual desire and arousal. This is true for both pre- and postmenopausal women. Chronic dyspareunia affects 15% to 20% of premenopausal women and is usually due to provoked vestibulodynia—a chronic pain disorder associated with central sensitization of the nervous system, but not with any confirmed hormonal etiology. **Established hormone therapy for sexual dysfunction exists for estrogen deficiency–invoked vaginal and vulvar pain from genital sexual stimulation and penetrative sex: local estrogen therapy is the mainstay of treatment.**

Despite the limited role of hormonal causation in women's sexual dysfunction, many patients believe that their sexual difficulties do have a hormonal basis. They consult an endocrinologist. A clear explanation of women's sexual response can guide therapy.

II. PHYSIOLOGY OF SEXUAL RESPONSE: DESIRE AND AROUSAL

A. Sexual stimuli

Men and women have the potential to respond to sexual stimuli in the environment generally and from their own or their partner's sexual stimulation to initiate physical and psychological/subjective sexual arousal. With ongoing stimulation and consistent attention to those sexual stimuli and to the feelings of sexual arousal, the latter can increase in intensity to reach the threshold of orgasm: the sexual

tension that has built up is released to produce a sense of calm and well-being and relaxation. Women may have many orgasms in succession—all in association with sustained high arousal. Also, for women, there is no typical refractory period, and with further stimulation, arousal can recur with further orgasmic release.

B. Sexual motivation

The motivations or incentives to attend to sexual stimuli so as to allow arousal are highly complex. An awareness of sexual need/desire/urge/“libido” at the outset may or may not be present and tends to be less frequent with longer relationship duration and with age. Its absence at the beginning of sexual interaction, that is, before any stimulation, was formerly considered to be abnormal, meriting a diagnosis of female hypoactive sexual desire disorder (HSDD). Figure 73-1 illustrates how the sense of desire/urge is frequently accessed during the sexual experience along with sexual arousal. Subjective arousal correlates poorly with measures of genital congestion in both functional and dysfunctional women.

C. Women’s sexual dysfunction

For many women, desire and arousal are inseparable; women’s sexual experience does not follow discreet phases of desire, conscious awareness of genital engorgement/erection, single ejaculation/orgasm, followed by the loss of arousal and subsequent refractory period more typical of men. Consequently, female sexual dysfunction is typically a blunting of all phases: desire and subjective arousal are muted throughout the sexual experience, and orgasms are rare or absent. An exception is the complaint of high arousal but no orgasmic release, commonly induced by antidepressant medication.

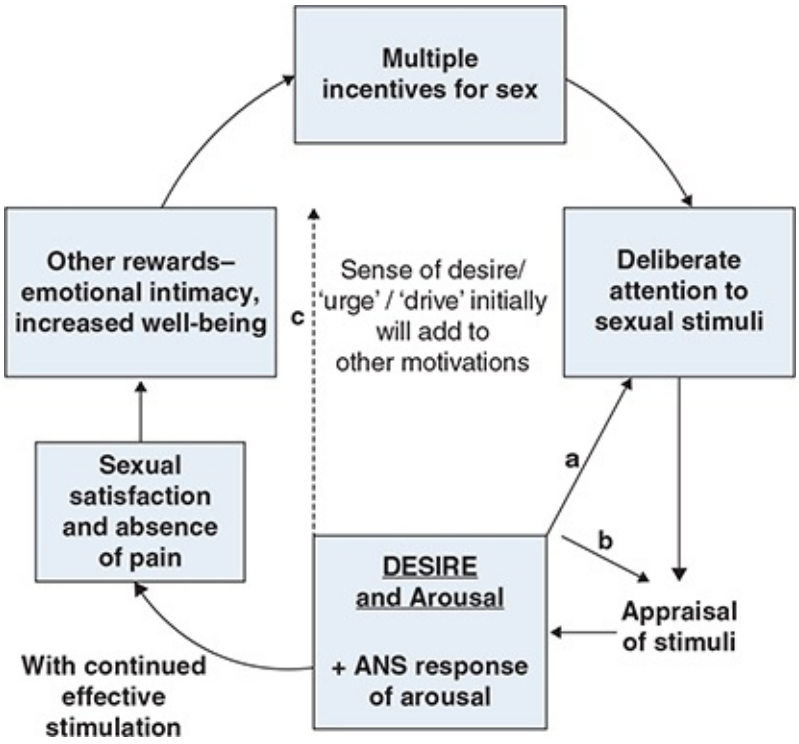

Figure 73-1. Sexual response cycle.

Women who are unable to sense arousal and trigger desire during the sexual encounter have not been recruited to trials of hormonal (notably, testosterone) or other pharmacologic therapies. Thus, the pharmacologic/hormonal approach to date targeting the normally highly variable desire for sex in between sexual encounters and at the beginning of sexual activity has been of very limited benefit: (note the discontinuation of marketing of testosterone patches for treatment of HSDD in Europe where they are approved because of low sales).

The current definition of disordered sexual desire—"sexual interest and arousal disorder" in the American Psychiatric Association Diagnostic Statistical Manual 2013 (DSM5) includes a lack of responsive or triggered desire (Table 73-1).

III. ENDOCRINE CONSULTATION FOR FEMAL SEXUAL DYSFUNCTION

Careful history-taking will identify the reasons for a woman's lack of desire and arousal during her sexual encounters. A lack of a rewarding outcome—for example from pain or loss of genital sexual sensitivity, or from a male partner's erectile dysfunction, commonly leads to her complaint of "low libido." Similarly, identifying a lack of appropriate

context (e.g., poor emotional relationship, absence of an erotic environment, lack of privacy, attempting sexual contact late at night when sleep is needed, etc.) allows endocrinologists to explain the interruption in the woman's cycle. Inquiry into her thoughts during sexual stimulation is also needed. Inability to stay focused on the sexual stimuli and on the sensations of arousal is particularly common: distractions may be nonsexual, but nonerotic thoughts about body image are also frequent. For the woman, reporting the absence of desire, to understand the logic of her situation, is therapeutic in and of itself.

IV. PHYSIOLOGY OF SEXUAL RESPONSE: PHYSICAL CHANGES

Physical changes of arousal are increased body temperature and muscle tone, flushing of face and chest, engorgement of breasts, nipples, and genitalia, elevated respiratory rate, and when close to orgasm, possible moaning or sighing. Increased genital blood flow is associated with swelling of the labia and clitoris and an increase in vaginal p. 909p. 910elasticity and lubrication. The latter is mainly a transudate from plasma: interstitial fluid from the submucosal capillaries percolates through the vaginal epithelium onto its surface in increasing amounts as the blood flow increases. At least to visual stimuli, the neurovascular genital response is automatic and involuntary, occurring within seconds of the stimulus. In contrast, subjective arousal/excitement may take many minutes or not occur at all despite genital changes.

TABLE 73-1 Definitions of Sexual Disorders in Women

Female Sexual Interest/Arousal Disorder

Lack of sexual interest/arousal for a minimum duration of 6 mo as manifested by at least three of the following indicators:

1. Absent/reduced frequency or intensity of interest in sexual activity
2. Absent/reduced frequency or intensity of sexual/erotic thoughts or fantasies
3. Absence or reduced frequency of initiation of sexual activity and is typically unreceptive to a partner's attempts to initiate
4. Absent/reduced frequency or intensity of sexual excitement/pleasure during sexual activity on all or almost all (~75%) sexual encounters
5. Sexual interest/arousal is absent or infrequently elicited by any internal or external sexual/erotic cues (e.g., written, verbal, visual, etc.).
6. Absent/reduced frequency or intensity of genital and/or nongenital sensations during sexual activity on all or almost all (~75%) sexual encounters.

Female Orgasmic Disorder

At least one of the two following symptoms where the symptom(s) must have been present for a minimum duration of ~6 mo and be experienced on all or almost all (~75%) occasions of sexual activity:

1. Marked delay in, marked infrequency, or absence of, orgasm
2. Markedly reduced intensity of orgasmic sensation.

Genitopelvic Pain/Penetration Disorder

Persistent or recurrent difficulties for a minimum duration of ~6 mo with one or more of the following:

1. Marked difficulty having vaginal intercourse/penetration
2. Marked vulvovaginal or pelvic pain during vaginal intercourse/penetration attempts
3. Marked fear or anxiety about either vulvovaginal or pelvic pain on vaginal penetration
4. Marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration

American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5);2013.

A. Role of estrogen in genital sexual response

Nitric oxide is a major neurotransmitter allowing the vasodilatation of the bulbs, shaft, and head of the clitoris and of the submucosal vaginal plexus. Its biologic activity is increased by an estrogen receptor–mediated antioxidant effect. At least in nongenital areas, it is known that endothelial function is impaired postmenopause. Local estrogen therapy is associated with the upregulation of estrogen receptors on the endothelium. The identification of neurotransmitters in the vagina is limited, but importantly, nitric oxide synthase is reduced postmenopause. Vasoactive intestinal polypeptide (VIP) is also involved in the neurogenic vasodilatation of vulva and vagina and requires a minimum amount of estrogen for its activity. Following menopause, vaginal tissue shows a paucity of VIP. Estrogen may also contribute to genital sexual sensitivity (the latter may lessen postmenopause). When lack of estrogen precludes adequate vasodilation, lubrication, and elasticity, the resulting dyspareunia frequently leads to other dysfunction. Unless the sexual couple adopt a sexual menu that excludes vaginal penetration, the woman's sexual motivation may markedly lessen. In time, stimuli will fail to arouse and she may report a general loss of desire/libido.

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B. Role of androgen in genital sexual response

Vulvar structures including the vestibular glands are thought to be sensitive to androgens. In rodents, the density of androgen receptors on

vaginal sensory nerves is increased by local dehydroepiandrosterone (DHEA) (and not by local estrogen), and a role for vaginal DHEA for postmenopausal loss of genital sexual sensitivity as well as lack of dyspareunia and lubrication is emerging. Research into the role of vaginal testosterone for sexual dysfunction is scant.

C. Estrogen therapy in female sexual dysfunction

1. Sexual consequences of low estrogen

Genital sexual stimulation can be unpleasant and painful. Insufficient vaginal lubrication may cause a burning type of dyspareunia that may continue for many minutes after intercourse. Loss of vaginal elasticity may preclude penile entry. In reaction, there may be a reflexive tightening of superficial and deeper pelvic muscles. In time this tightening might overshadow the sensitivity of the tissues, so that physical examination proves difficult or impossible because of the so-called “vaginistic” response. An estrogen deficiency state may progress to a stenosis of the vagina and diminution or even to a loss of the labia minora. If penetration is attempted under these circumstances, there may be tearing, especially of the posterior fourchette. The signs and symptoms of vulvar vaginal atrophy have recently been termed “genitourinary syndrome of menopause” (GSM).

2. Differential diagnosis

Vulvar dystrophies, especially lichen sclerosus, may be comorbid with atrophy or the dominant finding postmenopause. The typical whitening of lichen sclerosus can, in its early phases, be confused with the pallor from estrogen deficiency–related atrophy: biopsy may be needed. When burning introital dyspareunia continues despite the treatment of any atrophy, it is important to consider provoked vestibulodynia (PVD) and examines for allodynia of the introital margin, specifically the inner edge of the labia minora/outer edge of hymenal remnants. Although the majority of women with PVD are young, a second peak incidence occurs at menopause.

V. PREVALENCE OF ESTROGEN DEFICIENCY–RELATED ATROPHY

A. Background

After menopause, estrogen is produced within peripheral cells from precursor hormones including DHEA and androstendione (A4) in the

blood originating from the adrenal glands and to a small degree from the ovaries. How much precursor hormone is metabolized to testosterone and how much of this testosterone is aromatized to estrogen is highly variable. Adipose tissue allows more aromatization such that thin women are typically more at risk of harm from low estrogen. Given its intracellular production and metabolism, the measurement of this “intracrine” production is difficult.

B. Low estrogen states

The prevalence of sexual symptoms due to low estrogen is greatest postmenopause (natural, surgical, postchemotherapy), but is also seen temporarily postpartum as well as in the context of hypoestrogenic hypothalamic amenorrhea, with the use of gonadotropin-releasing hormone (GnRH) agonists and with very low-dose estrogen contraceptives.

C. Variable symptoms

Symptoms of vulvar atrophy are by no means universal despite the marked decline in estrogen activity after menopause. Limited evidence suggests that when intracrine production of estrogen from precursor hormones allows serum levels to reach beyond 20 pmol/L, symptoms are infrequent. The signs and symptoms of atrophy do not correlate well. Studies that measure increases in blood flow over baseline (but not absolute levels of flow) suggest that there is a similar increase in clitoral volume in response to arousing erotic stimuli in both pre- and post-menopausal women. The vast majority of North American women discontinuing estrogen therapy will show signs of vaginal atrophy within 12 months, but it is unclear why only some women are sexually symptomatic. Most studies report an incidence of 20% p. 911p. 912to 45% with symptoms increasing over time. Although continued sexual activity can be helpful, it is not sufficient to maintain vascularity and the activity of many genes governing growth factors, immune factors, and interleukins, all of which require estrogen. One study indicated that some 60% of postmenopausal women acknowledged symptoms of atrophy despite being sexually active. Urinary tract infections may occur due to the increased pH and altered vaginal flora associated with the lack of estrogen, which, in turn, can reduce sexual motivation and be associated with dyspareunia.

Surprisingly, symptoms from vulvar vaginal atrophy may spontaneously remit within 1 year of onset: risk factors for more serious ongoing symptoms include diabetes, younger age, and lower body mass. Recent evidence confirms the importance of psychological factors in determining symptomatology.

D. Local estrogen therapy

Local vaginal estrogen is the approved therapy for vulvar vaginal atrophy. This can be given in the form of a vaginal tablet (typically 10 μg estradiol twice weekly), an estrogen ring releasing 7.5 μg estradiol daily, and a conjugated equine estrogen cream with doses ranging from 0.3 to 1.25 mg (the frequency ranging from daily to weekly). Estriol 0.2 to 0.3 mg twice weekly is the most common formulation of local estrogen used in Europe, but it is not marketed in North America. It can be compounded. A recent study suggests that doses as low as 0.02 to 0.05 mg twice weekly are sufficient.

E. Comorbid PVD

Clinical experience suggests that when there is comorbid PVD, estriol 0.2 to 0.3 mg twice weekly is superior to estradiol or conjugated estrogens. The compounded estriol is applied directly to the sites of allodynia around the introital rim as well as into the lumen of the vagina.

F. Ospemifene for genital atrophy

Ospemifene is an oral selective estrogen receptor modulator (SERM) recently approved for the treatment of vulvovaginal atrophy, also described as a nonestrogen tissue-selective estrogen receptor agonist/antagonist. Preclinical and early clinical data suggest that it to have a neutral or antiestrogenic effect on breast tissue and a positive effect on bone. Ospemifene's actions on the endometrium are similar to those of vaginal estrogens. The incidence of deep vein thrombosis, thromboembolic stroke, and hemorrhagic stroke appears to be similar to that associated with systemic estrogen. Hot flashes are the most common side effect (7.5% incidence).

Early study suggests that clinically relevant improvement in dyspareunia is noticeable by 4 weeks of treatment. When other measures of sexual function are taken into account, by 12 weeks of treatment, there may be an increase in arousal and desire ($p < 0.05$).

G. Treating vulvovaginal atrophy in breast cancer survivors

Studies suggest that the estradiol levels remain in the range of postmenopausal women when conventional doses of vaginal estrogen

formulations are employed. However, systemic absorption can occur especially when atrophy is marked. Current research focuses on minimal effective estrogen dosage and confirms clinical benefit from low and ultralow dosage. Ultralow doses of vaginal estrogen have recently been studied: 50 μg estriol daily has been shown to be effective with a negligible increase in plasma levels. Pessaries containing 0.2 and 0.03 mg estriol showed similar superiority over placebo. Low-dose preparations include the 7.5 μg vaginal ring and the 10 μg estradiol vaginal tablet. Intermediate doses include the 25 μg estradiol tablet and 0.3 mg conjugated estrogens, and high-dose formulations include 50 to 2 000 μg of estradiol or 0.625 to 2.5 mg of conjugated estrogens. To date, studies do not indicate an increase in the recurrence of breast cancer with low-dose vaginal estrogen therapy.

Estriol, with its extensive history of use in Europe, has been considered relatively safe on breast tissue. Past reassurance was based on the clinical experience as well as the fact that **estriol has lower estrogenic potency than estradiol** (ranging from 1:10 to 1:100) and greater relative affinity for estrogen receptor-*β* than that for estrogen receptor-*α*, thus minimizing extravaginal effects. However, a very recent in vitro study compared the effects of estradiol and estriol on the growth of human p. 912p. 913breast cancer cell lines: **both of these estrogens triggered a similar response in the cancer cells** suggesting caution regarding the use of estriol in cancer survivors.

H. Aromatase inhibitors and local estrogen

Even minute amounts of systemic absorption of estrogen may be of concern for women using aromatase inhibitors. A prospective trial with 10 μg estradiol vaginal tablets of breast cancer survivors using aromatase inhibitors is ongoing. A previous trial of similar women using either 25 μg estradiol tablets or an estradiol ring delivering 7.5 mg/day showed an increase in serum levels with both formulations, higher from the ring and sustained only in those using the ring. A recent small study of ultra-low-dose 0.03 mg estriol combined with lactobacillus (daily for 4 weeks and then three times a week for 8 weeks) showed no increase in estradiol or estrone and a very slight increase in estriol but with benefit to the dryness and dyspareunia. Another small study failed to find increased serum levels of estriol or estradiol using 0.5 mg estriol daily per vagina for 2 weeks.

I. SERMs

Ospemifene may prove to be a safe option in the context of past breast cancer and even prove to be a chemoprotective agent.

VI. DHEA THERAPY IN FEMALE SEXUAL DYSFUNCTION

A. Background

In otherwise healthy women, there is no documented endocrine deficiency disorder due to a lack of DHEA. This is despite the reduction of some 60% of DHEA production which peaks in early adulthood to decrease from the mid-30s to the mid-60s. The intracrine production of testosterone in peripheral cells from mostly adrenal sources of DHEA accounts for some 50% of testosterone activity premenopause and up to 100% postmenopause. Moreover, following menopause, all estrogen is produced in peripheral cells from DHEA.

B. Systemic DHEA therapy

Despite dependence on DHEA and other precursor hormones postmenopause, and despite universal age-related reduction in DHEA production, systematic review **does not support the use of systemic DHEA supplementation for female sexual dysfunction**, nor is it recommended by the American Endocrine Society.

For women with sexual dysfunction in the context of primary or secondary hypoadrenal states, most studies **do not show benefit from DHEA replacement**. This is surprising, and this may be due to a lack of assessment and management of other comorbid etiologic factors.

C. Local (vaginal) DHEA for genital atrophy

One group of researchers showed improved genital-sexual responsivity with easier and more intense orgasm as well as prompt reversal of vulvar vaginal atrophy from the use of vaginal DHEA. Both a 6.5 mg and a 13 mg dose at night allowed the reversal of symptoms and signs of vaginal atrophy by 2 weeks and the improvement in sexual function by 10 to 12 weeks. The women were recruited on the basis of dyspareunia and vaginal dryness. Importantly, the researchers found no increase in serum testosterone or estrogen using mass spectrometry methods, and the therapy is thought to be truly local. Longer term safety efficacy studies are now published and vaginal DHEA 6.5 mg nightly is now FDA approved for GSM.

D. Local (vaginal) DHEA for loss of genital sexual sensitivity

Subsequent to this research, the investigational use of 13 mg vaginal DHEA for postmenopausal loss of genital sexual sensitivity and orgasm is drawing increased attention. DHEA is compounded in either suppository or cream form. When specifically used for postmenopausal loss of genital sexual sensitivity, the clinical experience is that **benefit is frequent**. Orgasms return, sexual motivation and desire increase as the woman's sexual experiences are more rewarding, and she becomes more aware of a genital response to sexual stimuli in her environment. A repeated study of the beneficial vaginal DHEA for the sexual symptoms of atrophy has just been published.

Given early data confirming a lack of systemic absorption of either testosterone or estrogen, vaginal DHEA for dyspareunia may become another safe option for women after breast cancer.

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VII. TESTOSTERONE THERAPY IN FEMALE SEXUAL DYSFUNCTION: ROLE OF TESTOSTERONE IN WOMEN'S SEXUAL RESPONSE

A. Background

Despite the discontinuation of previously approved transdermal testosterone therapy for low sexual desire in Europe because of low sales, and its **lack of approval in North America**, endocrinologists still receive requests for systemic testosterone therapy for women's sexual difficulties. The role of testosterone in women's sexual response remains unclear. Supraphysiologic doses of testosterone have the expected effect of heightening the need to self-stimulate and, depending on nonhormonal factors, may increase the desire for partnered sex. In contrast, despite the many sexual stressors of living with complete **androgen insensitivity syndrome**, those women are able to sense sexual desire, arousal, and orgasms. Adjusting "low" postmenopausal serum testosterone levels to high premenopausal levels is of uncertain benefit. Past difficulties with assays, plus the inability to measure intracrine testosterone production, add to the complexity.

The following points indicate that although an endocrine deficit disorder characterized by signs and symptoms and corrected by hormone replacement exists for estrogen, this is not true for

testosterone.

1. Low sexual desire or other sexual dysfunction in women has not been confirmed to correlate with testosterone levels including those measured by mass spectrometry, nor to correlate with androgen metabolites.
2. Some studies confirm low DHEA to be associated with low desire, but given the lack of correlation between low desire and androgen metabolites, if low DHEA underlies the low desire, the mechanism is nonandrogenic. Hypothalamic pituitary adrenal axis dysregulation in women with low desire might account for the data linking low DHEA to low desire. Whether childhood trauma in terms of neglect, abuse, and other stress is associated with low sexual desire in adult life and with low DHEA and other markers of hypothalamic pituitary adrenal axis dysregulation is the subject of current research.
3. Similarly, the **high testosterone levels associated with polycystic ovarian syndrome are not associated either with robust sexual function** or consistently with dysfunction. Results of mostly small studies are conflicting. Any associated obesity, hirsutism, or acne may lessen sexual self-image to reduce desire and motivation. There is no evidence that the higher testosterone levels protect against these psychosocial factors.
4. Trials of testosterone therapy have not targeted women with known testosterone deficit.
5. Identifying testosterone deficit is not currently possible. Intracellular production from mainly adrenal precursor hormones is not easily measured. The optimal androgen metabolites to measure are not yet established.

B. Systemic testosterone therapy: the evidence

Testosterone therapy for women's sexual dysfunction has been researched over the past 40 years, with doses ranging from supraphysiologic intramuscular injections in the 1980s to transdermal testosterone achieving high or slightly above premenopausal testosterone levels in the last decade. These more recent studies have been conducted on postmenopausal women complaining of low desire in contrast to their premenopausal years. The majority were surgically menopausal and receiving systemic estrogen.

1. Conflicting results

Studies using a transdermal patch delivering 300 μg of testosterone

daily achieved statistical significance in that on average the women who reported at baseline some two to three rewarding satisfying sexual experiences per month indicated an increase to three to four similarly satisfying episodes when receiving placebo and four to five when receiving active drug. A second sponsor used a testosterone gel which also delivered 300 μg of testosterone daily: these studies were negative but have been published only in abstract form.

2. **Dysfunctional women not targeted**
   Women who are unable to have any rewarding sexual experiences because of both absent responsive desire (triggered desire) and absent desire at the outset of sexual engagement were not targeted in any of the trials.

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3. **Sexual effects only at highly supraphysiologic dose**
   Studying 71 postmenopausal women with previous hysterectomy and for most, previous bilateral oophorectomy, but not recruited on the basis of sexual dysfunction, researchers found sexual dysfunction resistant to testosterone treatment until doses exceeding serum levels five to six times the upper limit of normal were used.
4. **Potential role for testosterone for women with hypopituitary states**
   Just one small study supports the use of testosterone for women with hypopituitary states. Long-term effects are unknown.

C. Systemic testosterone therapy: the practice

Despite the lack of strong scientific foundation to do so, testosterone is frequently prescribed off-label in North America to postmenopausal women complaining of low desire, but typically not for long term. **Problems include**:

1. To date, low androgen activity has not correlated with sexual dysfunction. Thus, for clinicians, the therapy lacks logic.
2. Clinicians have no evidence on which to base testosterone therapy for women with a disorder as is currently understood. The lack of both desire at the outset of sexual engagement and triggered desire and arousal during sexual stimulation is now the focus of the definition of sexual interest arousal disorder as defined in DSM5. Of note, the women in the recent transdermal testosterone trials did

report satisfactory sexual experiences, but simply fewer than they would wish.

3. Long-term safety is unknown and yet the concern of low sexual desire is long term. Breast cancer and cardiovascular risks remain unclear.
4. Safety data indicate that systemic estrogen therapy needs to be instituted at or shortly after menopause: beginning estrogen plus testosterone therapy 5 to 10 years or more post menopause would therefore be precluded. Replacing only testosterone will increase an already “abnormal” (compared with premenopause), high testosterone:estrogen ratio. There is no evidence to suggest that estrogen is of benefit unless there is depletion (postmenopause or postpartum or with GNRH therapy) and then only of benefit for dyspareunia from atrophy (and only local vaginal estrogen is recommended). Physicians (in the United States mainly) are prescribing testosterone off-label as mentioned above—the practice is unregulated and how many women are also started on postmenopausal estrogen is unknown. Most of the women in the testosterone trials were prescribed estrogen as well as testosterone.
5. The clinical experience is that women receiving testosterone supplementation, even at supraphysiologic doses, report a temporary increase in sexual thinking, sexual dreams, desire to self-stimulate, and sometimes increased interest in partnered sexual activity, on a temporary basis subsequent to the recent increase in testosterone, only to fade after a few months.
6. The side effects of hirsutism and acne are bothersome clinically despite the recorded infrequency of hirsutism in the published trials. Clearly, hirsutism can be dealt with privately and not disclosed. Mood changes are reported and are seen clinically: anger and aggression can be troublesome.

Given the recent widespread off-label use in women, of transdermal testosterone, despite not advocating its use for sexual dysfunction as currently defined, the most recent guidelines of the North American Endocrine Society adopted a harm reduction approach (“Harm reduction” refers to policies, programs, and practices that aim to reduce the harm associated with the use of a substance [here testosterone] in people unwilling to stop [here by clinicians unwilling to desist prescribing]). The endocrine committee recognized that the criteria for disordered sexual desire

have changed with DSM5—HSDD is no longer recognized as a disorder. As well, there are no data on testosterone therapy for sexual interest arousal disorder, but the practice of off-label prescribing continues and so guidelines were given to minimize harm, such as advising only low dosage and monitoring the serum levels of testosterone plus regular follow-up.

D. Local testosterone therapy

Very limited study results suggest that adding 0.5 mg of a 2% testosterone cream twice a week to 0.625 mg conjugated equine estrogen cream may allow more sexual sensitivity as well as improvement of dyspareunia from atrophy.

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There are minimal data on intravaginal testosterone treatment after breast cancer, but one small trial involved women who were receiving aromatase inhibitors. Both 150 and 300 μg intravaginal testosterone gel for 28 days improved dyspareunia from atrophy: neither estradiol nor estrone serum levels were increased.

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Menopausal Hormone Therapy

Khalid Benkhadra and Ekta Kapoor

I. INTRODUCTION

Menopause is characterized by a permanent cessation of menses. It is defined as occurring 12 months after the last menstrual period, and is a result of complete/near-complete loss of ovarian follicles. The average age of menopause is 51 years, although it can vary significantly. The occurrence of menopause before the age of 40 is referred to as primary ovarian insufficiency (previously known as premature ovarian failure). The hormonal changes of menopause include a low estradiol level and elevated follicle-stimulating hormone and luteinizing hormone concentrations.

Menopause can lead to a variety of symptoms, including hot flashes, night sweats, sleep disturbance, mood changes, difficulty with memory and concentration, weight gain, vaginal dryness, urinary symptoms, and sexual dysfunction. Several of these symptoms first appear in the years before the final menstrual period (defined as the menopausal transition or perimenopause), and can last more than a decade after menopause in some women. The majority of these symptoms are thought to be a direct consequence of the low estrogen levels characteristic of the menopausal state. Systemic estrogen therapy (ET) has, therefore, been in use for decades to manage bothersome menopausal symptoms.

II. WHOM TO TREAT WITH MENOPAUSAL HORMONE THERAPY

Menopausal hormone therapy (MHT) has long been recognized as the most effective treatment for providing relief from bothersome vasomotor and vaginal symptoms of menopause. In addition, prior to the publication of the Women's Health Initiative trial in 2002, MHT was commonly advocated for the primary prevention of coronary artery disease, and age-related cognitive decline and osteoporosis in postmenopausal women. However, on the basis of the current research, **we no longer recommend the use of MHT for the primary prevention of any**

disease. The current consensus is to use MHT to manage bothersome menopausal symptoms (usually vasomotor) in recently menopausal women (<10 years since menopause or age <60 years), in the absence of any contraindication for systemic estrogen use (Table 74-1). Symptomatic women who are unable to use systemic ET as first-line therapy because of the presence of one of the conditions listed in Table 74-1, and therefore faced with an unfavorable p. 917p. 918risk–benefit ratio, should consider being on nonhormonal prescription medications including antidepressants, to manage bothersome vasomotor symptoms. However, if the symptoms are not adequately controlled by nonhormonal strategies, and result in significant impairment of the quality of life, a woman can choose to be on MHT as long as she clearly understands and accepts the potential associated risk. So, the decision to treat menopausal/perimenopausal women with systemic ET is an individualized one, and is made after weighing risks and benefits. The important factors to consider in decision making are a woman's age, the type and timing of menopause, the severity of symptoms and their impact on the quality of life, past medical and family history, and personal preferences.

TABLE 74-1 Conditions in Which to Avoid the Use of MHT

1. Prior history of cardiovascular disease (CVD) or elevated risk of CVD (>10% 10-yr CVD risk by ACC/AHA calculator)
2. Active or prior thromboembolic disease (low-dose transdermal estrogen may be safe in women with previous history of DVT)
3. Unexplained vaginal bleeding
4. Prior history of breast cancer or high risk of breast cancer
5. Active liver disease

DVT, deep venous thrombosis; MHT, menopausal hormone therapy.

Systemic ET also reduces menopause-related bone loss and fragility fractures, and improves the nonvasomotor symptoms of menopause including sleep disturbance, anxiety, depression, and joint pains, but it is not usually used for the primary management of these indications in the absence of vasomotor symptoms.

Women with menopause prior to the age of 40 represent a unique group, and MHT should routinely be recommended to them unless there is a contraindication like breast cancer. Systemic ET is critical in these women not for symptom management, but for reducing their risk of adverse consequences of premature estrogen deprivation that include coronary heart disease (CHD), osteoporosis, cognitive decline, and premature death.

III. MHT REGIMENS

Women with a prior hysterectomy are prescribed ET alone, whereas those with an intact uterus need a progestogen in addition for the prevention of endometrial hyperplasia and cancer. Women with a history of endometrial ablation also require a progestogen for endometrial protection.

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There is a variety of hormone formulations to choose from, and we recommend a shared decision-making approach between the patient and the provider after a detailed consideration of the patient's medical history and her preferences. The general principle is to use the lowest effective dose of ET, with upward titration for adequate symptom control.

The different forms of estrogens and progestogens are summarized in Table 74-2.

A. Estrogen preparations

Systemic ET is commonly administered via the oral or transdermal routes. Oral ET, the most extensively studied route of use, is convenient and reliably increases estrogen levels for most patients. However, unlike transdermal estrogen, it does have the first-pass hepatic metabolic effect leading to a dose-dependent increase in coagulation factors, triglycerides, and markers of inflammation. Therefore, a low-dose transdermal ET is preferable in women with an elevated risk of thromboembolic and cardiovascular disease. The latter include women with hypertension, dyslipidemia (hypertriglyceridemia), obesity, metabolic syndrome, and diabetes. The transdermal route is also preferable in women with gallbladder disease.

On the basis of our clinical experience, the transdermal route appears to be as effective as the oral route for the management of vasomotor symptoms in the majority of women, but there are no head-to-head randomized trials comparing clinical outcomes between the

two routes. A small proportion of women do not absorb well with the transdermal route and need to be changed to an oral preparation. Checking an estradiol level is helpful when the absorption of an estradiol preparation is in question. However, this is not feasible with **conjugated equine estrogens (CEE), which contain more than 200 compounds with variable estrogenic potency, the majority of which are not amenable to testing for levels in the blood**.

High-dose vaginal estrogen creams and rings can provide systemic estrogen levels that can help manage the vasomotor symptoms of menopause. These preparations have to be used with a progestogen in women with an intact uterus for the prevention of endometrial hyperplasia and cancer. This is in contrast to the low-dose vaginal ET used to manage vulvovaginal atrophy which does not require a simultaneous progestogen for endometrial protection.

TABLE 74-2 Commonly Used Menopausal Hormone Therapy

Preparation	Doses	Common product name(s)
Systemic Estrogens		
Oral Estrogens		
Conjugated equine estrogens	0.3, 0.45, 0.625, 0.9, 1.25 mg/d	Premarin
Micronized estradiol	0.5, 1.0, 2.0 mg/d	Estrace and others
Synthetic conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25 mg/d	Cenestin, Enjuvia
Transdermal Estrogens		
Estradiol patch	0.025–0.1 mg once or twice weekly depending on the product	Vivelle, Vivelle-Dot, Alora, Climara, Minivelle
	0.014 mg once/wk	Menostar (for osteoporosis)
Estradiol gel	0.25–1.5 mg once daily	Divigel, Estrogel
Estradiol spray	1.5 mg/d	Evamist
Vaginal Ring		
Estradiol acetate	0.05–0.1 mg/d for 90 d	Femring
Systemic Progestogens		
Oral Progestogens		

Oral progesterone		
Micronized progesterone	100–200 mg/d	Prometrium
Oral Progestins		
MPA	2.5, 5, 10 mg/d	Provera
Norethindrone	0.35 mg	Micronor
Norethindrone acetate	5 mg	Aygestin
Intrauterine System: Progestin		
Levonorgestrel	20 or 6 μg/d	Mirena, Skyla

B. Progestogens

Progestogens are a diverse group of progestational compounds that offer protection against endometrial hyperplasia and cancer in the context of ET use. Although the progestogens are essentially similar in their endometrial effects, their nonendometrial actions can be highly variable, conferring a diverse side-effect and safety profile.

The **most common route of progestogen delivery is oral**. The levonorgestrel containing intrauterine device, although not approved by the Food and Drug Administration (FDA) for this indication, can also be used for endometrial protection in premenopausal women (when contraception is needed), or in postmenopausal women who do not tolerate an oral progestogen. We generally recommend against transdermal use because of inconsistent absorption.

Oral progestogens include micronized progesterone (MP, bioidentical to natural progesterone), and synthetic progestins like medroxyprogesterone acetate (MPA) and norethindrone. On the basis of the current research, it appears that MP may have a better safety profile than that of synthetic progestins like MPA, in terms of breast cancer risk, and adverse metabolic effects including dysglycemia and dyslipidemia. We do not have any convincing data linking MP use to an increased risk of breast cancer. MP also improves sleeping difficulties in women. The levonorgestrel intrauterine device, designed to minimize systemic absorption of the progestogen, can, however, lead to increased blood levels, and one study has reported elevated breast cancer risk with its use.

The oral progestogens can be used in a sequential (12 to 14 days each cycle). This is given for the last 12 to 14 days in each 28-day cycle. It is continued as long as the patient is on estrogen or as a continuous regimen along with the estrogen. The sequential approach (estrogen continuously and progestogens for 12 to 14 days) may be preferable in younger perimenopausal or recently menopausal women in order to avoid breakthrough bleeding. Sequential progestogens are given in a higher dose, as they do a better job of preventing bleeding. We recommend the use of FDA-approved MHT formulations and not custom preparations from compounding pharmacies because of the lack of regulatory control.

IV. RISKS ASSOCIATED WITH MHT USE

A. CHD

MHT does not appear to increase the risk of CHD in women starting therapy before the age of 60, and ET alone may in fact be protective against CHD in these young women. However, MHT started, for the first time in women after the age of 60, or more than 10 years past menopause, may in fact increase their risk of CHD. A recent meta-analysis did not report any differences in CHD outcomes between oral and transdermal ET.

The effect of the extended use of MHT on CHD risk in women who start using it soon after menopause is unclear at this time.

B. Breast cancer

The risk of breast cancer with short-term (less than 5 years) ET alone appears to be small. However, observational studies do raise a concern regarding increased risk with extended use, in a dose-dependent fashion.

Studies using combined MHT (ET and progestogen) have more consistently demonstrated an increased risk of breast cancer. Progesterone seems to have a lower risk of breast cancer than MPA, but this needs confirmation in larger trials.

C. Stroke

Oral ET has been associated with increased stroke risk, although low-dose transdermal estrogen seems to be safe from that standpoint. However, there are no randomized controlled trials comparing stroke risk between different doses and routes of estrogen use. If MHT is considered for women with an increased stroke risk, we suggest the use of transdermal estradiol in doses ≤ 50 μg.

D. Venous thromboembolism (VTE)

Oral ET has been consistently shown to be associated with an increased risk of VTE. CEE may have an even higher risk than oral estradiol therapy. There are no randomized controlled trials evaluating this, but observational studies and meta-analyses have not found an increased risk with transdermal ET, even in women with obesity or thrombophilia. In terms of the VTE risk with progestogen use, it appears that MPA may be associated with a greater risk than progesterone. However, a recent meta-analysis did not find any difference in the VTE risk between ET and combined MHT.

V. MONITORING

We recommend a follow-up visit a few months after starting MHT to assess for treatment response, the need for dose adjustment, and side effects. Thereafter, these women should be seen on an annual basis to reassess the risk–benefit ratio of continued therapy, and decide about the need for continued treatment. They should also undergo appropriate breast cancer screening. Women experiencing persistent unscheduled vaginal bleeding should be evaluated with a pelvic ultrasound to rule out abnormalities like endometrial hyperplasia and cancer.

VI. STOPPING MHT

The decision about the timing of MHT discontinuation is an individualized one. There is no standardized algorithm for this. In general, the practice is to use the smallest possible dose that appropriately manages symptoms for the shortest duration of time. We **no longer advocate against the use of MHT beyond a certain age**. It is reasonable to use an extended MHT for women in whom the perceived benefits are greater p. 920p. 921than any potential risk. This is ultimately a shared decision made between the patient and the provider, and is driven by an individual patient's needs, preferences, treatment goals, and risk profile.

For patients who decide to stop MHT, there has to be a discussion regarding abrupt cessation versus gradual taper. Studies comparing the two approaches have not found any difference in outcomes. Therefore, this decision is driven by patient preference.

VII. CONCLUSION

The benefits of MHT clearly outweigh the small potential risk in symptomatic recently menopausal women, who are otherwise healthy, and have a low risk of cardiovascular disease and breast cancer. Withholding MHT from such women may impair their quality of life and increase their risk of conditions like CHD and osteoporosis.

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SECTION 11

Special Topics in Clinical Endocrinology

75

Endocrine Diseases in Pregnancy

Martin N. Montoro and Jorge H. Mestman

Endocrine diseases may complicate the maternal course of pregnancy as well as affect the growth and development of the fetus. A team approach to the management of these conditions with close cooperation among obstetricians, endocrinologists, and anesthesiologists will provide the best maternal and neonatal outcomes.

I. PITUITARY DISEASES

A. Pituitary changes in normal pregnancy.

1. **Gonadotrophs.** Their number decreases, resulting in lower, and even undetectable, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels as well as a decreased response to gonadotropin-releasing hormone (GnRH) because of feedback inhibition from elevated levels of placental 17-β-estradiol and progesterone.
2. **Thyrotrophs.** They remain unchanged in number and appearance, but thyroid-stimulating hormone (TSH) levels are low or suppressed in up to 20% of women in the first trimester, 4.5% in the second, and 1.2% in the third, caused by elevated levels of human chorionic gonadotropin (hCG) which are much higher in

early pregnancy.

3. **Somatotrophs:** They decrease in number, and the pituitary growth hormone (GH) levels are low. The reduction of pituitary GH secretion is in response to placental GH (GH-V) production from the 5th week of pregnancy, peaking at 35 to 37 weeks and clearing 30 minutes after the delivery of the placenta. Placental GH-V binds to hepatic GH receptors and stimulates insulin-like growth factor (IGF-1). It promotes placental and fetal growth.
4. **Corticotrophs:** Their numbers are unchanged, but the overall hypothalamic-pituitary-adrenal (HPA) axis activity is increased as evidenced by high free urinary cortisol as well as higher plasma levels of 17-hydroxysteroids, total and free cortisol, cortisol-binding globulin (CBG), resistance to cortisol action, and an increased set point for pituitary adrenocorticotropic hormone (ACTH). The circadian rhythm of both cortisol and ACTH is preserved, an important point when evaluating these patients because cortisol suppression to low-dose exogenous steroids may be incomplete and urinary levels of free cortisol may p. 923p. 924overlap with some cases of Cushing syndrome. The free cortisol levels increase from the 11th week through the third trimester and increase markedly during labor. The main stimulus for the increased HPA axis activity comes from placental corticotropin-releasing hormone (CRH), similar to hypothalamic CRH, which is important for fetal adrenal steroidogenesis, fetoplacental circulation, and the onset of labor. Placental CRH levels fall abruptly after placental delivery. Fetal protection from the increased maternal HPA axis activity is provided by placental 11 β-beta-hydroxysteroid-dehydrogenase (HSD) which disables active steroids.
5. **Lactotrophs:** Experience marked hyperplasia and hypertrophy mainly because of estrogen effect, with gradual involution postpartum which is slower in breastfeeding women. The increased pituitary volume starts in early pregnancy and peaks the first few weeks postpartum. It is primarily caused by lactotroph enlargement and does not have adverse clinical repercussions. Prolactin (PRL) levels also increase gradually, up to 10-fold, from a mean of 50

ng/mL at 12 weeks to 270 ng/mL at term (range 100 to 600 ng/mL). PRL levels normalize by 2 weeks after delivery but persist longer in breastfeeding women who experience rapid, transient elevations every time they breastfeed. The diurnal rhythm and response to thyrotropic-releasing hormone (TRH) are maintained, as well as responses to arginine, meals, and sleep (similar to nonpregnancy). The main role of PRL is the initiation and maintenance of lactation. Older studies suggested that PRL might also have a role to play in fetal lung maturation.

B. Disorders of the Anterior Pituitary Gland

Prolactinomas are the most common. Other lesions include injury from trauma, hypophysectomy or radiation therapy, and postpartum infarction (Sheehan syndrome). Less common lesions are intrapituitary hemorrhage, infiltration from granulomatous diseases, hemoglobinopathies (e.g., thalassemia), necrosis (in increased intracranial pressure), lymphocytic hypophysitis and, in some cases of type 1 diabetes, pituitary infarction may occur.

1. Pituitary Tumors

a. Prolactinomas are the most common tumors (40%) in women of childbearing age (prevalence 30 to 90/100 000 and peak incidence at 25 to 43 years of age) as well as the most common during pregnancy. The higher prevalence is due to improved diagnostic methods (PRL assays, computed tomography [CT], and magnetic resonance imaging [MRI]) rather than estrogen use. The diagnosis is suspected when PRL levels are high enough to cause oligoamenorrhea, galactorrhea, and infertility, usually when the tumor size is still <10 mm (microadenoma). Hyperprolactinemia suppresses LH secretion, response to GnRH, loss of positive estrogen feedback at mid-cycle, and direct ovarian suppression of estrogen and progesterone synthesis and secretion. A single measurement of serum PRL at any time of day, avoiding excessive venipuncture stress, is sufficient for diagnosis. In asymptomatic hyperprolactinemia, measuring macroprolactin levels is advised; in large tumors but only mildly elevated PRL, a serial dilution of samples is recommended.

In the most recent reports, the risk of tumor growth during pregnancy was 1.6% to 5.5% (2.7%) for microadenomas (<10 mm) and 23% for macroadenomas (≥10 mm). The growth risk

is lower, 4.8%, for prepregnancy, surgically treated macroprolactinomas even if residual tumor is still present. Results from one study suggested that treatment with **dopamine agonists** (DA) for 12 months or longer reduced the risk of subsequent enlargement during pregnancy. Recent reports of tumor size when MRIs are performed routinely during pregnancy show that tumor enlargement is far more common than clinical symptoms alone indicate. An MRI should be done before pregnancy to document tumor size, to determine whether it decreased with DA therapy, and to establish a baseline for comparison if an MRI is needed during pregnancy.

Medical therapy with DA is very effective in restoring ovulation in up to 90% of women and it is now the initial therapy of choice. Surgery is usually reserved for patients with large tumors threatening vision and those intolerant or resistant to DA. Some patients with microprolactinomas who p. 924p. 925prefer not to take long-term medication may choose transphenoidal surgery which is effective in 60% to 70% of cases. In general, DA therapy is needed only to induce ovulation and is stopped when pregnancy is confirmed. When pregnancy occurs in women with invasive macroprolactinomas with clinical symptoms (headache and/or visual disturbances) and active tumor growth, DA therapy throughout pregnancy is advised. At present, **cabergoline** (CAB) is considered to be more effective with lesser side effects than **bromocriptine** (BRC). **Quinagolide** has been associated with multiple complications and is **not considered safe for the fetus**.

Measuring PRL during gestation is not helpful and can be misleading because tumor growth may occur without any change in PRL levels and be falsely reassuring. Moreover, PRL levels may increase without tumor enlargement and set in motion unnecessary testing and needless concern.

Patients with microprolactinomas are counseled to stop DA therapy as soon as pregnancy is confirmed. Additional testing (visual field, MRI exams) during pregnancy is done only if symptoms suggestive of tumor enlargement appear (headaches,

visual disturbances). Patients with macroprolactinomas should be pretreated until the tumor becomes <1 cm before pregnancy is attempted, and DA therapy is stopped when pregnancy is diagnosed. Women who become pregnant with tumors still measuring ≥1 cm are generally advised to continue DA therapy during pregnancy, under close observation.

The number of pregnancy-desiring patients treated with BRC is around 6 000 to date, as against just over 900 such patients treated with CAB. BRC use throughout pregnancy has been reported in just over 100 cases and CAB use in only 15. Fortunately, **neither medication has been associated with congenital malformations or other adverse pregnancy** outcomes when compared with the general population. Long-term follow-up of the children exposed has not shown physical or mental developmental abnormalities. The Endocrine and the Pituitary Societies recommend BRC over CAB. However, it is now widely believed that as more cases accumulate, CAB will become the treatment of choice because of its higher efficacy and tolerability. The risk of CAB possibly causing cardiac valvular disease is now considered very low (0.17%), and cardiac evaluations are recommended only when there is a dosage use of >3 mg/week for longer than 5 years.

Attempting vaginal delivery is recommended in most cases. A team decision for the route of delivery is advised for actively enlarging tumors. Patients experiencing symptomatic tumor growth are generally treated with DA. If growth continues despite medical therapy and surgery might become necessary, delivery is recommended if the fetus is mature, rather than pituitary surgery in late pregnancy.

Breastfeeding is not contraindicated in mothers with prolactinomas and it does not generally cause tumor enlargement. Women with macroadenomas requiring postpartum therapy with DA will not be able to breastfeed. Long-term follow-up of all such patients is recommended.

The choice of treatment for patients who wish to conceive is summarized in Table 75-1.

b. Acromegaly (see Chapter 9). GH-secreting tumors are the **second most common** of the hormonally active pituitary tumors during pregnancy. Infertility is common due to

concurrent hyperprolactinemia (40%), the compression or destruction of gonadotrophs by direct mass tumor effect, and hyperandrogenemia caused by the ovarian effect of excess GH/IGF-1. The main treatment is surgical removal and sometimes radiotherapy. Medical therapy is becoming increasingly effective. The agents used include DA, somatostatin analogs ([SA] octreotide and lanreotide), and the GH receptor antagonist pegvisomant.

Acromegalic women with autonomous GH-secreting tumors have both forms of GH, placental and tumoral, during pregnancy. However, sensitive assays to distinguish the two are not yet widely available. Measuring IGF-1 levels for the purpose of diagnosis is not helpful during pregnancy.

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TABLE 75-1 Management of Women with Hyperprolactinemia before Conception

Tumor	Management	Pregnancy follow-up
No tumor	Bromocriptine or cabergoline	Clinical follow-up
Microadenoma	Bromocriptine[a]/cabergoline[a] or surgery	Visual field/MRI only if clinically indicated
Macroadenoma	Surgery + bromocriptine/cabergoline Bromocriptine/cabergoline until tumor <1 cm	Visual field each month vs. each trimester. MRI if clinically indicated

[a]Therapy for 1 year before conception?
MRI, magnetic resonance imaging.
Reprinted with permission from Mestman JH. Endocrine diseases in pregnancy. In: Sciarra JJ, ed. *Gynecology and Obstetrics.* Philadelphia, PA: Lippincott-Raven; 1997:chap 23:6.

The main concern in pregnancy is tumor enlargement. Other serious complications often develop, including impaired glucose tolerance in 30% or overt diabetes mellitus in 10% to 20%, hypertension in 25% to 35%, and also heart disease. Carpal tunnel syndrome may develop or worsen if previously present.

Current recommendations include stopping SA and/or DA therapy when pregnancy is confirmed in both micro- and

macroadenomas, but in high-risk macroadenomas maintaining medical therapy throughout pregnancy is advised. Periodic visual field testing and MRI scans as indicated are recommended. If tumor growth is detected, medical therapy is reinstated and if growth continues, transphenoidal surgery might be necessary. There are limited data regarding the use of SA during gestation, but in the few cases reported, no adverse effect on pregnancy or in fetal development was noted.

Breastfeeding is allowed in women with microadenomas, but in macroadenomas, there is concern about tumor growth if a prolonged period without treatment is allowed.

C. Diabetes insipidus (DI). This may result from central antidiuretic hormone (ADH) deficiency (central DI), renal tubular resistance to ADH (nephrogenic DI), or compulsive water drinking (psychogenic DI). During pregnancy, **vasopressinase levels produced by the placenta increase** markedly, resulting in accelerated ADH degradation. This may result in a transient form of DI developing during pregnancy, or may unmask mild DI and worsen preexisting DI. It occurs more often in the third trimester, particularly when liver dysfunction (preeclampsia, HELLP syndrome, fatty liver) occurs, which causes decreased degradation of placental vasopressinase. It resolves a few weeks after delivery. The water deprivation test is the standard procedure to establish the etiology of DI. Women with isolated DI antedating pregnancy and normal anterior pituitary function usually carry their pregnancies uneventfully if the DI is properly managed. Desmopressin (DDAVP) is the drug of choice. The nasal form has minimal effect on uterine contractility and there is almost no **passage into breast milk**. The usual dose is 10 to 25 μg once or twice a day. If the injectable form becomes necessary, the dosage is 2 to 4 μg subcutaneously every 12 to 24 hours. There is scant information about the oral (tablet) form of desmopressin in pregnancy, but it should also be safe.

DI during pregnancy may occur in other clinical settings as depicted in Table 75-2.

D. Anterior pituitary insufficiency. Infertility is usually associated with anterior pituitary insufficiency. Nevertheless, a number of pregnancies have been reported in women with hypopituitarism because of advances in infertility treatments. Pregnancy and birth rates have been reported to be 47% and 42% respectively.

TABLE 75-2 Clinical Presentations of Diabetes Insipidus in Pregnancy

1. Pregestational diabetes insipidus
2. Presenting for the first time in pregnancy and persisting thereafter
3. Transient, occurring during gestation, or in the immediate postpartum period, associated with preeclampsia, HELLP syndrome, and fatty liver
4. Transient, recurrent in pregnancy, patients with latent diabetes insipidus, manifesting only in pregnancy because of increased placental vasopressinase
5. Postpartum diabetes insipidus in patients with acute pituitary insufficiency, such as Sheehan syndrome or lymphocytic hypophysitis
6. An unusual transient form of diabetes insipidus that is resistant to both vasopressin and dDAVP administration.

dDAVP, desmopressin; HELLP, hemolysis, elevated liver enzyme levels, and low platelet count.

More favorable outcomes are also reported in women with isolated GH deficiency. **GH treatment results in increased ovarian sensitivity to endogenous gonadotropins**, although GH treatment does not seem to be effective in infertility from other causes. The treatment of these women once pregnancy is diagnosed has not yet been standardized. GH therapy (0.3 to 0.8 mg/day of recombinant human GH) has been reported to be safe. **GH treatment later in pregnancy (particularly after 20 weeks) might be unnecessary** because the placental GH is then thought to be sufficient to meet placental function and fetal growth needs. At present, either the GH treatment is stopped when pregnancy is confirmed or the prepregnancy dose is maintained through the first trimester with gradual tapering to a complete stop at the end of the second.

There is very scant information about pregnancy in women with isolated TSH or ACTH deficiencies, but outcomes should be favorable if adequate hormonal replacement is maintained. Women on glucocorticoid replacement therapy do not generally need a dose increase in pregnancy. The daily dose of hydrocortisone is between 20 and 30 mg, two thirds in the morning and one third in the evening. The equivalent amount of prednisone is 5.0 to 7.5 mg daily and of

dexamethasone is 0.5 to 0.75 mg daily. Mineralocorticoid replacement is not necessary in secondary adrenal insufficiency. In hypothyroidism, the prepregnancy dose of levothyroxine is generally increased by 25% to 30% when pregnancy is confirmed. If thyroxine therapy is started de novo during pregnancy, the initial dose should be 1.2 to 2.3 μg/kg/day; this amount should be adjusted to keep the free thyroxine index (FT4I) (the **free T4 used outside of pregnancy gives inaccurate results in pregnancy**) in the upper third of the normal range.

E. Sheehan syndrome or postpartum pituitary necrosis refers to partial or complete hypopituitarism typically occurring **after a delivery** complicated by severe blood loss and hypotension, although in a small (10%) number of cases, a history of bleeding or hypotension cannot be elicited. In some patients, acute adrenal insufficiency with hypotension, hypoglycemia, and shock are the presenting symptoms. Usually, a more insidious onset occurs, with anorexia, nausea, lethargy, weakness, weight loss, waxy skin (hypopigmentation from a lack of ACTH), fine skin wrinkling around the mouth and eyes (GH and estrogen deficiencies), postural hypotension, a lack of breast milk production as well as breast atrophy and a loss of libido later on, amenorrhea, and a loss of pubic and axillary hair or failure to regrow it if shaved before delivery.

Hormonal deficiencies following postpartum pituitary necrosis include PRL in 67% to 100% of cases, GH in 88%, LH/FSH in 58% to 75%, ACTH in 66%, TSH in 42% to 53%, and DI in 2% to 3%.

The diagnosis is suspected from a typical history (peripartum bleeding with hypotension or shock requiring fluid resuscitation and/or blood transfusion), and p. 927p. 928failure to lactate and to resume menses. Hormonal deficiencies compatible with partial or complete pituitary insufficiency and MRI or CT evidence of an empty or partially empty sella confirm the diagnosis.

Subsequent pregnancies can be successful (miscarriage 13%, 87% live births) if adequate hormonal replacement is instituted and maintained, including glucocorticoids, thyroxine, estrogen, progesterone, and GH depending on the number of hormonal deficiencies present.

The differential diagnosis includes spontaneous infarction of a pituitary tumor and lymphocytic hypophysitis. A possible role of autoimmunity in the pathogenesis of Sheehan syndrome has been

suggested.

F. Lymphocytic hypophysitis: This is an uncommon inflammatory disorder of the pituitary gland and the pituitary stalk. It is now being recognized with increasing frequency as a cause of sellar mass lesions and of partial or total hypopituitarism. It has an autoimmune pathogenesis and it is more commonly diagnosed **during pregnancy or in the postpartum period**, although it may occur in women of any age and in men. About 20% to 30% of these patients also have another autoimmune disorder, most frequently autoimmune thyroid disease, which provides a diagnostic clue. In the postpartum period, it may present as pituitary insufficiency resembling Sheehan syndrome but without the history of bleeding during or after labor, another diagnostic clue. Headache is the most common clinical presentation, either retroorbital or bitemporal, as well as visual disturbances, most often bitemporal hemianopsia, if there is compression of the optic chiasm. Other symptoms may include diplopia and orbital pain related to pressure from the expanding lesion mimicking a pituitary tumor. The symptoms and signs of acute hypopituitarism (mainly cortisol deficiency) include nausea, vomiting, hypotension, and hypoglycemia. Mild hyperprolactinemia, along with hormonal deficiencies (more commonly thyroid and adrenal) and DI, has been reported. MRI changes include ill-defined, symmetrical enlargement of the pituitary, often described as "pear-shaped," a thickened but nondeviated pituitary stalk, and isointensity with the brain gray matter on TI-weighted images. The dural tail sign on MRI (when gadolinium is administered) is considered to be more specific for hypophysitis.

A definitive differentiation from a pituitary tumor can be made only by a histologic examination. Initial therapy with glucocorticoids is recommended when the clinical diagnosis is strongly suspected, and there are no detectable visual field defects. Pituitary surgery is indicated for worsening neurologic symptoms, visual impairment, or other compressive signs.

II. PARATHYROID DISEASES

A. Calcium homeostasis during pregnancy. About 50% of the total serum calcium is bound to albumin. **This bound calcium decreases by 0.8 mg/dL for every 1 g/dL fall in the plasma albumin concentration** which is caused by hemodilution and starts in early pregnancy. However, the free (unbound), **ionized calcium**

remains unchanged throughout gestation and it is what should be measured. Maternal serum parathyroid hormone (PTH) levels are slightly decreased in early pregnancy and returns gradually to the mid-normal range by term. Despite lower PTH values, maternal 1, 25-dihydroxyvitamin D (1, 25-$(OH)_2$ D_3) levels increase because of the placental production of parathyroid hormone–related protein (**PTHrP**) (see Chapter 34). It may also be involved in embryogenesis, fetal differentiation and growth, the onset of labor, milk production, maternal–fetal calcium transfer, and the protection of the maternal skeleton. Higher 1, 25-$(OH)_2$ D_3 levels stimulate maternal intestinal calcium absorption. These changes provide the extra calcium required to meet the fetal needs (30 g total, most [80%] of it in the third trimester) instead of being extracted from the mother's skeleton.

Maternal calcium metabolism changes after delivery. The amount of calcium that goes into the milk of lactating women is 300 to 1 000 mg/day. Active vitamin D (1, 25-$(OH)_2$ D_3) and PTH levels have returned to normal and the extra calcium now required is mobilized from the maternal skeleton because of a combination of **high PTHrP from breast tissue** and reduced estrogen during lactation.

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B. Hyperparathyroidism: The true incidence in pregnancy remains unknown. The most frequent cause is a single parathyroid adenoma in 90% of cases, primary hyperplasia of the four parathyroid glands in 8% to 9%, and parathyroid carcinoma in 1% to 2%. Other causes are very rare and include hyperparathyroidism as a part of multiple endocrine neoplasia syndromes or secondary to renal insufficiency. Hypercalcemia of malignancy is extremely rare in reproductive-age women.

The diagnosis is made on the basis of elevated total and ionized calcium and a "normal" (but inappropriate) or elevated PTH level. Other findings include hypercalciuria, and low levels of phosphorus, magnesium, and bicarbonate but higher values of chloride and citrate. The chloride/phosphorus ratio is >30 in hyperparathyroidism and <30 in hypercalcemia of other causes. Presurgical adenoma localization in pregnancy is limited to ultrasound (69% sensitivity and 94% specificity) or MRI. CT with abdominal shielding should pose minimal risk to the fetus.

Hyperparathyroidism during pregnancy carries serious complications for mother and fetus. Maternal symptoms are present in almost 70% of cases and include nausea, vomiting, and anorexia in 36%; weakness, tiredness, and fatigue in 34%; and mental symptoms such as headaches, lethargy, agitation, emotional lability, confusion, and inappropriate behavior in 26%. Other complications include nephrolithiasis in 24% to 36%, bone disease in 13% to 19%, pancreatitis in 10% to 13% (the incidence in nonpregnant hyperparathyroid women is 1.5% and <1% in normal pregnancies), and hypertension in 10% to 25%. **Hypercalcemic crisis**, a very serious complication, has been reported during pregnancy and postpartum. It is characterized by severe nausea and vomiting, generalized weakness, changes in mental status, and severe dehydration. The serum calcium is usually >14 mg/dL; hypokalemia and elevated serum creatinine are routinely seen. If not recognized and treated promptly, uremia, coma, and even death may occur. Maternal death occurred in 30% and perinatal mortality in 40% of the reported cases.

1. **Fetal risks** include spontaneous abortion, fetal growth restriction, intrauterine death, prematurity, and particularly neonatal hypocalcemia, which can be severe and include tetany and death. **Neonatal hypocalcemia** develops between **days 2 and 14 after delivery** and is usually temporary but may persist for weeks, even months, depending on the severity of the maternal hypercalcemia. It resolves eventually, but there are reports of permanent occurrence. It is a consequence of chronic maternal hypercalcemia causing suppression of fetal PTH secretion.
2. **Surgery** is recommended for pregnant women with significant hyperparathyroid disease. The safest time to perform surgery during pregnancy is the second trimester. Surgery in the first trimester increases the risk of miscarriage and of premature labor in the third trimester. However, a number of successful parathyroid surgeries in the third trimester have been reported.

   For asymptomatic pregnant women and serum calcium <11 mg/dL, close follow-up with proper hydration and the avoidance of medications that could elevate calcium are reasonable approaches, although there are no studies supporting any nonsurgical approach. Nevertheless, all women with hyperparathyroidism should be offered surgery in the second trimester because at present the

risk/benefit ratio favors surgery. Medical therapy is reserved for those patients who are not surgical candidates or who refuse it. Maintaining adequate hydration is imperative. Oral phosphates, 1.5 to 2.5 g of inorganic phosphorus/day in divided doses, have been shown to be effective in controlling hypercalcemia in some patients (avoid in renal failure or hyperphosphatemia). Successful and safe use of **cinacalcet in pregnancy** has been reported in a few cases when surgery was not possible, but it is not generally recommended due to the potential effects on placenta and fetus.

C. Hypoparathyroidism. The most common cause is injury to the parathyroid glands during neck surgery. Infrequent causes include idiopathic hypoparathyroidism and some familial autoimmune disorders.

D. Pseudohypoparathyroidism is another rare hereditary disorder in which PTH is secreted, but bones and kidneys are resistant to its action.

Symptoms of hypocalcemia may develop acutely following neck surgery or develop more gradually and include perioral and acral paresthesias, facial twitching, p. 929p. 930muscle and carpopedal spasms, irritability, depression, and even psychosis. In more severe hypocalcemia, laryngeal spasms, convulsions, and even respiratory arrest may occur. Clinical exam reveals dry, scaly skin, coarse hair, and brittle nails. Positive Chvostek and Trousseau signs are elicited. A prolonged Q-T interval may be seen on the electrocardiogram. Most patients with pseudohypoparathyroidism also exhibit short stature, round face, brachydactyly, and soft tissue calcifications.

Laboratory testing reveals hypocalcemia and inappropriately “normal” PTH levels, but usually they are low or undetectable. Measuring serum magnesium, renal panel, and vitamin D (25-OH) as well as 1, 25-$(OH)_2$ D_3 levels is recommended in order to diagnose other disorders such as hypomagnesemia, chronic renal failure, vitamin D deficiency, rickets, and pseudohypoparathyroidism.

Frequent laboratory determinations (every 2 to 4 weeks) are warranted and more often if hyper or hypocalcemia develops. Pregnancy outcome will be favorable if the mother is kept normocalcemic. In chronically hypocalcemic mothers, complications

include second trimester miscarriage and premature labor. The **fetus will have parathyroid gland hyperplasia**, subperiosteal bone resorption, generalized skeletal demineralization, and even osteitis fibrosa. The perinatal mortality is very high, but the surviving newborns will recover after 4 to 7 months if they are properly treated.

The goal of treatment is to maintain the serum calcium in the normal range. The usual 1200 mg daily calcium supplementation in pregnancy should be maintained. Vitamin D in the form of calcitriol (1, 25-$(OH)_2$ D_3) at 0.5 to 3 μg/day is preferred because its shorter half-life and predictable bioavailability facilitate dose adjustments, especially if hypercalcemia develops.

Following delivery, the doses of calcium and calcitriol need to be reduced. During lactation, hypersensitivity to vitamin D develops as a result of the mammary epithelial cell production of **PTHrP** which stimulates endogenous calcitriol production. While breastfeeding, it is imperative to monitor calcium.

E. Osteoporosis. When spontaneous fractures occur, preexisting osteoporosis should be suspected. The vast majority of fractures (usually of the spine and rarely the hip) occur in women receiving long-term treatment with either unfractionated **heparin or corticosteroids**. Low-molecular-weight heparin poses very low osteoporotic risk. Osteoporosis is also a potential complication of chronic (>3 to 4 months) corticosteroid administration, but the risk associated with the short-term courses given for obstetric purposes (e.g., fetal lung maturation) is very low or is nonexistent. Calcium supplementation, calcitriol, and calcitonin have been used to treat pregnant women who developed fractures while on unfractionated heparin or steroids; however, there are no controlled trials to confirm their efficacy. **Biphosphonates** are **contraindicated** because they cross the placenta and may interfere with fetal skeletal development.

III. ADRENAL DISEASES

A. Cushing syndrome: Occurs infrequently during pregnancy because infertility from altered gonadotropin secretion in ACTH-producing pituitary tumors (Cushing disease) and elevated androgens in adrenal tumors are common. This is also the reason for the very different etiology of Cushing syndrome in pregnant and nonpregnant women. In pregnancy, Cushing disease accounts for only 30% of cases, whereas adrenal adenomas are 40% to 50% and carcinomas 10%.

The clinical course of Cushing syndrome, regardless of the etiology, is generally aggravated by pregnancy because of the **added effect of placental secretion of CRH**. The clinical diagnosis is complicated by the difficulty of distinguishing the symptoms of excess cortisol from the symptoms and signs of normal pregnancy. More specific for Cushing's are violaceous, hyperpigmented skin striae, easy bruising, mental changes, acne, hirsutism, proximal muscle weakness, and osteoporotic bone fractures (more often of the spine).

Levels of total (protein-bound) and free serum cortisol, as well as urinary free cortisol, may overlap with some cases of Cushing, particularly in the second and third trimesters. The response to the **overnight dexamethasone (1 mg) test is blunted and should not be used in pregnancy**. Fortunately, the diurnal variation p. 930p. 931of cortisol and ACTH is preserved in normal pregnancy, but it is lost in Cushing syndrome of any etiology and remains an important diagnostic clue. Patients with Cushing disease will show a loss of diurnal variation, elevated urinary free cortisol, a lack of suppression to the low-dose but suppression to the high-dose dexamethasone test, and "normal" (but inappropriate given the high cortisol) or elevated ACTH levels. In adrenal tumors, there will be no response to either the low or the high-dose dexamethasone test and the ACTH level will be low, but rarely undetectable as it is generally the case outside pregnancy. For confirmatory imaging, MRI is considered safer. **Gadolinium is probably safe, but its use remains controversial (**see Section I.B.1)

Only a few more than 140 cases have been published to date, with the majority being single case reports; maternal and perinatal morbidity and mortality are significantly elevated. Maternal complications include hypertension and preeclampsia in more than 70% of women, overt diabetes in 30%, infections, myopathy, hirsutism, acne, and emotional instability. **Congestive heart failure** is a particularly serious maternal complication and has been the reported cause of maternal death in 4% of cases of congestive heart failure occurring in the postpartum period. Fetal and neonatal complications include growth restriction (in >25% of cases), with the rest resulting from a very high rate (over 50%) of prematurity

including miscarriages, stillbirths, and neonatal deaths (>30%). Fetal adrenal suppression may occur, and the masculinization of female fetuses has been reported in cases of maternal adrenal carcinoma.

When treatment is successful and initiated before 20 weeks' gestation, the outcomes are significantly improved. Medical therapy will require using metyrapone or ketoconazole. **Metyrapone** has been associated with hypertension and preeclampsia and **ketoconazole** with growth restriction and antiandrogenic effects. A few reports of the successful use of these medications during pregnancy have been published, but **surgical intervention is more effective and is the preferred treatment**. Transsphenoidal pituitary surgery has been successfully performed to remove ACTH-secreting pituitary tumors. Adrenal surgery, using a laparoscopic approach, has also been successful in removing adrenal adenomas and carcinomas.

In the first two trimesters, adrenal surgery is indicated in the presence of an adrenal tumor, and if the MRI reveals a discrete pituitary lesion, transsphenoidal surgery may be attempted in specialized centers. When the source of the hypercorticolism cannot be determined, or if surgery is not feasible, drug therapy with metyrapone or ketoconazole may be considered.

B. Adrenal insufficiency (Addison disease). Primary adrenal insufficiency was reported to occur in 1 in 3 000 pregnancies in a Scandinavian population. The most common cause is the autoimmune destruction of the adrenal cortex. Tuberculosis is still a prevalent etiology in third-world countries. Pregnancy has been reported in a few women in whom the Addison disease was a part of the autoimmune polyglandular syndrome type 2 (Addison, type 1 diabetes, autoimmune thyroid disease). Other rare causes of adrenal destruction include fungal infections, hemorrhage, neoplastic metastases, and infarction.

C. Secondary adrenal insufficiency is more common than Addison disease, particularly impaired ACTH production resulting from chronic corticosteroid administration for a variety of disorders (e.g., asthma, systemic lupus erythematosus, rheumatoid arthritis, Crohn disease). Additional causes include pituitary tumors, other intracranial tumors (or the result of their treatment), Sheehan syndrome, or lymphocytic hypophysitis. Mineralocorticoid deficiency does not occur in secondary adrenal insufficiency.

In most cases, the diagnosis antedates gestation. The symptoms

are fatigue, dizziness, syncope, nausea, vomiting, weight loss, skin pigmentation, and lower Na concentrations. Hyperpigmentation in Addison's affects nonexposed skin, creases of hands, extensor surfaces, and mucous membranes. A **morning serum cortisol level of <3 μg/dL** in the setting of suspicious symptoms is considered diagnostic. A random serum cortisol ≥20 μg/dL would exclude adrenal insufficiency only in the first trimester, before significant changes take place because of pregnancy. In general, p. 931p. 932a serum cortisol >3 or ≤30 μg/dL warrants additional testing. At present, the ACTH stimulation test is the standard for the diagnosis of adrenal insufficiency. After injecting synthetic ACTH (cosyntropin) 250 μg IV, the serum cortisol 30 minutes later should be >20 μg/dL, and there also should be an increment of >8 μg/dL above the baseline value. (Both requirements must be met.) Salivary cortisol levels might become of more practical use in the future, but there are no standardized values at present. Detecting antiadrenal antibodies will provide additional evidence. A part of the diagnostic investigation in primary Addison disease should include measurements of renin and aldosterone. Patients with severe symptoms or adrenal crisis should be treated immediately and not made to wait until all the diagnostic tests are available.

Since the advent of steroids for clinical use, women with **Addison disease have shown very few complications during pregnancy** when properly managed. Hydrocortisone is preferred during pregnancy because the object of treatment is the mother. The usual dose is 12 to 15 mg/m^2, or 20 to 30 mg/day total; two thirds are given in the morning and one third in the late afternoon (generally with breakfast and dinner). The prepregnancy replacement dose does not, generally, need to be modified (see Section I.D). Patients with primary Addison disease also require mineralocorticoid supplementation; fludocortisone 0.1 mg/day by mouth is the usual dose and does not require modification during pregnancy. Symptoms suggesting insufficient mineralocorticoid replacement include light-headedness, salt craving, and lower extremity edema; electrolyte levels should be monitored when such symptoms occur. The physical examination should include checking for postural blood pressure

changes. For normal labor, hydrocortisone 50 mg IV is given during the second stage and additional doses every 8 to 12 hours if complications arise, with rapid tapering to maintenance doses postpartum. For cesarean sections, 100 mg IV is given at the onset of surgery and every 8 hours for the next 24 hours, with gradual tapering to maintenance over the following 48 hours in uncomplicated cases. **Breastfeeding is safe** and should be encouraged because there is minimal excretion into breastmilk at maintenance dosages.

Neonatal adrenal insufficiency is very rare in infants of mothers receiving corticosteroid therapy.

D. Congenital adrenal hyperplasia (CAH) (see Chapter 22). This includes a group of hereditary autosomal recessive disorders with defective steroidogenesis resulting in elevated adrenal hormones (androgens, 17-hydroxyprogesterone) and deficient final products (cortisol). The most common is 21-hydroxylase deficiency, which accounts for 95% of all CAH cases. Seventy-five percent of these have the salt-wasting form and the rest the simple-virilizing type. This CAH type is designated as classical CAH, and it occurs in 1 in 13 000 to 15 000 live births. The nonclassical form of 21-hydroxylase deficiency is reported to be much more frequent than the classical, particularly in some ethnic groups. It is associated with only mild to moderate enzyme deficiencies, lacks virilized genitalia, and is more often diagnosed later in life while investigating hyperandrogenemia and/or infertility. Other forms of CAH are very rare and include deficiencies of 11-β-hydroxylase, 3-β-hydroxysteroid dehydrogenase, 17-α hydroxylase, congenital lipoid adrenal hyperplasia, and cytochrome P450 oxidoreductase.

1. **The main cause of reduced fertility is anovulation** resulting from excessive adrenal androgen production. Women with classic CAH report lower sexual activity. Newer surgical techniques, which include nerve sparing, show improved results. Fertility in untreated classic CAH is very low. Steroid therapy will be required in order to ovulate, and women with the salt-wasting type will need mineralocorticoid replacement as well. Women with the nonclassic form will also benefit from steroid treatment to improve their fertility, but spontaneous pregnancy rates have been reported to occur in up to 60% of this group.
2. **The goal of therapy** is to correct the cortisol deficiency and suppress the excessive ACTH secretion which causes adrenal

androgen overproduction. Hydrocortisone, 12 to 15 mg/m^2/day in divided doses, with the higher dose given at bedtime, is preferred during pregnancy. For labor and delivery, stress doses should be given as in women with adrenal insufficiency (see Section III.B).

Women with prior p. 932p. 933genital reconstructive surgery may require cesarean delivery, although some vaginal deliveries have been reported.

3. **Dexamethasone** crosses the placenta freely and its use in early pregnancy to **prevent virilization of a potentially affected female fetus** is currently highly controversial. In order to be effective, dexamethasone has to be administered prior to the time that the fetus is able to synthesize adrenal androgens (<**9 weeks**). At this gestational age, it is not currently possible to easily find out the sex of the fetus, and if it is a female, whether or not it might be affected. Proponents of this approach administer 20 μg/kg (prepregnancy weight)/day in three divided doses for all at risk pregnancies until the time when the fetal gender (by karyotype) or the presence of a genetically affected female (by DNA analysis) can be established. At present, prenatal diagnosis is made by amniocentesis or by direct molecular analysis of the 21-hydroxylase (CYP21) gene obtained by chorionic villus sampling. If the fetus is a male or an unaffected female, dexamethasone is stopped. It is continued until delivery only if an affected female is identified. Critics of this approach state that it requires invasive procedures that carry potential risks, as well as unnecessary dexamethasone administration to 7 out of 8 potentially at-risk pregnancies for a number of weeks. Prenatal dexamethasone may have long-term unfavorable effects on fetal brain development.

   The ability to harvest fetal DNA from the maternal blood will hopefully provide a noninvasive technique to diagnose fetuses at risk of CAH and thus prevent unnecessary treatment.

E. Primary hyperaldosteronism. Primary hyperaldosteronism has been very infrequently (30 cases only) reported during pregnancy and the cause has almost always been a single adrenal adenoma. The complications commonly reported include hypertension in 85%, hypokalemia 55%, and proteinuria in 52%, as well as placental abruption and premature deliveries. Hypokalemia is frequently less

severe during pregnancy because the high levels of progesterone in pregnancy have an antialdosterone effect that disappears quickly after delivery when the hypokalemia becomes much worse. Symptoms include headaches, malaise, and muscle cramps. The diagnosis is usually suspected in the presence of arterial hypertension and persistent hypokalemia. Serum bicarbonate in most patients will be in the upper limit of normal, in contrast to the below-normal levels seen in uncomplicated pregnancies. Aldosterone levels are elevated but sometimes may overlap with those of normal pregnancy. However, in hyperaldosteronism, the renin activity is suppressed. Salt-loading testing is used to confirm the biochemical diagnosis in nonpregnant patients, but there are no standardized parameters for pregnancy and, in addition, it is considered risky for the fetus. MRI is safe and effective for localizing adrenal lesions. When the diagnosis remains equivocal, medical treatment is recommended and further diagnostic investigations are postponed until after delivery. It is often advised to delay surgery (laparoscopic approach preferred) until after delivery if the hypertension and hypokalemia can be successfully controlled. Surgery is safer when performed in the second trimester. **Spironolactone** is the treatment of choice outside pregnancy, but it is **contraindicated during gestation** because it crosses the placenta freely and will exert an antiandrogen effect in the fetus. **Epleronone**, an aldosterone receptor antagonist, could be effective, but there is no information yet about its safety in human pregnancy. Besides potassium administration, a number of antihypertensive agents have been used in pregnancy, including amiloride, labetalol, calcium channel blockers, and methyldopa.

F. Pheochromocytoma (see Chapter 18). Pheochromocytoma occurs infrequently (1 in 54 000 pregnancies), but when present, it creates a life-threatening situation for both mother and fetus. Maternal and fetal mortality is reported in 50% or more of previously undiagnosed pheochromocytomas, more often during labor or at induction of anesthesia in cases of cesarean deliveries. As pregnancy progresses, the enlarging uterus is likely to press on the tumor, trigger severe hypertension and the possibility of myocardial infarction, arrhythmias, congestive heart failure, cerebrovascular hemorrhage, and even hemodynamic vascular collapse. Extraadrenal tumors (about 10% of all pheochromocytomas) are frequently located in the aortic p.

bifurcation and very prone to set off hypertensive crises after postural changes, uterine contractions, fetal movements, and Valsalva maneuvers. The **fetus is not directly affected by catecholamines** because they are inactivated by placental catechol-O-methyltransferase and monoamine oxidase. Fetal injury results from hypoxia caused by catecholamine-induced vasoconstriction leading to uteroplacental insufficiency, which is further aggravated by the severe maternal hypertension. Placental abruption is also a common complication.

1. **Preconception screening** for pheochromocytoma is recommended in known patients with Multiple Endocrine Neoplasia (MEN) type 2, von Hippel-Lindau disease, and neurofibromatosis. The diagnosis of pheochromocytoma requires a high index of suspicion which should arise in the presence of severe sustained or paroxysmal hypertension, particularly in early or mid-pregnancy. Other clinical clues include diaphoresis, palpitations, anxiety, pallor, headaches, and chest pain; also, blood pressure aggravation with β-blockers. The laboratory diagnosis does not differ from outside of pregnancy. Twenty-four-hour urinary levels of metanephrines, normetanephrines, and catecholamines (dopamine, epinephrine, and norepinephrine) will be very elevated. Methyldopa and β-blockers should be stopped prior to the urinary collection because they may interfere with the quantification of catecholamines and vanillylmandelic acid. Provocative diagnostic tests are not recommended during pregnancy because they may trigger a hypertensive crisis. For imaging, MRI with high-intensity signals on T2-weighted images is preferred. Positron emission tomography should be postponed until after delivery.

   Pheochromocytomas are frequently mistaken for pregnancy-induced hypertension and preeclampsia, particularly in the presence of proteinuria. Some catecholamine elevation may be found in PIH/preeclampsia (pregnancy-induced hypertension) especially after an eclamptic seizure, but not in the pheochromocytoma range.
2. **Treatment.** An alphaadrenergic blocking agent should be started as soon as the diagnosis is confirmed. The preferred agent is phenoxybenzamine. The starting dose is 10 mg once or twice daily

and it is titrated upward by 10 mg every 2 to 3 days until blood pressure and symptoms are controlled. If the BP remains uncontrolled despite maximum doses, metyrosine (reduces catecholamine synthesis) has been used, but its effects on the fetus are unknown. Beta-blockers (propanolol preferred) are used only if maternal tachycardia and/or arrhythmias persist after achieving full α blockade. **If β-blockers are given before complete α blockade, a hypertensive crisis will occur.**

Hypertensive emergencies are treated with IV phentolamine 1 to 5 mg. Nitroprusside can be used only for very brief periods; otherwise fetal cyanide toxicity will occur.

Surgical removal is the treatment of choice and the second trimester is the safest time to perform it. In the first trimester, there is risk of spontaneous abortion (already high in pheochromocytoma) and of premature delivery in late pregnancy. Surgery should never be attempted without first achieving full α blockade, ideally, for the prior 10 to 14 days. Indicators of acceptable control include a blood pressure <165/90 mm Hg; if orthostatic changes are present, the standing blood pressure must be >90/45 mm Hg. There should be no electrocardiogram changes (ST-segment or T-wave abnormalities) and few or no premature ventricular contractions.

If medical therapy is successful, surgery can be delayed until a safer and more favorable time. Cesarean delivery, once the fetus is mature, followed by tumor removal is more often reported. Successful cases of tumor removal by laparoscopic approach have also been published. Vaginal delivery is considered riskier in general (catecholamine release from tumor compression and pain during labor). There is no information about the safety of phenoxybenzamine while breastfeeding.

IV. VIRILIZATION. When hirsutism and virilization occur during pregnancy, the cause is almost always a gestational hyperandrogenic condition. The most common are p. 934p. 935pregnancy **luteomas** and **hyperreactio luteinalis**. Malignant ovarian tumors are fortunately rare in pregnancy (≤5% of persistent ovarian masses). Luteomas are benign, hCG-dependent ovarian tumors developing during pregnancy and usually resolve spontaneously after delivery. A third of luteomas will be

hormonally active, leading to hirsutism and virilization in 25% to 35% of women with these tumors. Hyperreactio luteinalis occurs in pregnancies with very high hCG levels (e.g., twins). It usually arises in the third trimester and causes maternal virilization in 1/3 of the cases. Symptoms generally appear rapidly. Some protection in pregnancy is provided by high sex hormone–binding globulin (SHBG), placental aromatase, and high progesterone levels. When androgenization appears in pregnancy, a complete investigation is warranted because of the possibility, albeit small, of a malignant lesion as the cause of the excess androgen production (Table 75-3). A medical history will reveal medications that could cause hirsutism, the time when symptoms and signs began, a similar history in previous pregnancies, the degree of virilization, and the presence of systemic symptoms. Virilization of the newborn is not always dependent on the concentration of maternal androgens because some fetal protection is provided, in part, by placental aromatase (converts androgens to estrogens) and partly by SHBG. Nevertheless, there is a significant risk of virilization of female fetuses if the maternal hyperandrogenic condition is severe. No fetal virilization has yet been reported in hyperreactio luteinalis.

V. THYROID DISEASES

Thyroid diseases are very common in women (9 to 1 women vs. men) during their reproductive years and, therefore, very common in pregnancy. The course of thyroid diseases may be influenced by pregnancy and, in turn, the progression and outcome of pregnancy may be altered by thyroid disorders. Untreated thyroid diseases may cause serious risks to mother and fetus. In addition, therapy must be carefully managed to avoid further complications. A team approach to the care of these women will offer the best prognosis for a favorable outcome (Fig. 75-1).

TABLE 75-3 Causes of Fetal and Maternal Virilization in Pregnancy

Drugs
Dilantin
Danazol[a]
Progesterone
Stilbestrol[a] (large doses)
Ovarian lesions
Arrhenoblastomas[a]

Luteoma of pregnancy[a]
Krukenberg tumor[a]
Mucinous cystadenomas
Leydig cell tumor
Lipoid cell tumor
Granulosa—theca cell tumor
Dermoid cysts
Hyperreactio luteinalis
Polycystic ovarian syndrome

Adrenal lesions
Virilizing adenoma[a]
Virilizing carcinoma[a]
Aldosterone-producing tumor

[a]Lesions and drugs that produce fetal virilization.
Reprinted with permission from Mestman JH. Endocrine diseases in pregnancy. In: Sciarra JJ, ed. *Gynecology and Obstetrics*. Philadelphia, PA: Lippincott-Raven; 1997:chap 23:25.

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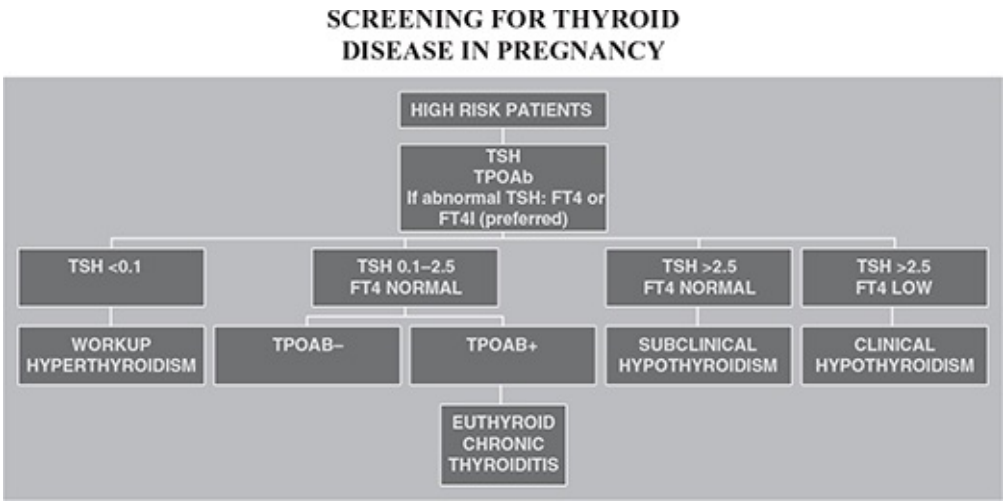

Figure 75-1. Algorithm for the diagnosis of thyroid disease. FT4, free thyroxine; FT4I, free thyroxine index; TPOAb, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

A. Thyroid function. Higher demand for thyroid hormones starts in early pregnancy. Both thyroxine (T4) and triiodothyronine (T3) are metabolized to inactive compounds faster than outside pregnancy. There is also increased thyroid hormone transport across the placenta. High circulating levels of estrogen stimulate the hepatic production (and also slow its metabolism) of thyroid-binding globulin (TBG), the

main thyroid hormone carrier protein. Total T4 (TT4) and total T3 (TT3) levels increase to approximately 50% above the nonpregnant upper reference range. Normal pregnancy levels of TT4 and TT3 are calculated by multiplying the nonpregnancy values by 1.5. The normal thyroid gland is able to compensate by increasing thyroid hormone secretion.

1. **Free thyroxine**. Free thyroxine measured by direct immunoassay is the preferred test outside of pregnancy. However, because of the high TBG and lower albumin levels in pregnancy, this method is inaccurate. When measured by equilibrium dialysis, free thyroxine levels remain normal; there are some fluctuations, with higher values in the first trimester not exceeding the normal range. The free thyroxine index (FT4I) provides a more reliable estimate of true free thyroxine levels. TT4 and FT4I measurements are preferred because free thyroxine determinations by equilibrium dialysis are not widely available.
2. **TSH** measurements are widely used for screening, diagnosing, and monitoring the therapy of most thyroid disorders. **TSH levels decrease in early pregnancy** when human chorionic gonadotropin (hCG) concentrations are highest (10 to 12 weeks) because hCG has a weak stimulating effect on TSH receptors. TSH may decrease to below nonpregnant levels in up to 20% of normal pregnant women in the first trimester. Subsequently, it increases gradually through the second and third trimesters. The most widely accepted trimester-specific TSH values are: first trimester: 0.1 to 2.5 μIU/L, second: 0.2 to 3.0 μIU/L, and third: 0.3 to 3.0 μIU/L.

   When there is very **high production of hCG**, such as in pregnancies with multiple fetuses, hydatidiform mole, or hyperemesis gravidarum (HG), **the TSH will be suppressed** and **the TT4 and FT4 concentrations elevated** to values that may overlap with those seen in thyrotoxicosis. The differentiation from Graves hyperthyroidism may be difficult. **Transient gestational hyperthyroidism** usually occurs in the first trimester (seldom persisting >20 weeks) and is self-limited. The thyroid gland is not enlarged, extrathyroidal signs of Graves disease (eye or skin involvement) are absent, and TSH-receptor antibodies (TSHRAb) are not detected. Hyperemesis or multiple pregnancies will also be apparent. Most cases of Graves are known before pregnancy (Table 75-4).

TABLE 75-4 Etiology of Hyperthyroidism in Pregnancy

Intrinsic Thyroid Disease
Graves disease
Toxic nodular goiter (single or multinodular)
Painless thyroiditis (autoimmune etiology)
Initial hyperthyroid phase of chronic autoimmune (Hashimoto) thyroiditis
Subacute thyroiditis (viral infection)
Acute thyroiditis (bacterial infection)
Thyroid Hormone of Extrathyroidal Origin
Iatrogenic hyperthyroidism (overtreatment with thyroid hormone)
Factitious levothyroxine intake (self-induced overtreatment)
Struma ovarii
Functional metastatic thyroid cancer
Gestational Thyrotoxicosis
Normal pregnancy (up to 15% to 20% of pregnancies)
Multiple gestation
Hyperemesis gravidarum (transient hyperthyroidism of hyperemesis gravidarum)
Trophoblastic disease
TSH-receptor mutation (becomes oversensitive to hCG: "familial gestational hyperthyroidism")
TSH-secreting pituitary tumors (very rare).

hCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone.

3. **Thyroid size**. The size of the thyroid gland increases, sometimes greatly, in areas of iodine deficiency.
4. **Iodine requirements**. Higher iodine amounts are needed to offset the increased thyroid hormone synthesis during pregnancy and lactation, and the increased urinary losses from a higher renal glomerular filtration rate during pregnancy, and to meet the increased fetal iodine requirements during pregnancy. **A daily intake of 250 *μ*g/day is recommended.** It is important to make sure that the prenatal multivitamins prescribed contain iodine (potassium iodide preferred, 150 to 250 μg) because only half of the prenatal vitamin preparations currently available in the United States contain iodine.

B. Prepregnancy counseling

1. **Hyperthyroidism under drug treatment.** In order to avoid

any exposure to antithyroid medications during pregnancy, a definitive **treatment of the hyperthyroidism, preferably >6 months prior to attempting pregnancy**, should be strongly considered. If the patient still decides to conceive while taking antithyroid medications, propylthiouracil **(PTU) is the drug of choice during the first trimester because methimazole (MMI) has been linked to specific congenital malformations**.

2. **Previous treatment of Graves disease with radioactive iodine.** It is recommended to **wait at least 6 months following radioiodine ablation before attempting pregnancy**. Hypothyroidism usually results and thyroxine replacement becomes necessary. However, high maternal TSHRAb titers may persist after radioiodine ablation. Women with this condition should be made aware that the fetus might develop hyperthyroidism if the TSHRAb is still very elevated (≥threefold above baseline) and despite themselves being asymptomatic on thyroxine replacement.
3. **Previous treatment of thyroid carcinoma with radioactive iodine.** Most reports have shown that pregnancy does not alter the natural history of differentiated thyroid cancer. Therefore, women previously treated can be reassured that **pregnancy will not increase thyroid cancer–related death** or overall p. 937p. 938survival. It is recommended to **wait 1 year after treatment before conception** because the radioiodine doses are much higher than those given for hyperthyroidism. A recent report suggested that thyroid cancers that are first diagnosed during or shortly after pregnancy might be more aggressive and require closer scrutiny than those that are not.
4. **Treated hypothyroidism.** Most women on thyroid hormone replacement will require higher dosages soon after conception. Postpartum, the prepregnancy dosage is resumed (See Section V.D.1).
5. **Euthyroid chronic thyroiditis.** Elevated Thyroid Peroxidase (TPO) antibodies are found in a high percentage (5% to 15%) of pregnant women, with the majority being clinically and biochemically euthyroid. An **increased risk of miscarriage**

and of preterm delivery has been reported, and also that these **complications could be reduced with thyroxine therapy**. One study reported that 57 TPO-positive euthyroid pregnant women treated with thyroxine had a significantly lower number of miscarriages and premature deliveries than 57 also TPO-positive and euthyroid women who were not treated. **However**, the American Thyroid Association, the Endocrine Society, and the American College of Obstetrics and Gynecology **do not currently recommend treating TPO-positive antibody euthyroid women** during pregnancy on the basis of the findings of only one small study.

C. Hyperthyroidism. Hyperthyroidism is diagnosed in **0.5% to 1.3% of pregnancies** and Graves disease accounts for ≥85% of cases. Other etiologies occur infrequently. (See the complete list of etiologies on Table 75-4). However, transient hyperthyroidism (gestational thyrotoxicosis) occurs very frequently and might be difficult to differentiate from Graves hyperthyroidism (Table 75-5).

1. **Transient hyperthyroidism of hyperemesis gravidarum (THHG). Hyperemesis occurs in up to 10% of all pregnancies.** THHG is characterized by severe nausea and vomiting starting between 4 and 8 weeks, ≥5% loss of body weight, ketosis and dehydration; abnormal liver function tests and hypokalemia also occur in more severe cases. Abnormal thyroid function tests, low or undetectable TSH, and elevated T4 are all found in 60% to 65% of women with hyperemesis gravidarum. Free thyroxine levels may also be elevated, sometimes considerably. However, T3 is elevated in only 12% of these women, which is a helpful diagnostic clue. **The T3/T4 ratio will be <20 in THHG, whereas in Graves hyperthyroidism it is usually >20.** Despite the significant biochemical hyperthyroidism, the signs and symptoms of hypermetabolism are mild or absent. Some patients may complain of mild palpitations and some heat intolerance, but more severe p. 938p. 939symptoms such as perspiration, proximal muscle weakness, severe anxiety, or frequent bowel movements are rare. THHG patients will have a negative personal and family history of thyroid

disease, no goiter, and **negative antibodies** (TPO and TSHRAb). T3 is infrequently elevated and when it is, the T3/T4 ratio will still be <20. Color flow Doppler thyroid sonography may be a useful adjuvant to the laboratory studies when differentiating Graves from non-Graves thyrotoxicosis. In Graves, there is diffuse thyroidal enlargement with homogeneous ecogenicity, absent nodularity, increased vascularity, and high arterial blood flow velocity. **Most cases of THHG resolve spontaneously**, more often **between 15 and 20 weeks**. However, the TSH may remain suppressed for several weeks after thyroxine normalization (Fig. 75-2). **Antithyroid medication is not indicated**; furthermore, because of the severity of the vomiting, antithyroid drug therapy is poorly tolerated.

TABLE 75-5 Screening for Thyroid Disease in Pregnancy

1. Personal or family history of thyroid disease
2. Previous thyroid surgery or radioiodine for hyperthyroidism or cancer
3. Symptoms and signs of thyroid disease (i.e., a palpable goiter)
4. Elevated TPOAb and/or history of postpartum thyroiditis
5. Type 1 diabetes mellitus
6. Autoimmune disorders (lupus erythematosus, rheumatoid arthritis) (Addison disease and any other endocrinopathy)
7. History of postpartum depression
8. History of miscarriage(s) and/or preterm delivery
9. Previous neck radiation
10. Previous birth of a child with intellectual impairment
11. Infertility
12. Suspected hypopituitarism

TPOAb, thyroid peroxidase antibodies.

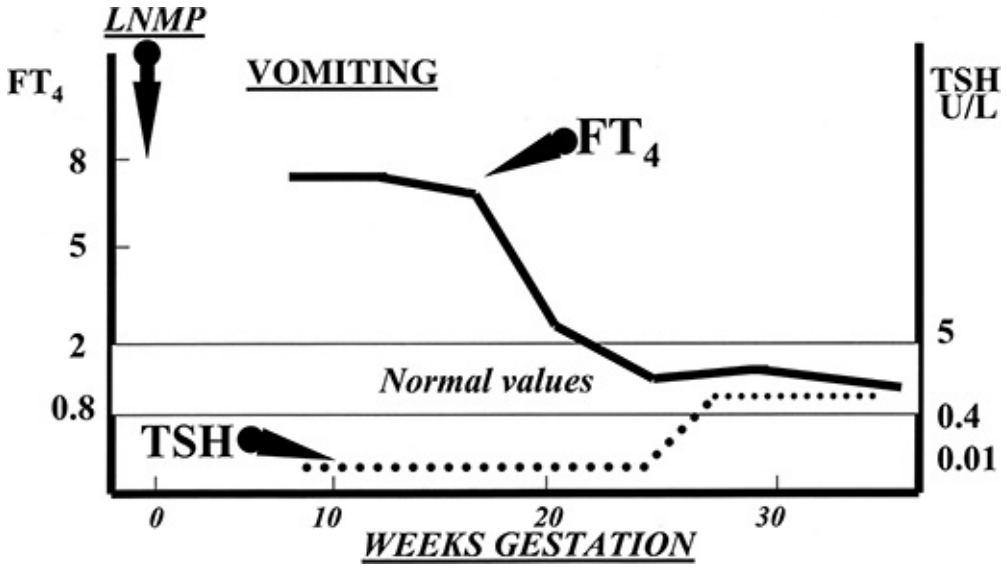

Figure 75-2. Clinical course of transient hyperthyroidism of hyperemesis gravidarum (THHG). FT4, free thyroxine; LNMP, last normal menstrual period; TSH, thyroid-stimulating hormone.

2. **Graves disease** tends to worsen in the first trimester and after delivery but usually improves in the second half of pregnancy.

   When Graves hyperthyroidism is properly managed, the prognosis for mother and fetus is good (Table 75-6).

   Graves disease antedates pregnancy in the vast majority of patients. The clinical diagnosis of thyrotoxicosis may be difficult because some symptoms and signs are also common in normal pregnancy, such as palpitations, rapid heart rate (seldom >100 per minute), mild heat intolerance, shortness of breath, and

p. 939p. 940warm skin. Findings favoring the diagnosis of Graves hyperthyroidism are the following: a diffuse goiter, ophthalmopathy, proximal muscle weakness, severe anxiety, tachycardia (>100 per minute), weight loss or inability to gain weight despite good appetite, and a positive family history. In addition, the symptoms are likely to have been present before pregnancy. Laboratory findings more compatible with Graves hyperthyroidism include **higher levels of TT4, free T4 and particularly T3, as noted above, as well as the presence of thyroid antibodies, TPO but mainly TSHRAb.** The presence of TSHRAb will help not only in the differential diagnosis, but also in assessing the risk of fetal/neonatal hyperthyroidism.

TABLE 75-6 Maternal and Fetal Complications of Hyperthyroidism

Maternal	Fetal
Miscarriage	Low birth weight
Preeclampsia	Prematurity
Placental abruption	Fetal death/Stillbirth
Congestive heart failure	Hyperthyroidism (fetal and neonatal)
Thyroid storm	Hypothyroidism (inappropriate antithyroid drug therapy)

a. Treatment goals include achieving thyroid hormone normalization. Close attention should be paid to avoid iatrogenic hypothyroidism. Initially, the thyroid function tests should be performed every 2 weeks, and every 2 to 4 weeks once euthyroidism is achieved. The antithyroid drugs more widely used are PTU and MMI. Both PTU and MMI are effective in the treatment of hyperthyroidism, and euthyroidism is achieved with equivalent amounts of either drug and in the same period of time. Their main mechanism of action is to reduce thyroid hormone synthesis, but PTU has the additional property of reducing the peripheral conversion of T4 to T3, which makes PTU the drug of choice in the treatment of thyroid storm.

Minor adverse reactions to antithyroid medications occur in 5% to 10% of cases and include itching, rash, fever, and gastrointestinal upset. Major complications are less common (0.3% to 0.5%) and include vasculitis, agranulocytosis, and hepatotoxicity. The potential liver damage from MMI is cholestasis, but it is not considered life-threatening, as opposed to the injury from PTU which is hepatocellular necrosis and acute liver failure, which could be either fatal or require liver transplantation. **In pregnancy, PTU is now recommended only during the first trimester, and once embryogenesis has been completed, the treatment is switched to MMI.**

Methimazole is avoided during the first trimester because it has been associated with some specific birth defects now labeled “methimazole embryopathy”: **aplasia cutis, choanal atresia** (failure of the nasal passages to develop), **tracheaesophageal fistula, omphalocele,**

hypothelia/athelia (failure of nipples to develop), **developmental delay and some peculiar facial features** (upward slanting of palpebral fissures, small nose with wide nasal bridge, and arched eyebrows). No malformations have been reported with PTU until recently, although these have been both minor and infrequent.

The initial dose of PTU is 100 to 300 mg daily in divided doses every 6 to 8 hours, and of methimazole 5 to 30 mg daily which could be given as a single dose, greatly improving compliance. Higher doses of either are rarely needed. In patients with mild symptoms, an initial daily MMI dose of 5 to 10 mg or PTU 50 mg two or three times a day may be sufficient. In most patients, clinical and laboratory improvement is seen in 2 to 4 weeks. Once clinical improvement occurs, the dose of antithyroid medication may be reduced by half in most patients. Further adjustments are made according to the clinical response and thyroid hormone levels, with the goal of maintaining euthyroidism with the minimal effective dose (see above).

b. **Antithyroid medication can be stopped successfully in up to 35% of patients by the mid to late third trimester and thus avoid fetal exposure before delivery.** If there is an exacerbation of symptoms or worsening of the thyroid tests, antithyroid medication is resumed or readjusted upward. The serum TSH may remain suppressed long after TT4 and FT4 concentrations normalized, which could last the remainder of the pregnancy. Fetal goiter may be detected by ultrasonography.

c. **Other treatments.** *β*-adrenergic-blocking agents improve hyperdynamic symptoms very effectively and are used on a temporary basis, until the hyperthyroidism improves. In very symptomatic patients, **propranolol** 20 to 40 mg every 6 to 8 hours is more frequently prescribed, but **metoprolol** 100 mg once p. 940p. 941or twice daily is also effective. **IV labetalol** (which also has some *α*-blocking properties) given at 2 mg/minute has been reported to successfully control maternal and fetal tachycardia in cases of severe hyperthyroidism during labor.

Selenium might enhance the effectiveness of antithyroid

medications and/or reduce thyroid autoimmunity, but there are no studies showing a beneficial role in thyroid disorders during pregnancy.

d. **Surgery** is rarely needed during pregnancy. Indications include allergy to both MMI and PTU, a lack of response to even very high doses (over 40 to 60 mg/day of MMI or 800 to 1 200 mg/day of PTU), poor adherence to treatment, or severe neck compression from a very large goiter. If indicated, surgery should be performed in the second trimester when the risk of pregnancy loss is lower.
e. **Pregnancy is an absolute contraindication for radioiodine therapy**. It is also mandatory to **perform a pregnancy test before administering radioactive iodine to any woman of childbearing age**.
f. **Breastfeeding.** The concentration of **antithyroid medications in breastmilk is very low, and breastfeeding is considered safe**. Thyroid function in breastfed newborns remained normal, and no long-term abnormalities have been detected.
g. **Antepartum surveillance.** In suboptimally controlled hyperthyroidism, twice weekly antepartum testing, starting at 32 to 34 weeks, is usually recommended. The timing and route of delivery should be determined by obstetric indications.

3. **Fetal and neonatal hyperthyroidism.** TSHRAb crosses the placenta and may stimulate the fetal thyroid when it becomes functional in the second half of pregnancy. It is reported in **1% to 5% of infants born to Graves disease mothers** with very high TSHRAb levels (threefold or higher above baseline). The antithyroid medication given to the mother will also benefit and protect the fetus from the TSHRAb-stimulating effect during pregnancy. However, this protection is lost after delivery, and **neonatal hyperthyroidism may develop within a few days after birth. More severe fetal hyperthyroidism may occur in mothers previously treated with surgery or radioiodine and no longer requiring antithyroid medications.** These women may still have very high TSHRAb concentrations, even though they may now be euthyroid on thyroxine replacement. Maternal TSHRAb levels should be measured. Fetal blood for thyroid function testing could be

obtained by cordocentesis, but because it is a risky procedure, the fetus is usually monitored clinically for any symptoms and signs of hyperthyroidism. A **fetal heart rate faster than 160 per minute** should arouse suspicion. Ultrasound examination may reveal a **fetal goiter**, as well as other potential complications such as accelerated bone ossification, oligohydramnios, and growth restriction or hydrops if there is fetal heart failure. Mortality can be as high as 30%.

Treatment consists of antithyroid medication given to the mother. MMI is preferred after the first trimester, but PTU could be used if therapy with MMI is not possible. **The dose should be the lowest that keeps the fetal heart rate below 160 per minute.** The resolution of fetal goiter and the normalization of fetal growth are indicators of good therapeutic response.

4. **Central neonatal hypothyroidism.** Infants born to women with uncontrolled hyperthyroidism, because of either the lack of treatment or noncompliance, may experience a prolonged suppression of pituitary TSH secretion resulting from excessive amounts of thyroxine crossing the placenta. It is usually transient, but cases of persistent pituitary-thyroid dysfunction have been reported. The diagnosis is made in the presence of decreased T4 and normal (but inappropriate) or low TSH. This complication can be avoided with the proper management of the maternal hyperthyroidism.

D. Hypothyroidism

1. **Overt hypothyroidism** (elevated TSH and low T4) is reported in 0.2% to 0.9% of pregnancies. Chronic autoimmune thyroiditis is the most common etiology. Other causes include radioiodine ablation and partial or complete surgical thyroid removal to treat Graves disease or tumors, inadequate thyroxine replacement (poor

p. 941p. 942compliance, the failure to realize that higher doses are needed in pregnancy, and the fear that thyroxine may harm the fetus), and thyroid dysgenesis. Untreated overt hypothyroidism is associated with many serious maternal and fetal complications as detailed on Table 75-7. Patient education is of the utmost importance to insure euthyroidism at conception, and especially in early pregnancy. As soon as pregnancy is confirmed,

the thyroxine dosage should be increased by 25% to 35%. Subsequent adjustments are made as indicated by the thyroid function studies (see trimester-specific TSH levels above). The outcome of pregnancy is excellent in women who are euthyroid before and remain so during pregnancy.

a. **Levothyroxine is the medication of choice.** Triiodothyronine (T3) alone or T4/T3 combinations (e.g., desiccated thyroid preparations) are best avoided. **The fetus cannot use T3 directly transferred from the mother.** The fetus has to obtain T3 from the maternal T4 transported across the placenta. For patients not already receiving thyroxine, the initial dose could be 100 to 150 μg/day, but preferably 2 to 2.4 μg/kg (actual weight) per day. Thyroid function tests are repeated frequently.
b. **Some compounds combine with thyroxine and decrease its absorption** if ingested together, particularly **ferrous sulfate** and calcium which are prescribed to, essentially, all pregnant women. Thyroxine should be taken ≥30 minutes before breakfast. Any medications that may interfere with thyroxine absorption should be postponed to at least 2 hours, and preferably to 4. If there is severe morning sickness, taking the thyroxine at bedtime until the vomiting subsides can be very helpful. After delivery, the thyroxine dose is readjusted to the prepregnancy amount. Breastfeeding should be encouraged and the women reassured, because many believe that breastfeeding is unsafe when thyroxine is taken.

2. **Subclinical hypothyroidism (SC)** (Elevated TSH and normal T4). SC is reported in 3% to 5% of pregnancies, and the etiology is autoimmune thyroid disease in most cases. A number of studies have reported an association between SC and adverse pregnancy outcomes. Although fewer and less severe than in overt hypothyroidism, a number of serious complications have been reported, including miscarriages, premature deliveries, preeclampsia, abruptio placentae, more cesarean deliveries because of fetal distress, low birth weight, and various degrees of impaired neurointellectual development. However, big controversies currently exist as to whether or not these complications are preventable by maternal thyroxine administration. Several other studies, including a large, randomized controlled trial, have not

found that treatment with levothyroxine was better than the one with placebo. Nevertheless, it has been suggested that the 13 weeks' mean gestational age when thyroxine treatment was started might be too late p. 942p. 943to be effective. The American **Thyroid Association recommends thyroxine treatment for SC only if TPO antibodies are present. The Endocrine Society recommends treatment for all pregnant women with SC regardless of antibody status**, as does the European Thyroid Association. The American College of Obstetrics and Gynecology **does not recommend treatment regardless of thyroid antibody status**. When choosing to treat, the initial thyroxine level may be calculated according to the TSH level: a) 2.5 to 5 μIU/L: 1.2 μg/kg (actual weight)/day, b) 5.1 to 10 μIU/L: 1.5 μg/kg/day, and c) >10 μIU/L: 2.4 μg/kg/day. A starting dose of 125 to 150 μg/day for all women has also been used, but a weight-based calculation appears to be more accurate.

TABLE 75-7 Maternal and Fetal Complications of Hypothyroidism

Maternal	Fetal
Miscarriage	Low birth weight
Anemia	Prematurity
Pregnancy-induced hypertension	Small for gestational age
Preeclampsia/eclampsia	Intrauterine growth restriction
Preterm delivery	Fetal death
More cesareans for fetal distress	Neonatal respiratory distress
Placental abruption	More NICU admissions and longer stays
Postpartum hemorrhage	Neurointellectual deficits
	Rare transient congenital hypothyroidism

NICU, neonatal intensive care unit.

3. **Isolated hypothyroxinemia** (Low-free T4 and normal TSH). Some studies, mainly from the Netherlands, have reported a variety of neurocognitive impairments in the offspring of mothers suffering from isolated hypothyroxinemia, although many other studies have not found any adverse outcomes. Levothyroxine therapy is not recommended. If iodine deficiency is present, it

should be corrected (see Section V.A.4).

Screening for thyroid disorders during pregnancy. It should be noted that several studies have reported that targeted screening will miss as many as 30% to 80% of pregnant women with subclinical or overt hypothyroidism. Table 75-5 lists the risk factors that warrant screening for thyroid disease during pregnancy.

E. Thyroid nodules. Nodular thyroid disease (NTD) is clinically detectable in up to **10% of pregnant women**. Although most cases antedate pregnancy, the initial detection is frequently made while undergoing pregnancy care. Once detected, further assessment for high-risk characteristics is needed including family history (differentiated thyroid cancer, multiple endocrine neoplasia type 2, medullary thyroid cancer), history of previous head/neck radiation, residence near a nuclear-reactor accident, or the patient states that the nodule is rapidly enlarging. Thyroid function studies will help identify the rare hyperfunctioning nodule. A thyroid ultrasound will further assess size, shape (e.g., longer than wide), the presence of irregular margins, microcalcifications or cervical lymphadenopathy, all suspicious features. A fine-needle aspiration can be performed during pregnancy, but there should be a clearly defined plan of action in case malignancy is found, which is reported in approximately 15% of NTD cases.

Most women will choose to postpone definitive therapy until after delivery. There is no evidence of improved survival by performing surgery during pregnancy instead of waiting until the postpartum period. In addition, surgical complications are reported to be higher when surgery is performed during pregnancy. A group of 61 pregnant women with differentiated thyroid carcinoma was followed for a period of 22.4 years. Fourteen had surgery during pregnancy, and in 47, it was postponed until 1 to 84 months after delivery. The outcome was similar in both groups. It was concluded that **diagnostic studies and initial surgery may be safely delayed until after delivery in most patients**.

Suppressive therapy with levothyroxine to keep TSH levels ≥0.1 to ≤1 μIU/L has been suggested for women with differentiated thyroid cancer who postpone definitive therapy until after delivery. Possible indications for surgery during the second trimester include a 50% tumor growth and the detection of lymph node metastases before 24 weeks.

Figure 75-3 depicts the approach to the management of a single thyroid nodule detected on physical examination in our institution.

F. Chronic autoimmune thyroiditis (Hashimoto thyroiditis). Women with known chronic thyroiditis on levothyroxine therapy are managed as described in the "overt hypothyroidism" section. Euthyroid women with elevated TPOAb titers should be followed closely, because up to 40% will develop hypothyroidism with the progression of pregnancy (see Section V.B.5). In addition, up to 50% will develop postpartum thyroiditis and half of those with postpartum thyroiditis go on to develop permanent hypothyroidism within the first year after delivery. In view of these potential complications, euthyroid women with elevated TPO antibodies should have their thyroid function monitored every month until 20 weeks' gestation and at least once during the second half of pregnancy.

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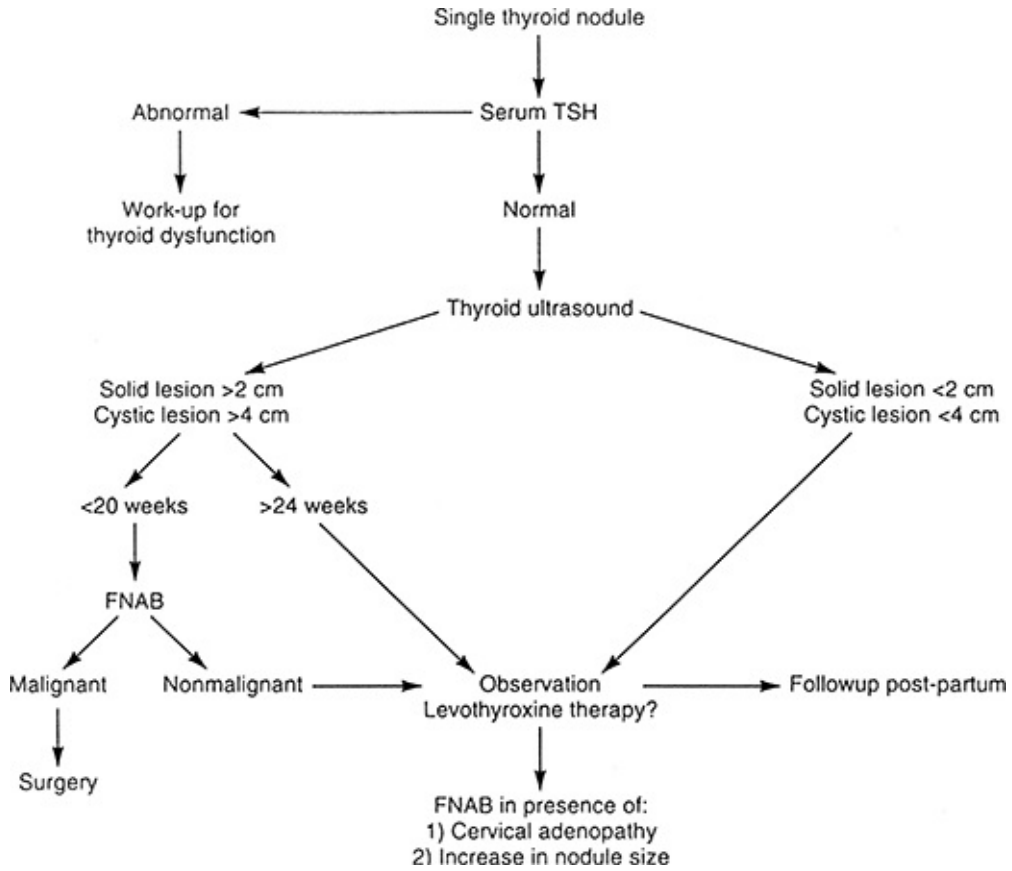

Figure 75-3. Evaluation of single thyroid nodules in pregnancy. FNAB, fine-needle aspiration biopsy; TSH, thyroid-stimulating hormone.

G. Postpartum thyroid dysfunction. Postpartum thyroiditis (PPT) is very common and occurs in **5% to 10% of all women**. Chronic autoimmune (Hashimoto) thyroiditis is the most common cause. Women with type 1 diabetes have a very high prevalence of autoimmune thyroiditis and an incidence of PPT close to 30%. Most symptoms are nonspecific. PPT may resemble postpartum depression. PPT may also occur after a miscarriage or abortion.

The several clinical presentations of PPT are graphically depicted in Figure 75-4. **(1)** An initial hyperthyroid phase (2 to 4 months postpartum), followed by hypothyroidism (4 to 6 months) and back to euthyroidism (7 to 8 months) occurs in 25% of cases; **(2)** a single hyperthyroid phase (2 to 4 months) in 32%; **(3)** a hypothyroid episode only (4 to 6 months) is the most common, accounting for 43% of PPT cases; **(4)** permanent hypothyroidism without recovery may also occur.

Although most patients recover spontaneously, temporary treatment may be needed for very symptomatic patients. **For hyperthyroidism**, propanolol 20 to 40 mg every 6 to 8 hours or metoprolol 100 mg once or twice daily are effective. **Antithyroid drugs (PTU, MMI) are not indicated** or are not effective, because the hyperthyroidism is due to passive thyroid hormone release from autoimmune destructive injury and not from increased synthesis. For significant hypothyroid symptoms, small amounts of L-thyroxine, 50 μg/day, will control symptoms and still allow spontaneous thyroid function recovery after it is stopped. Euthyroid women with positive TPOAb titers should undergo thyroid function studies (TSH, free T4) 2 to 4 months postpartum, and if euthyroid, they are repeated at 6 and 9 to 12 months.

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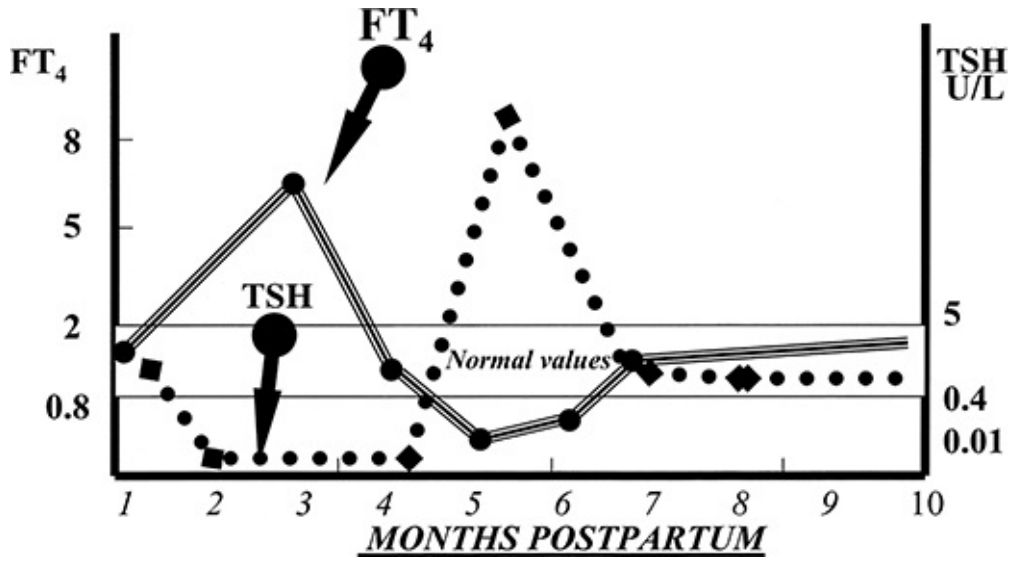

Figure 75-4. Clinical course of postpartum thyroiditis. FT4, free thyroxine; TSH, thyroid-stimulating hormone.

Women with Graves disease may also experience exacerbation of hyperthyroidism after delivery. Favoring the diagnosis of Graves are more severe symptoms, larger goiters, and eye/skin involvement; higher thyroxine, T3 and T3/T4 ratio determinations, as well as a positive TSHRAb titer. The 24-hour I-131 radioiodine uptake is contraindicated if the woman breastfeeding or if she is in the early postpartum. However, if breastfeeding is suspended for 48 hours, thyroid uptake with technetium-99m or I-123 might be possible, given their short half-life. A positive TSHRAb titer and increased thyroid blood flow by color Doppler sonography will be compatible with hyperthyroidism from Graves disease without the need of using any tests involving radioactive material during this vulnerable time.

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76 Fetal Endocrinology and Neonatal Emergencies

Phillip D. K. Lee and C. Joan Richardson

The development of the endocrine system begins during blastocyst implantation and proceeds at a rapid pace throughout gestation in concert with essential actions of placental and maternal factors, concluding with adjustments to the extrauterine environment. This chapter reviews relevant aspects of this complex process pertaining to the embryo and fetus, concluding with a discussion of neonatal endocrine emergencies. Maternal endocrine disorders during pregnancy are discussed in Chapter 75. By convention and for the purposes of this chapter, embryo refers to the first 8 weeks of gestation and neonatal refers to the period from birth to 1 month of age.

I. THE PLACENTA is a dynamic, interactive interface between the mother and the fetus. Unlike in lower primates and other mammals in which fetal (chorionic) and maternal (uterine epithelial) membranes form unique boundaries (epitheliochorial placenta), the human placenta is hemochorial, that is, the maternal circulation is in direct contact with the outermost layer (chorion) of the developing embryo. This interaction is established at implantation, during which the blastocyst is embedded in the uterine endometrium. Prior to implantation, cytotrophoblasts fuse to form a syncytium (syncytiotrophoblast) which then attaches to the uterine epithelium and disrupts the uterine endometrial capillaries, facilitating exchange between the maternal circulation and the developing embryo. This initial invasive process and early embryogenesis, which occur in a relatively hypoxic tissue environment, is supported by the uterine endometrial glands; the resultant uterine endometrial hyperplasia bears histologic resemblance to endometrial malignancy (Arias-Stella reaction).

Maternal nutrients and hormones are initially transported into the extraembryonic coelom. Toward the end of the first trimester, cytotrophoblasts migrate through the endometrium into the myometrium and participate in the evolution of the uterine spiral arteries into dilated maternal arterial vessels that interface with the developing chorionic

circulation. Cell nuclei and exosomes from the syncytiotrophoblast released into the maternal circulation may participate in fetal–maternal signaling. During the second and third trimesters, the cellular composition of the syncytiotrophoblast becomes less distinct, further facilitating fetal–maternal interchange.

In addition to its other roles, the placenta is a multifunctional endocrine organ secreting >100 hormones. A few important examples are discussed below (see also Chapter 75).

A. Protein and peptide hormones

1. **Human chorionic gonadotropin (hCG)** is secreted by the syncytiotrophoblast beginning at blastocyst implantation with detectable levels in the maternal circulation by postovulation days 8 to 11; levels double every 2 to 3 days, peaking and leveling for approximately 8 to 12 weeks, then declining gradually to term. hCG, which consists of an *α*-subunit identical to that for follicle-stimulating hormone (FSH), luteinizing hormone (LH), and thyroid-stimulating hormone (TSH), and a *β*-subunit that is homologous to LH, binds to the ovarian LH receptor, increasing estrogen synthesis and sustaining the corpus luteum during the first trimester. The resultant progesterone secretion by the corpus luteum maintains the gestational uterine endometrium (decidua) and provides substrate for fetal and placental steroid synthesis. As pregnancy progresses, hCG maintains placental estrogen p. 948p. 949synthesis. hCG also possesses TSH-like activity, leading to increased maternal thyroid hormone synthesis.
2. **Placental growth hormone (GH)** and **placental lactogens** are synthesized by the syncytiotrophoblast. The highly homologous genes coding for pituitary GH (*GH1*), placental GH (*GH2*), and the human placental lactogens chorionic somatomammotropin hormone 1 (CSH1, *aka* hPL-A; *CSH2*), CSH2 (*aka* hPL-B, *CSH2*), and CSH-like 1 (*aka* hPL-L, *CSHL1*) are located in a gene cluster at 17q23.3 and likely arise from gene duplication. This redundancy indicates the importance of a GH entity in fetal growth. *GH1* is expressed by the maternal and fetal pituitary glands but is not expressed by the placenta; maternal production of pituitary GH is suppressed and fetal production does

not appear to be essential for fetal growth. However, placental GH and placental lactogens may play important roles in stimulating placental and fetal production of insulin-like growth factors (IGFs)-I and II.

3. **Corticotropin-releasing factor** secretion by cytotrophoblasts and decidua increases several hundred fold during pregnancy, stimulating placental, maternal, and fetal adrenocorticotropic hormone (ACTH) production and probably playing an essential role in parturition.
4. **Insulin-like growth factor binding protein-1 (IGFBP-1)** is the primary protein product of the decidua and may play a role in inhibiting the actions of IGF-I and IGF-II in the fetal circulation.

B. Steroid hormones

1. **Progesterone** is the primary substrate for maternal, placental, and fetal steroidogenesis. By 6 to 8 weeks, the placenta becomes the primary synthetic source of progesterone, surpassing production by the corpus luteum, and maternal and fetal levels increase progressively to term. Progesterone inhibits uterine contractility, reduces prostaglandin formation, and plays a role, with hCG and decidual cortisol, in inhibiting maternal rejection of the fetus. The placenta also possesses aromatase, steroid sulfatase, and 11-hydroxylase (CYP11B1 and CYP11B2) activities, but lacks CYP17A1 (17-hydroxylase and 17,20 lyase) activity.
2. Maternal **estrogen** (estrone, estradiol, and estradiol) levels progressively increase during pregnancy, largely because of placental 16-hydroxylase activity on C19 steroids (e.g., dehydroepiandrosterone [DHEA]). Because of the lack of CYP17A1 activity, the placenta itself does not produce C19 (androgenic) steroids; therefore, the substrate for estrogen synthesis apparently originates from the maternal circulation in early pregnancy and then primarily from the fetal adrenal gland. Estrogen is required for maintenance of a normal pregnancy; the level of production exceeds the theoretical requirement.

II. EMBRYO AND FETUS

Endocrine embryogenesis starts at approximately day 16 with gastrulation, the formation of three germ layers that give rise to the body tissues:

A. Ectoderm: epidermis (including **anterior pituitary**, sebaceous, and

mammary glands) and the nervous system (including **hypothalamus**, **posterior pituitary**, pineal, thyroid parafollicular *aka* **C cells**, and **adrenal medulla).**

B. **Mesoderm:** musculoskeletal, lymphatic, and cardiovascular systems, **gonads**, **adrenal cortex, and the fetal zone of the adrenal gland.**

C. **Endoderm** (*aka* entoderm): gastrointestinal epithelium (including **thyroid** and **parathyroids**), bladder, liver, and **pancreas.**

1. Secretion of pituitary regulatory hormones from the **hypothalamus**, a derivative of the ventral diencephalon, is demonstrable by 6 weeks gestation; however, the hypophyseal portal system is not developed until approximately 18 weeks.
2. The **anterior pituitary gland** derives from the epidermal layer of Rathke pouch, an invagination of the oral ectoderm. By approximately 6 to 8 weeks gestation, production of all six anterior hormones (GH, TSH, prolactin, ACTH, FSH, and LH) can be demonstrated, although hypothalamic regulatory pathways are not demonstrable for another 10 to 12 weeks. Particularly during the third trimester, fetal gonadotropin secretion is essential for testicular development and consequent virilization of the male fetus.

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3. The **pituitary stalk** (infundibulum) and **posterior pituitary gland** arise from the ventral diencephalon with neuronal connections from hypothalamic areas that form the supraoptic, suprachiasmatic, and paraventricular nuclei. The posterior pituitary hormones antidiuretic hormone (ADH) and oxytocin are synthesized in the magnocellular neurons of the hypothalamic supraoptic and paraventricular nuclei and undergo neuronal transport to the posterior pituitary by the 11th week of gestation. ADH may be active in the fetus, and fetal oxytocin may be involved in induction of labor; however, the roles of fetal ADH and oxytocin are not completely defined.
4. The **adrenal medulla** is composed primarily of chromaffin cells (*aka* pheochromocytes) derived from neuroblasts that migrate from the preaortic sympathetic ganglia at approximately 4 to 5 weeks and become encased in the developing adrenal cortex. These modified neurons are responsible for the endocrine secretion of

epinephrine and norepinephrine, and also secrete small amounts of dopamine and enkephalins. Proximity to glucocorticoid-producing cells enhances the enzymatic conversion of norepinephrine to epinephrine and may also inhibit the development of neuronal processes. The role of fetal adrenal medullary secretion has not been defined.

5. The **adrenal cortex**, gonad, and kidney form from the urogenital ridges of the mesoderm. Steroidogenic tissue is identifiable by approximately 4 weeks, with distinct gonadal and adrenal tissues by approximately 7 weeks; encapsulation of the adrenal glands occurs 1 to 2 weeks thereafter. At term, the fetal adrenal is approximately the size of the adult gland, with an approximately fivefold greater steroidogenic rate; 80% to 90% of the gland consists of a **fetal adrenal zone** with a thin outer layer of **adrenal cortex** (80% to 85% of gland). The fetal adrenal zone lacks 3β-hydroxysteroid dehydrogenase activity, inhibited in part by placental progesterone, and CYP21A1 (21-hydroxylase) activity; therefore, the primary secretory products are pregnenolone and DHEA.

   Fetal adrenal steroidogenesis is stimulated by placental hCG to approximately 20 weeks and then by fetal ACTH. The fetal adrenal zone gland regresses after birth and is usually negligible by 1 year of age.

   DHEA is sulfated then hydroxylated by 16-hydroxylase in the fetal liver. Dehydroepiandrosterone sulfate (DHEAS) and 16-hydroxy-DHEAS are converted to DHEA and 16-hydroxy-DHEA by placental sulfatase and then converted to androstenedione, testosterone, or 16-hydroxyandrostenedione by placental 3β-hydroxysteroid dehydrogenase. Placental aromatase then converts androstenedione and testosterone to estrone and 16-hydroxyandrostendione to estriol. Estrone is reversibly converted to estradiol by placental 17-hydroxysteroid dehydrogenase. Estradiol created by this fetal–placental partnership primarily enters the maternal circulation, whereas estriol, a relatively weak estrogen, enters the fetal circulation where it may play a role in blocking estradiol effect.

   Cortisol and aldosterone production by the transitional and definitive zones of the **adrenal cortex**, respectively, increase during late gestation; the increased endogenous fetal cortisol is

involved in tissue maturation. The fetus is protected from the much higher maternal cortisol levels by conversion of maternal cortisol to cortisone by placental 11*β*-hydroxysteroid dehydrogenase isoenzyme type 2; a process that is regulated in part by estrogen.

6. Bipotential **gonads** arising from the coelomic epithelium of the mesodermal urogenital ridges are demonstrable by 4 weeks, followed at 5 weeks by primordial germ cell migration from the extraembryonic ectoderm to the developing urogenital ridges.

   In the **absence of sex-determining region Y (*SRY*)** (Yp11.2) expression, the urogenital ridges give rise to the ovarian granulosa and müllerian ductal system (fallopian tubes, uterus, and proximal vagina). The primordial wolffian duct regresses because of the lack of testosterone. Oocyte proliferation proceeds at a rapid pace from approximately 10 weeks until mid-gestation; the oocytes are surrounded by granulosa cells that induce meiotic arrest. The latter half of gestation is characterized by net oocyte degeneration and maturation of the p. 950p. 951remaining follicles; regulation of this process is incompletely defined. The ovaries associate with the müllerian duct derivatives; these structures are passively repositioned below the kidney because of the relative rates of fetal tissue growth.

   ***SRY* expression** drives differentiation of the gonadal ridges to Leydig and Sertoli cells. Leydig cell production of testosterone is measurable by approximately 7 weeks, with a rapid increase at 12 to 18 weeks stimulated by both placental hCG and the progressive secretion of fetal pituitary gonadotropins. Leydig cells also produce insulin-3 that stimulates growth of the gubernaculum testis (*aka* genital-inguinal ligament). Antimüllerian hormone, produced by the Sertoli cells, acts locally to cause ipsilateral regression of the primordial müllerian ducts. Direct exocrine testosterone secretion onto the wolffian (*aka* mesonephric) ducts triggers the development of the epididymis, vas deferens, and seminal vesicles, whereas testosterone released into the fetal circulation undergoes tissue conversion by 5*α*-reductase to dihydrotestosterone, which then stimulates the development and growth of the prostate and male external genitalia.

   Beginning at 8 weeks, the developing fetal testes are passively anchored near the developing inguinal ring by the growth of the

gubernaculum testis coupled with testosterone-mediated regression of the cranial suspensory ligament. Between 25 and 35 weeks, a complex series of events mediated by testosterone, insulin-3, and calcitonin gene–related peptide causes descent of the gubernaculum and testes through the inguinal ring into the scrotum. The gubernaculum also gives rise to the cremasteric muscle.

7. The primordial **thyroid** gland can be identified as an outpouching of the pharyngeal floor by approximately 3 to 4 weeks. The developing gland demonstrates iodide uptake and thyroglobulin synthesis by approximately 11 weeks, and thyroxine (T_4) secretion by approximately 16 to 18 weeks. In early pregnancy, maternal T_4 and T_3 transferred to the fetus primarily by placental transthyretin is largely inactivated to T_2 and reverse T_3 by placental and fetal inner ring deiodinase type III, or is inactivated by fetal sulfatase. After 24 weeks, fetalfree T_4 and TSH concurrently increase, with a progressive rise in free T_3 starting at approximately 30 weeks; these events may be induced by a rise in fetal cortisol levels. Immediately after birth, there is a surge in TSH secretion peaking within the first 24 hours, perhaps triggered by the lower ambient temperature in the ex utero environment, followed by a rise in T_4 peaking at approximately 48 hours. TSH and T_4 levels subsequently decline to usual postnatal ranges. A blunted rise in TSH and T_4 has been observed in preterm infants, with delayed timing in very preterm infants (e.g., <30 weeks gestation).
8. The endocrine, exocrine, and ductal elements of the **pancreas** derive from the endoderm of the distal foregut. The islets of Langerhans, which account for pancreatic endocrine secretion, are composed of α-cells (glucagon), β-cells (insulin, amylin), δ-cells (somatostatin), ε-cells (ghrelin), and γ-cells (pancreatic polypeptide).

   Glucose is transported from the maternal circulation to the embryo and fetus by facilitated diffusion across the placenta primarily via glucose transporter 1 (GLUT1) that is present on both the fetal- and maternal-facing placental members. The high rate of fetal glucose utilization (~5 to 7 mg/kg/min as compared to 2 to 3 mg/kg/min in adults) leads to differential fetal and maternal

glucose levels (~3.0 vs. 3.5 to 5.5 mmol/L, respectively); the consequent continuous net positive transfer to the fetus leads to fetal glycogenesis (starting at ~8 weeks) and lipogenesis. Fetal insulin secretion is thought to play a limited role in the regulation of fetal glycemia. With poorly controlled maternal diabetes mellitus, the provision of excess glucose leads to fetal hyperinsulinemia and overgrowth. Conversely, decreased glucose supply because of maternal factors or placental insufficiency can result in fetal glycogenolysis or failure of adequate glycogenesis, an increased utilization of alternate energy substrates, intrauterine growth retardation, and an increased risk for significant neonatal hypoglycemia.

The embryogenesis and roles of fetal glucagon, amylin, somatostatin, ghrelin, and pancreatic polypeptide secretion have not been fully defined.

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9. Fetal **parathyroid hormone** (PTH) and **calcitonin** (from thyroid C cells and placenta) are demonstrable by approximately 10 weeks of gestation; neither of these hormones nor calcitriol cross the placenta. Calcium, phosphorous, and magnesium are actively transported from the maternal circulation by the placenta, favoring the fetus, with fetal levels significantly higher than maternal by 15 weeks. Placental calcium transport may be regulated by PTH and PTH-related peptide (PTHrp), the latter originating from the fetal parathyroid and placenta. This positive mineral balance results in low fetal levels of PTH, calcitriol, and the phosphaturic hormone FGF23, whereas calcitonin levels are elevated relative to maternal levels. 25-Hydrodroxyvitamin D transferred from the maternal circulation is converted to 1,25-dihydroxyvitamin D in the placenta and fetal kidney. Fetal ossification centers are identified by approximately 8 weeks; however, significant ossification does not begin until the third trimester, with the rate of fetal bone mineral accretion peaking near term.

III. FETAL ENDOCRINE DISORDERS

The in utero environment protects the fetus from most of the severe consequences of defective endocrine embryogenesis; fetal demise because

of fetal endocrinopathy is uncommon.

A. GH deficiency and related disorders. In utero growth appears to be largely independent of maternal or fetal pituitary GH and may be primarily related to fetal insulin and IGF (IGF-I and IGF-II) production; the latter possibly dependent on placental GH and placental lactogens. Infants with pituitary GH deficiency or GH receptor defects typically have normal birth size for gestational age, whereas fetal insulin deficiency, primary IGF-I deficiency (e.g., *IGF1* mutation), and IGF-I receptor defects are associated with intrauterine growth retardation and small for gestational age. *IGF1* mutation has also been associated with impaired neurodevelopment. Fetal IGF bioactivity is regulated by IGFBP-1, which is a major protein product of the decidua and fetal liver. Cord blood and fetal IGFBP-1 levels have been inversely related to birth size.

B. Severe fetal **thyroid hormone deficiency** may result in delayed fetal skeletal ossification and may have longer term effects on neurodevelopment (see Chapter 48). Fetal hyperthyroidism may result from maternal transfer of thyroid-stimulating immunoglobulin (TSI).

C. Fetal **ACTH deficiency**, for example, in anencephalic infants, has been associated with fetal adrenal hypoplasia and atrophy. Low maternal estrogen levels starting in mid-gestation are characteristic of this condition because of the lack of fetal DHEA production.

D. Congenital adrenal hyperplasia (CAH) because of CYP21A2 (21-hydroxylase) deficiency is associated with progressive inappropriate virilization of genetic female fetuses starting in mid-gestation, presumably because of hyperproduction of adrenal androgen precursors followed by peripheral fetal tissue conversion to testosterone. Maternal or fetal glucocorticoid treatment may prevent this occurrence; however, such treatment is currently considered to be experimental.

E. Fetal **gonadotropin deficiency** is associated with underdevelopment of the male external genitalia (e.g., micropenis and hypoplastic scrotum) and cryptorchidism. Female genital abnormalities have not been conclusively demonstrated.

F. Aromatase deficiency leads to an inability to convert DHEA to estrone and estradiol. The excess fetal DHEA consequently undergoes peripheral conversion to testosterone and can cause inappropriate virilization of the female fetus and her mother.

G. Fetal **insulin** deficiency is associated with intrauterine growth

retardation and small for gestational age. Fetal insulin excess on account of maternal gestational diabetes is associated with large for gestational age.

H. Several maternal and placental **disorders of calcium metabolism** can adversely affect fetal bone mineralization. Maternal hypoparathyroidism with hypocalcemia can lead to fetal secondary hyperparathyroidism, decreased fetal bone mineralization (osteopenia), and growth and skeletal abnormalities. Fetal osteopenia can also result from maternal hypovitaminosis D. Placental insufficiency on account of preeclampsia p. 952p. 953or infection may lead to decreased 1α-hydroxylation of 25-hydroxyvitamin D, resulting in decreased phosphate transport, fetal osteomalacia, and rickets associated with intrauterine growth retardation related to the placental insufficiency. Decreased fetal movement may result in reduced cortical bone formation. Maternal and placental factors generally protect the fetus against intrinsic fetal disorders of calcium or vitamin D metabolism.

IV. NEONATAL ENDOCRINE EMERGENCIES

With parturition, several endocrine and metabolic conditions can lead to serious morbidity, long-term adverse effects on growth and development, or death. This section summarizes key points regarding some of these conditions; additional details can be found in the cross-referenced chapters.

A. Hypoglycemia (Chapters 46, 47). At birth, the continuous maternal provision of glucose is interrupted, and the neonate may experience a physiologic hypoglycemia, with blood glucose levels ranging as low as approximately 30 mg/dL (1.7 mmol/L) in healthy term infants at 1 to 2 hours old. This phenomenon stimulates glucose counterregulatory mechanisms (glycogenolysis and gluconeogenesis) necessary for extrauterine life. Blood glucose levels usually reequilibrate at 60 to 100 mg/dL (~3.5 to 5.5 mmol/L) by 72 to 96 hours in healthy infants, although lower levels may be observed. A universally accepted glucose cutoff for the definition of neonatal hypoglycemia is not available. However, in the absence of clinical signs and symptoms of hypoglycemia, blood glucose <30 to 40 mg/dL after 72 hours is generally considered to be low. In the presence of signs and symptoms, blood glucose <50 to 60 mg/dL may indicate

hypoglycemia.

Signs and symptoms of significant neonatal hypoglycemia are often nonspecific and may include poor feeding, lethargy, jitteriness, hypotonia, respiratory distress, apnea, and seizures. Significant neonatal hypoglycemia may be related to prematurity, small or large for gestational age, maternal gestational diabetes, respiratory distress, and sepsis; such cases do not involve permanent intrinsic defects in glucose regulation and resolve with appropriate treatment.

Prolonged or recurrent symptomatic hypoglycemia may also signal intrinsic pathology. Congenital GH deficiency, with or without ACTH deficiency, may manifest with hypoglycemia because of the essential roles of GH and cortisol in neonatal glucose counterregulation. Primary adrenal insufficiency (e.g., congenital adrenal hypoplasia or hyperplasia) may present with profound hypoglycemia, hyponatremia, hyperkalemia, progressive dehydration, and circulatory collapse. Hyperinsulinemia on account of intrinsic pathologic β-cell hyperplasia (distinct from the transient fetal/neonatal insulin hypersecretion related to maternal diabetes) usually results in a rapidly progressive increase in glucose requirements, often exceeding 10 to 20 mg/kg/min. Inborn errors of metabolism may cause hypoglycemia because of defective gluconeogenesis or disordered glycogen storage and/or mobilization.

If pathologic hypoglycemia on account of an intrinsic cause is suspected, a “critical blood sample” should be obtained during hypoglycemia with measurement of glucose, GH, cortisol, insulin, and β-hydroxybutyrate levels.

The primary treatment of neonatal hypoglycemia is provision of glucose. In cases involving intrinsic pathology, treatment of the underlying etiology should be implemented. Of note, a low GH level (<10 ng/mL) measured during significant hypoglycemia is sufficient for the diagnosis of neonatal GH deficiency; a concurrently low cortisol may indicate congenital panhypopituitarism.

B. Hyperglycemia because of permanent neonatal diabetes mellitus (PNDM) is rare (~1:200 to 800k births) and can be associated with genetic mutations causing either pancreatic dysgenesis or agenesis (e.g., *GATA6*, *PDX1*, *PTF1A*, and *HNF1B*); these cases are accompanied by exocrine pancreas dysfunction (resulting in gastrointestinal malabsorption) and usually include other congenital anomalies. PNDM can also be caused by mutations that more

specifically affect *β*-cell differentiation (e.g., *RFX6*, *MNX1*, *NEUROG3*, and *GLIS3*), insulin synthesis (*INS*), or the potassium (K-ATP) channel (*KCNJ11* and *ABCC8*). Intrauterine growth retardation and small for gestational age are typical, reflecting the important role of insulin in fetal growth. PNDM p. 953p. 954typically presents before 3 months old with hyperglycemia, absence of ketoacidosis (except in *INS* and in severe cases of *KCJN11* and *ABCC8* mutations), diuresis, and failure to thrive; with gastrointestinal malabsorption and fatty stools if there is exocrine dysfunction. Insulin treatment (with pancreatic enzyme replacement, if necessary) is usually efficacious for immediate treatment; sulfonylurea is the ultimate treatment of choice in K-ATP channel mutations. PNDM is distinguished from transient neonatal diabetes mellitus which occurs with similar incidence but with a different spectrum of etiologies and usually does not require aggressive treatment.

C. Hypocalcemia (see Chapter 35). At birth, the maternal and placental supply of calcium, phosphorous, magnesium, vitamin D, and PTHrp are abruptly interrupted. In addition, the physiologic increase in arterial blood pH decreases ionized calcium. Urinary loss of calcium and other minerals no longer undergo recirculation via swallowed amniotic fluid. In a healthy, full-term newborn, these physiologic events lead to an approximately 25% decrease in total and ionized serum calcium by 24 to 48 hours after birth, accompanied by a rise in serum phosphorous and surges in PTH and calcitonin secretion, followed by reequilibration to normal postnatal levels over several days. The initial physiologic hypoparathyroidism and decreased calcium can be accentuated and symptomatic in infants fed with cow milk–based formula due to the high phosphate-to-calcium content. Other risk factors for severe or prolonged hypocalcemia include prematurity, maternal gestational hyperparathyroidism, and inadequate nutritional intake of calcium.

Intrinsic abnormalities causing hypocalcemia are less common and include hypoparathyroidism (including 22q11.2 deletion, *aka* DiGeorge or velocardiofacial syndrome), pseudohypoparathyroidism, and abnormalities of vitamin D synthesis or action. Very rare, heritable gain-of-function calcium-sensing receptor (*CASR*) mutations and loss-of-function mutations of *PTH* and *GCM2*, as well as parathyroid dysgenesis and mitochrondrial DNA disorders, can be associated with

severe neonatal hypocalcemia. Signs and symptoms of significant neonatal hypocalcemia may include lethargy, poor feeding, jitteriness, myoclonus, tetany, and seizures; clinical presentation may not occur until several days to weeks after birth. Acute treatment involves parental administration of calcium; a typical neonatal protocol is calcium gluceptate 100 mg/kg IV slow push followed by 250 to 500 mg/kg/day. Long-term treatment depends on the etiology and usually involves oral calcium and vitamin D coupled with transitioning feeds to breast milk or lower phosphate commercial formula.

D. Osteopenia of prematurity is not a clinical emergency per se; however, failure of early detection and treatment can lead to severe osteopenia, respiratory distress, pathologic fractures, and failure to thrive. The pathophysiology of this condition, which typically affects preterm infants, involves premature removal of the maternal supply of calcium, phosphorous, magnesium, and 25-hydroxyvitamin D. The resultant negative mineral balance, coupled with normal functional parathyroid, results in inappropriate mobilization of bone mineral; laboratory testing typically shows elevated PTH with normal calcium and normal or low phosphorous. A similar condition of progressive osteopenia with elevated PTH may occur in preterm or term infants; risk factors include very low birth weight, bronchopulmonary dysplasia, prolonged reliance on parenteral nutrition, and chronic administration of glucocorticoid, methylxanthines, or loop diuretic treatment. Generally accepted guidelines recommend screening of neonates who meet one or more of the following criteria: birth weight <1 500 g, natal gestational age ≤28 weeks, treatment with diuretics or glucocorticoids, and total parenteral nutrition for >4 weeks. Treatment involves provision of calcium and phosphorous supplementation (including high calcium and phosphorous containing formula), vitamin D, and magnesium. Concurrent passive or active physical therapy may improve bone mineralization.

E. Neonatal hypercalcemia (also see Chapter 35) can occur with calcium or vitamin D overload, for example, in hospitalized infants receiving nutritional supplementation; in such cases, PTH levels are low and the condition is easily resolved. Heterozygous **loss-of-function mutations of *CASR*** usually cause a benign condition of familial hypocalciuric hypercalcemia, with serum calcium <12 mg/dL (<3 mmol/L), normal PTH (although elevated for the calcium level),

and low urinary calcium. Rare p. 954p. 955heterozygous mutations (e.g., *CASR* R185Q) and rare homozygous or compound heterozygous *CASR* mutations cause **severe neonatal hyperparathyroidism**, a progressive, potentially life-threatening condition presenting in the neonatal period with hypotonia, respiratory distress, failure to thrive, dysphagia, and poor feeding. Serum calcium is typically >16 mg/dL or 4 mmol/L with elevated PTH and alkaline phosphatase. Skeletal abnormalities may include osteopenia, fractures, subperiosteal erosion, metaphyseal widening, and shortened ribs causing a bell-shaped chest. Delayed diagnosis and inadequate treatment can result in severe growth retardation, neurodevelopmental delay, and respiratory failure. The severity of the phenotype varies with the genetic etiology. Anecdotal reports indicate that bisphosphonate treatment may temporarily lower calcium levels and that cinacalcet may be efficacious for chronic preoperative management; definitive treatment is total parathyroidectomy.

F. Congenital hypothyroidism (Chapter 40), incidence approximately 1:2 500, is considered an urgent or emergent neonatal condition because of the risk for permanent adverse effects on growth and neurodevelopment if treatment is delayed; clinical presentation is rarely an emergency per se. Virtually all cases of congenital hypothyroidism are detected via newborn screening programs in the United States and other developed countries. All infants with congenital GH deficiency should be tested for central hypothyroidism and vice versa.

G. Neonatal hyperthyroidism (*aka* neonatal Graves disease, Chapter 40), incidence approximately 1:50k, is usually transient and due to transfer of maternal TSH-receptor-activating immunoglobulin. Elevated levels of T_4 and/or T_3, suppressed TSH, and elevated TSI levels are characteristic. Symptoms of neonatal hyperthyroidism can range from none to severe hypermetabolism (hyperkinesis, emesis, tachycardia, weight loss with increased linear growth, and rarely cardiovascular decompensation). Symptomatic cases are usually apparent in the first 2 weeks of life. Autoimmune neonatal hyperthyroidism may begin in utero, with transfer of maternal TSI starting during the second trimester and reaching maternal levels by 30 weeks, in some cases causing fetal hyperthyroidism with tachycardia

and accelerated skeletal maturation. In severe cases, maternal methimazole treatment (with maternal thyroid hormone replacement as needed) has been used to suppress fetal thyroid function, although this may be associated with a risk for fetal and neonatal hypothyroidism. Maternal methimazole treatment is contraindicated during the first trimester because of potential teratogenicity; however, fetal hyperthyroidism typically has onset in the second or third trimester.

Because maternal antibodies are usually cleared from the infant circulation within a few weeks, postnatal treatment of autoimmune neonatal hyperthyroidism is generally supportive (e.g., β-blockers for tachycardia); methimazole and glucocorticoids have been used in severe cases. An increased risk for craniosynostosis begins in utero and is apparently not affected by postnatal treatment; no other long-term sequelae have been conclusively demonstrated. It should be noted that most cases of neonatal autoimmune hyperthyroidism are not associated with a maternal history of known or active hyperthyroidism. In addition, women with a history of treated or remitted autoimmune hyperthyroidism may continue to have elevated TSI.

Nonautoimmune, permanent congenital neonatal hyperthyroidism is very rare and has been associated with McCune–Albright syndrome and inherited or sporadic activating mutations of the TSH receptor.

H. Pathologic **hyponatremia** is a rare occurrence in neonates and should be distinguished from normal physiologic changes affecting neonatal sodium balance. Physiologic postnatal salt and water loss can be accentuated in preterm infants due to immature renal concentrating ability, and this may be compounded by the low salt content of breast milk and commercial infant formulas. A transient resistance to aldosterone, with increased aldosterone, renin activity, and potassium levels, has been described in normal newborns.

Pathologic hyponatremia in full-term newborns has been reported following provision of excessive hypotonic fluid to the mother during labor and as a consequence of maternal use of diuretics.

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Congenital syndrome of inappropriate antidiuretic hormone secretion (SIADH) is very rare. In the ill-term or preterm newborn with decreased free water clearance (associated with cardiac disorders, central nervous system infections or hemorrhage, chronic lung disease, and/or extrinsic factors causing decreased cardiac output), acutely

decreased intravascular volume (because of diuretic treatment) with resultant increased ADH secretion, followed by provision of hypotonic fluid, can lead to hyponatremia; this situation is characterized by normo or hypervolemia. Acute salt-wasting can occur with adrenal mineralocorticoid deficiency (e.g., adrenal hypoplasia or salt-wasting adrenal hyperplasia), renal disease (e.g., acute pyelonephritis and treatment of obstructive uropathy), and gastrointestinal fluid and salt loss.

Most cases of neonatal hyponatremia are detected during routine monitoring of hospitalized, usually preterm, infants. In such cases, careful assessment of volume status (fluid history and weight changes), urinary sodium excretion, medications, and other information will usually reveal a cause; treatment will typically involve adjustment of fluid and salt replacement. Symptoms and sequelae specifically attributable to hyponatremia are rarely encountered; therefore, more aggressive treatment (e.g., fludrocortisone, salt supplementation, etc.) should be carefully considered on the basis of the etiology and clinical condition. A more problematic situation is a previously healthy neonate who presents with lethargy, poor feeding, and inappropriate weight loss or gain and is found to have hyponatremia. Such cases may require rehospitalization and evaluation for intrinsic pathophysiology, including the disorders mentioned above.

I. The most common cause of neonatal **primary adrenal insufficiency** is CAH because of classical 21-hydroxylase (CYP21A2) deficiency, leading to incomplete cortisol deficiency, variable mineralocorticoid deficiency, excessive production of androgen precursors (17-hydroxyprogesterone, DHEA, and androstenedione) and consequent inappropriate virilization of a female, and isosexual sexual precocity in males (Chapter 22). All affected females are inappropriately virilized in utero, which may be evident on fetal ultrasound and at birth enabling preemptive detection of mineralocorticoid deficiency before onset of clinically significant salt-wasting. Affected male infants appear normally virilized; if mineralocorticoid deficiency is present, male infants may present with hyponatremic hyperkalemic dehydration, projectile emesis, inanition, and death, typically after 2 to 4 weeks of life. In the United States and other countries, virtually all cases of classical 21-hydroxylase deficiency are detected via newborn screening programs, usually

relying on detection of elevated 17-hydroxyprogesterone; acute clinical presentation with salt-wasting is no longer common. Treatment is replacement of glucocorticoid and mineralocorticoid.

Neonatal primary adrenal insufficiency is much less commonly caused by a loss-of-function mutation of *NR0B1* (aka *DAX1*; Xp21.2), resulting in X-linked congenital adrenal hypoplasia. Affected male infants typically present with severe salt-wasting within the first month of life, with low levels of cortisol and aldosterone, and elevated ACTH and plasma renin activity. The associated hypogonadotropic hypogonadism typically manifests with delayed puberty; genital underdevelopment may not be evident at birth. Mutation or deletion of contiguous genes can cause glycerol kinase deficiency and X-linked mental retardation.

J. Ambiguous genitalia (see Chapter 30) is a medical emergency because it may signal significant endocrine pathology. In addition, severe genital ambiguity, often suspected on the basis of fetal ultrasound, may raise immediate issues regarding postnatal gender assignment. True genital ambiguity involves inappropriate virilization of a genetic female (because of virilizing CAH) or undervirilization of a genetic male (because of defects in androgen synthesis or action, including 5α-reductase deficiency). Male genital hypoplasia (micropenis, scrotal hypoplasia, and cryptorchidism) may indicate fetal panhypopituitarism, reflecting the dependence of male external genital development on fetal gonadotropin production. Immediate evaluation is indicated in all cases with treatment addressing both the genital abnormalities and the underlying etiology.

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77 Hormones and Aging

Alexis M. McKee and John E. Morley

By the middle of the 21st century, 16% of the global population will be elderly, a stark contrast from 1950 when only 5% of the world population was older than 65 years.

Aging is any change in an organism over time. The aging process is a continuous and linear one, beginning in the early 30s and continuing throughout life. In women, the first clear aging event is the onset of menopause around the mean age of 52 years. Menopause has been demonstrated to be a marker for longevity; the later the onset, the longer the woman's life. In most, but not all countries, women not only live longer than men, but also live more years with some degree of disability.

In men, the onset of the hormonal signs of aging begins in the early 30s, but decreased testosterone in the hypogonadal range is not commonly seen until most men are in their 60s or 70s.

One of the greatest conundrums to be solved is the role of hormones and nutritional factors in the pathogenesis of sarcopenia (muscle wasting of aging), age-related cognitive decline, bone loss, and the pathogenesis of atherosclerosis —all of which contribute to the aging process. Figure 77-1 provides a conceptual framework of the factors involved in the pathogenesis of frailty.

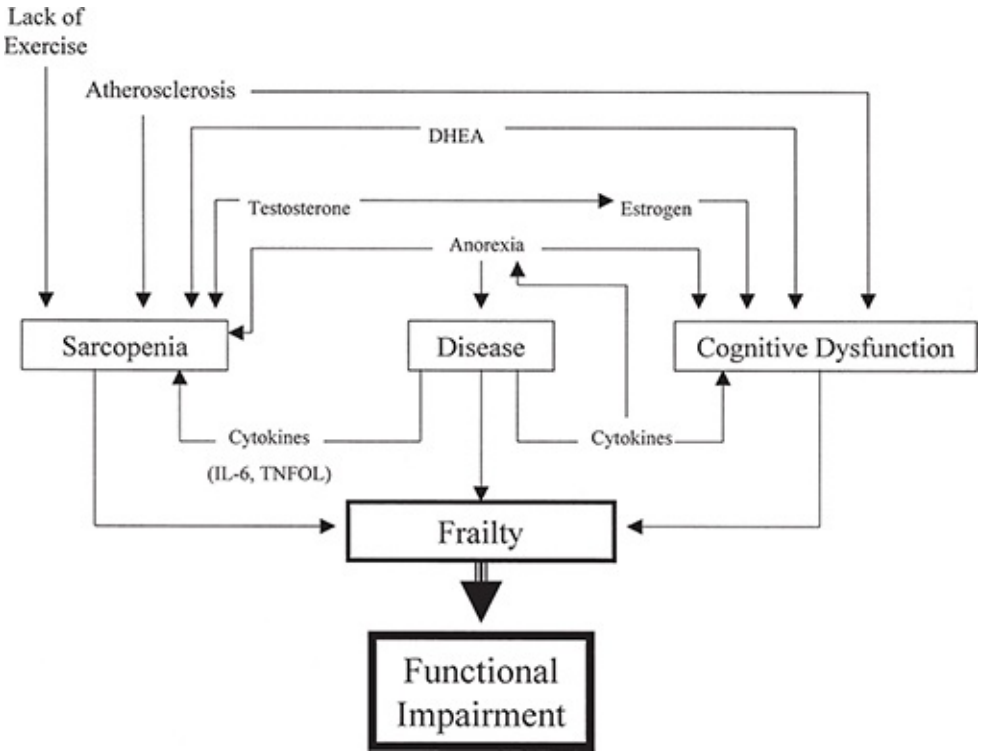

Figure 77-1. Factors involved in the pathogenesis of frailty. DHEA, dehydroepiandrosterone; IL-6, interleukin-6; TNFOL, tumor necrosis factor-ol.

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This chapter first briefly reviews the hormonal changes associated with aging. It then focuses on the potential role of some hormones on the aging process. Finally, it reviews hip fractures in the old and the anorexia of aging.

I. HORMONAL CHANGES ASSOCIATED WITH AGING

A. Factors affecting hormone levels. Numerous hormone levels decline with aging. Some increase and others remain unchanged (Table 77-1). With aging, it is particularly important to distinguish the changes that are due directly to aging and those that are associated with disease or with protein-energy malnutrition, such as euthyroid sick syndrome. In addition, it is important to recognize that polypharmacy is common in older persons, and that drugs can have direct effects on circulating hormone levels (e.g., high doses of β-adrenergic blockers may increase thyroxine levels by blocking entry into cells). Psychiatric disease may also result in hormonal changes. For example, psychosis leads to stress-induced hyperthyroxinemia, and Alzheimer disease is associated with multiple changes in

hormonal levels.

B. Target-organ functioning. With aging, there are changes in receptors and post receptor function. The classical changes are the decline in postreceptor β-adrenergic function. Mooradian et al. demonstrated that there are marked decreases in the tissue responsiveness to thyroid hormones with aging. There are abnormalities in the urinary cyclic adenosine monophosphate and cyclic guanosine monophosphate production to arginine vasopressin (AVP) and atrial natriuretic factor with aging. The decline in AVP-2 receptor activation leads to a decrease in aquaporin-2 receptors. These hormone/receptor mismatches are certainly a component of the cause of the high incidence of hyponatremia in older persons.

C. Circadian rhythms. Alterations in circadian rhythms are common with aging. Thus, although circulating AVP levels increase during the day with aging, the nocturnal peak is attenuated. This attenuation of AVP is the reason for the physiologic nocturia that develops with aging. In rodents, the age-related decline in AVP is related to the decline in testosterone and can be restored with testosterone replacement.

D. Plasma clearance rates. In the case of some hormones, when the production rate declines, there is also a decline in plasma clearance rates, resulting in maintenance of circulating hormone levels. Thus, when the thyroxine production rate declines with aging, so does the plasma clearance rate, resulting in no decline in plasma thyroxine levels. Circulating cortisol levels are slightly increased with aging as a result of a decline in clearance rate.

TABLE 77-1 Alterations in Hormones with Aging

Increase	No change	Decrease
Luteinizing hormone (women)	Luteinizing hormone (men)	Growth hormone
Follicle-stimulating hormone	Prolactin	IGF-I
Parathyroid hormones	Thyroid-stimulating hormone	Testosterone
Atrial natriuretic factor	Amylin	Estradiol (women)
Vasopressin (basal)	Thyroxine	DHEA
Insulin	Tri-iodothyronine	Vasopressin (nocturnal)
Norepinephrine	Epinephrine	
Vasoactive intestinal polypeptide	Glucagon-like peptide type 1	Vitamin D
Cortisol (mild)	Gastric inhibitory peptide	DHEA sulfate

Cholecystokinin	Calcitonin gene-related peptide	Melatonin

DHEA, dehydroepiandrosterone; IGF-I, insulin-like growth factor type I.

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II. THYROID-STIMULATING HORMONE (TSH). TSH tends to increase with aging, but this does not necessarily indicate a pathologic process and underscores the need for age-specific reference ranges according to iodine status. The presence of antithyroid peroxidase (TPO) and antithyroglobulin (Tg) thyroid antibodies are common in the elderly and may predict a greater risk of thyroid disease. Hypothyroidism is typically autoimmune in etiology or iatrogenic due to treatment of hyperthyroidism. Treatment with levothyroxine at low doses (typically 25 μg daily) with slow uptitration every 4 weeks is recommended. Whether or not to treat subclinical hypothyroidism, defined as an elevated TSH in conjunction with a normal free thyroxine test (FT4), is a topic of debate. According to the Whickham reanalysis, when controlling for age, levothyroxine treatment resulted in fewer ischemic heart disease events in younger patients (age 40 to 70 years) but not in older patients age 70 and above. This finding has been echoed in other studies where a mildly elevated TSH level has been associated with a decrease in mortality in the elderly, suggesting that **mild hypothyroidism in persons >80 years of age may not benefit from treatment**. Hyperthyroid elderly persons typically present with atrial fibrillation and weight loss, and when investigated, the most common etiologies are Graves disease and toxic multinodular goiter. The same modalities for treating younger patients apply to older individuals and include radioactive iodine ablation, antithyroid medication, or thyroidectomy, although radioactive iodine ablation is generally preferred. Subclinical hyperthyroidism, defined as a low TSH and normal FT4, is most commonly attributed to toxic adenomas or toxic multinodular goiters, although a repeat TSH should always be undertaken for the purpose of confirmation. Treatment should be considered with persistently suppressed TSH values less than 0.1 mU/L in patients 65 years and older, symptomatic individuals, patients with cardiac risk factors, and postmenopausal women not on hormone-replacement therapy or bisphosphonates.

III. ANDROGEN DEFICIENCY IN AGING MALES

A. Testosterone measurement. It has now been clearly demonstrated in cross-sectional and longitudinal studies that serum testosterone concentrations in men **decrease by 1% per year as they age**. As testosterone declines, sex hormone–binding globulin increases, which, in turn, makes the change in total testosterone a poor measurement of tissue-available testosterone. It is now accepted that free and bioavailable testosterone (free and albumin-bound) is the most appropriate measurement to diagnose hypogonadism in older persons.

B. Pathogenesis. The cause of the decline in testosterone in aging males is multifactorial. There is a deficit in the production of testosterone by the Leydig cells of the testis. More importantly, however, there is a failure of the hypothalamic–pituitary unit. Thus, the majority of older men present with secondary hypogonadism. With aging, gonadotropin-releasing hormone (GnRH) is secreted chaotically, resulting in a lesser stimulus to the gonadotropes. In addition, the GnRH is less capable of stimulating the pituitary to produce luteinizing hormone (LH). Thus, despite the low circulating testosterone level with aging, the LH level remains in the normal range. In very old men (>80 years old), primary hypogonadism with elevated LH levels is more common.

C. Sperm cells. Although spermatozoa levels decline with aging, most men usually have sufficient sperm to procreate. With aging, there is a decline in sertoli cell production of inhibin, leading to an increase in follicle-stimulating hormone.

D. Clinical presentations. Cross-sectional data have suggested that the testosterone decline in older men is associated with decreased libido, decreased strength of erection, decreased muscle mass and strength, increased visceral fat, dysphoria, decreased cognition, osteopenia, and a decline in functional status. Subsequently, interventional studies confirmed the capacity of testosterone to restore these age-related changes to normal.

E. Treatment. The effects of testosterone in older men are summarized in Table 77-2. Testosterone increases upper-arm strength and possibly lower-limb strength. Low testosterone levels have been associated with minimal hip trauma fracture, and testosterone replacement increased bone mineral density. Testosterone has improved some cognitive elements. In a recent study of testosterone replacement in men aged

p. 960p. 961 65 years and older, raising levels to low-middle normal range for men aged 19 to 40 years demonstrated improvement in sexual function, mood, and depressive symptoms.

TABLE 77-2 Effects of Testosterone in Older Men

Increased libido
Increased strength of erection
Increased lean body mass
Increased upper-limb strength
Increased bone mineral density
Decreased adiposity
Decreased leptin
Increased hematocrit
Improved cognition
Coronary artery vasodilation
Decreased angina

F. Side effects of treatment. The major side effect of testosterone therapy in older men is **erythrocytosis**. **Sleep apnea** occasionally develops or worsens during androgen-replacement therapy. The accumulation of lean body mass and fluid retention generally causes **weight gain**. Mild **gynecomastia** may result occasionally, as testosterone can be aromatized to estradiol in peripheral tissues. Studies have suggested that low testosterone levels are associated with coronary artery disease prevalence, and that testosterone replacement causes coronary artery vasodilatation and either positive or no effects on lipids. Testosterone replacement does not appear to be particularly deleterious in men with benign prostatic hypertrophy, but it **should not be given to men with prostatic cancer**.

G. Androgen deficiency in aging males (ADAM) questionnaire. In order to identify older males with hypogonadism, we have developed the ADAM questionnaire (Table 77-3). This questionnaire has been demonstrated to have high sensitivity and adequate specificity. The major false positives are due to the result of depression. The questionnaire is easily used in the primary care physician's office. The ADAM is shorter and performs at a level similar to that of the Aging Male Survey.

IV. GROWTH HORMONE (GH) (see Chapter 12)

A. Physiology. Human aging leads to a decline in circulating concentration of both GH and insulin-like growth factor type I (IGF-I). Much of the decline in GH begins at 40 years of age, and by 70 years of age, mean GH concentration is approximately one quarter of the values seen in adults in their 20s. GH secretion decreases by p. 961p. 9621.6% per year over the life span. GH continues to demonstrate a nocturnal peak in older persons. With aging, there is a reduction in the GH response to growth hormone–releasing hormone (GHRH), insulin-induced hypoglycemia, and exercise. Overall, animal and human studies suggest that with aging there is both an increase in somatostatin tone and a reduction in GHRH input to the pituitary that result in the decline in GH production. **Ghrelin** is a peptide hormone that is produced from the fundus of the stomach and that **increases GH** and improves appetite and memory.

TABLE 77-3 **The Saint Louis University Androgen Deficiency in Aging Males Questionnaire. Positive score if answers to questions No. 1 or No. 7 or any three answers are "yes".**

Yes	No	**1.** Do you have a decrease in libido (sex drive)?
Yes	No	**2.** Do you have a lack of energy?
Yes	No	**3.** Do you have a decrease in strength and/or endurance?
Yes	No	**4.** Have you lost height?
Yes	No	**5.** Have you noticed a decreased enjoyment of life?
Yes	No	**6.** Are you sad and/or grumpy?
Yes	No	**7.** Are your erections less strong?
Yes	No	**8.** During sexual intercourse, has it been more difficult to maintain your erection to the completion of intercourse?
Yes	No	**9.** Are you falling asleep after dinner?
Yes	No	**10.** Has there been a recent deterioration in your work performance?

B. GH treatment (see Chapter 12). Rudman noticed the similarity between the effects of GH deficiency and physiologic aging and suggested that older persons go through a "GH menopause." This

spawned a panoply of GH replacement studies in older persons. GH increases lean body mass and decreases fat mass in older persons. However, it does not increase muscle strength because of the fact that it increases protein synthesis but not satellite cell formation. Furthermore, GH fails to produce any additional benefit in older persons who are exercising. GH has not been shown to produce any clear-cut positive effects on bone mineral density. GH increases skin thickness. In the elderly, GH therapy has been, in fact, associated with numerous side effects, including carpel tunnel syndrome, fluid retention, fatigue, arthralgias, gynecomastia, joint swelling, and headache. These side effects are dose-related. When given short term, GH has been shown to improve function in malnourished older persons.

C. Replacement. If replacement is desired, it should be noted that is not feasible to mimic the variable and pulsatile secretion of endogenous GH. In general, GH is administered initially as 0.1 to 0.2 mg SQ daily in the evening, and doses are titrated according to the mean IGF1 level for age monitored every 4 weeks.

D. Side effects. Of greater concern are the facts that high-normal physiologic GH levels in the Paris policeman study were associated with increased mortality, and the Snell dwarf (GH-deficient) mouse lives longer than control mice. These findings suggest that the long-term administration of GH may increase mortality in older persons. At present, the antiaging effects of GH are clearly not proven, and a number of troublesome side effects suggest that GH should not be used for this purpose.

V. DEHYDROEPIANDROSTERONE (DHEA) AND PREGNENOLONE

A. Physiology. Both pregnenolone and DHEA and their sulfated moieties decline dramatically with aging. By 80 years of age, both DHEA and its sulfate (DHEAS) are 20% of the values seen in young persons. This observation led to multiple epidemiologic studies demonstrating a positive association between the decline in DHEA and DHEAS and a higher degree of physical disability.

B. DHEA treatment. A multitude of studies have examined the effect of DHEA replacement in older persons, only to yield mixed results. DHEA administration results in an increase of other circulating androgenic hormones, namely, testosterone, androstenedione, and

dihydrotestosterone. However, high-quality intervention studies such as the DHEAge study found only small increases in both testosterone and estradiol in both elderly men and women as well as increased libido only in older women. There was no effect on muscle strength or volume.

C. Pregnenolone treatment. Pregnenolone is the true "mother hormone," being the precursor of all known steroid hormones. Studies in the 1940s suggested that pregnenolone was a safe and effective therapy for many symptomatic persons with arthritis. Pregnenolone improves sleep, reduces fatigue, and increases production efficiency. In mice, pregnenolone is a potent memory enhancer. However, the effect of pregnenolone on memory in humans has not been established.

D. Summary. Similar to GH, pregnenolone and DHEA have occasionally generated excitement among antiaging enthusiasts. However, the experimental evidence lags far behind the promise. A further concern is that many of the DHEA products on the market contain minimal amounts of absorbable DHEA. Overall, there is a need for carefully controlled long-term studies to establish the role of DHEA and pregnenolone in aging. At present, the positive effects of these hormones in humans have yet to be convincingly established.

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VI. MELATONIN

Melatonin is derived from tryptophan and produced by the pineal gland, "the seat of the soul." Melatonin levels fluctuate with increasing levels in the evening and peaks in the middle of the night. There is a gradual decline in levels with aging. In the elderly, low levels of melatonin at night have been linked to disturbances in the sleep/wake cycle, which is particularly true of individuals with Alzheimer disease. Melatonin and/or ramelteon may, therefore, be beneficial in the treatment of delirium and sundowning syndrome. In addition to its effects on sleep, melatonin in animals has been demonstrated to extend the life span. Free radicals have been considered to be a major factor in support of the aging process. Melatonin is a potent scavenger of the highly toxic hydroxyl radical and other oxygen-centered radicals. Melatonin seemed to be more effective than other known antioxidants, for example mannitol, glutathione, and vitamin E, in protecting against oxidative damage. Serum melatonin concentrations vary considerably according to age. Most studies suggest

that melatonin levels decline in middle and old age. In humans, higher melatonin levels have been correlated with better cognitive function.

A. Vitamin D. 25-Hydroxyvitamin D levels have been shown to decrease even in very healthy elderly men living in a sunny climate. This results in an increase in parathormone, leading to loss of calcium from bone and osteopenia. Recent studies have indicated that low levels of 25-hydroxyvitamin D are associated with increased falls, sarcopenia, and a decline in functional status that can be reversed with vitamin D replacement. More recent studies have focused on the importance of measuring vitamin D binding protein, and as future data on these measurements in the elderly become available, our understanding of vitamin D pathophysiology will change drastically.

VII. HIP FRACTURES

"We come into the world through the brim of the pelvis and go out through the neck of the femur."

Hip fracture is one of the most seriously debilitating but preventable injuries among individuals aged 65 years and older. Among this group, approximately one half of white women and one quarter of white men will sustain at least one osteoporotic fracture in their remaining lifetime. The burden of hip fracture among older adults requires continued vigilance in primary and secondary prevention. Osteoporosis causes 1.5 million fractures every year.

A. Causes. Hip fracture rates increase with aging. The causes of hip fracture are multifactorial and include osteoporosis, falls, prostate cancer, orchiectomy, androgen-deprivation therapy, and malnutrition. Persons who have had a hip fracture are often not treated for osteoporosis despite the fact that they are two-and-a-half times as likely to have another fracture within the next 2 years (Fig. 77-2).

B. Risk factors. The risk factors for osteoporosis, according to the World Health Organization and the International Osteoporosis Foundation, are advanced age, previous fracture, parental history of proximal femur fracture, low body mass index, low bone mass, glucocorticosteroid treatment, rheumatoid arthritis, secondary osteoporosis, smoking, and the overuse of alcohol. A major risk factor for the loss of bone with aging is the decline in vitamin D levels. This decline has many causes, including decreased synthesis of cholecalciferol in aging skin, decreased conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in the kidney, and

reduced vitamin D receptor function.

C. Treatment. Mortality is increased after a hip fracture, and strategies that improve outcomes are needed. Treatment combines a limitation of fracture risk-factor effects, including fall prevention and improvement of bone quality, by applying pharmacotherapy. Newly admitted nursing facility residents only infrequently received an indicated osteoporosis treatment despite the expected high prevalence of osteoporosis in this setting.

Prevention of hip fracture in older persons requires administration of calcium and vitamin D. When osteoporosis is established, bisphosphonates should be added. The three approved bisphosphonates are **alendronate, risedronate**, and **ibandronate**. Alendronate and risedronate are dosed daily or weekly, and ibandronate has been approved for monthly oral dosing or as an IV formulation to be given intermittently p. 963p. 964p. 964p. 965(every 3 months). In addition, **zoledronic acid** is the only once-yearly treatment for women with postmenopausal osteoporosis.

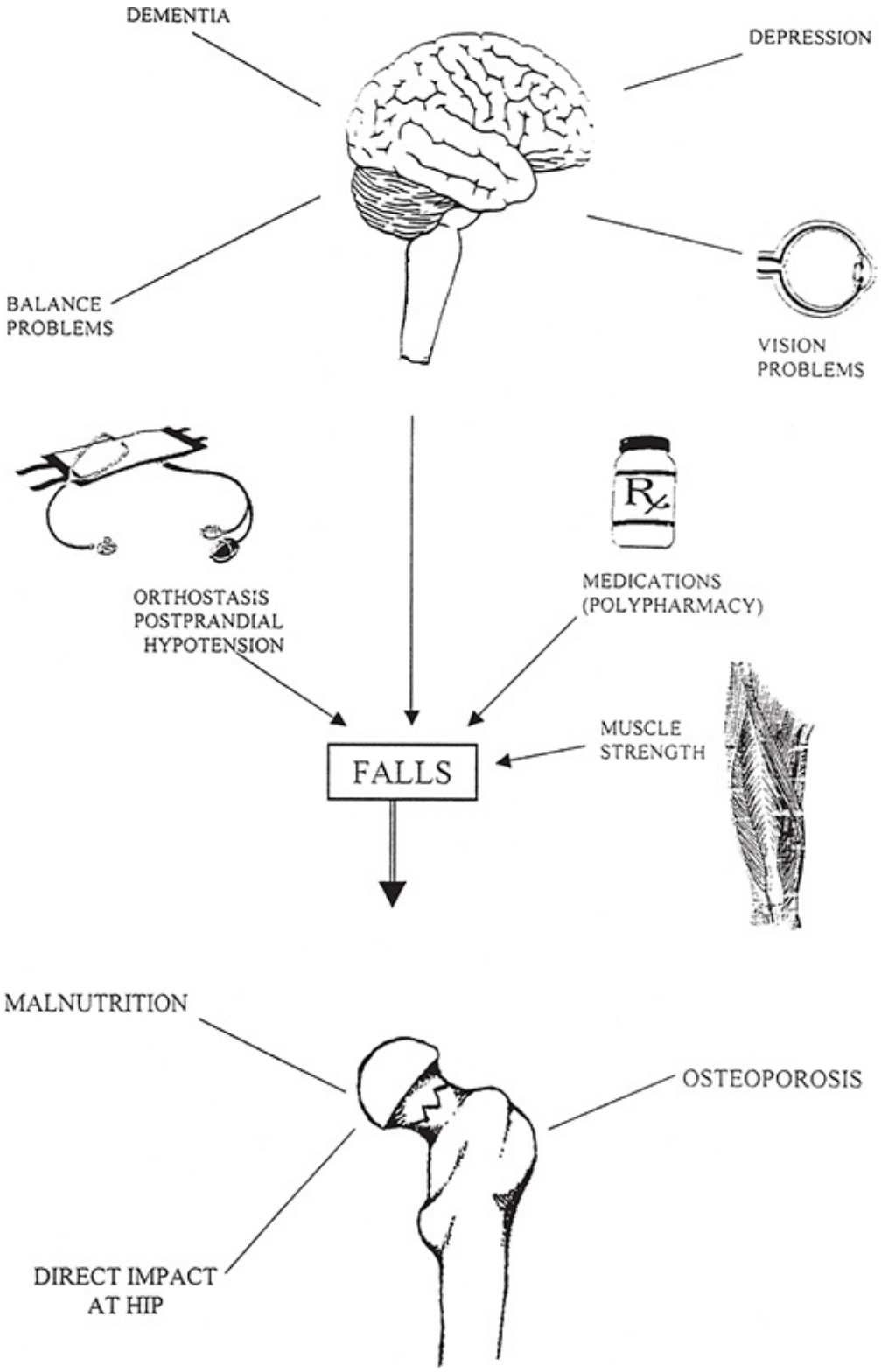

Figure 77-2. Causes of falls and hip fractures.

Risk factors for falls include intrinsic factors, extrinsic factors, or

situational factors. New-onset falls in older persons are often due to delirium. Intrinsic causes of falls are muscle weakness, balance problems, gait problems, orthostasis, postprandial hypotension, depression, visual problems, arthritis, impairment of activities of daily living, cognitive impairment, and polypharmacy (hypnotics, antidepressants, and antipsychotics). Selective serotonin receptor–inhibitor antidepressants are more likely to be associated with hip fractures than are tricyclics.

The Cochrane Collaboration found in their meta-analytic review of effective fall-prevention interventions for elderly living in the community that a multifactorial assessment is required to reduce fall rates. Both group- and home-based exercise programs, in addition to home safety interventions, reduce the rate of falls and risk of falling. In nursing home residents, the use of hip protectors, when worn regularly, may help reduce hip fracture rate, though this is controversial. Restraints are not fall-prevention devices.

The **30-day mortality after hip fracture was 7.2%**. Patients who were operated on within 2 days of admission had a 30-day postoperative mortality rate of 5.8%, versus 9.4% in those patients who experienced a delay of more than 2 calendar days. Studies on the benefit of multidisciplinary rehabilitation for people who have sustained hip fracture showed that there is a 16% reduction in the pooled outcome, combining death, or admission to a nursing home.

VIII. ANOREXIA OF AGING

A. Diet and exercise. Food intake declines throughout the life span. Thus, at middle age, in which obesity is endemic in the United States, persons are actually eating less than when they were younger. This suggests that the major cause of middle-aged obesity is a reduction in physical activity coupled with a decrease in resting metabolic rate. Over age 50, weight loss without an exercise program results in loss of muscle as well as fat. With aging, replacement of muscle mass becomes harder. Thus, in older persons, dieting can lead to a vicious cycle of fat and muscle loss followed by regaining of fat mass only. This can eventually lead to the development of “the fat frail syndrome.” Persons who develop “fat frail syndrome” have worse outcomes than underweight frail older persons. Thus, from middle age on, exercise is the key to weight loss. The exercise regimen should include muscle strengthening as well as endurance exercises.

B. Anorexia. People tend to experience less hunger and become rapidly satiated as they age. With aging, the energy expenditure decreases and results in overall less food consumption. This age-related physiologic decline in food intake over the life span has been termed “anorexia of aging.” The etiology of anorexia of aging is multifactorial, including both central and peripheral causes. Alterations in taste and smell sensitivity with aging appear to play a minor role in the decreased food intake. The cause of this change is mainly age-related decline in taste-bud receptors with decreased food palatability, as well as potential side effects of multiple medications the elderly population is prescribed because of their multiple comorbidities. However, alterations in satiating signals from the stomach appear to play a major role in the early satiation that occurs with aging. Hormonal factors contributing to the development of anorexia of aging are decreased levels of testosterone, higher circulating levels of cholecystokinin (CCK), possible reduced activity of ghrelin, alterations in leptin release and sensitivity, and decreased endorphin concentrations in brain cerebrospinal fluid. The role of increased activity of certain cytokines such as interleukins (IL) IL-1, IL-2, IL-6, and tumor necrosis factor-α (TNF-α) with aging has also been examined in different studies. The nonendocrine factors linked to anorexia of aging are social isolation, psychological causes, and coexisting medical illnesses.

C. Anatomic characteristics. With aging, the ability of the fundus of the stomach to demonstrate adaptive relaxation to the presence of food particles declines, which results in less food being eaten at every meal.

Aging has also been shown to be p. 965p. 966associated with **delayed gastric emptying** for both liquids and solids, which is probably caused by increased phasic pyloric pressures or autonomic neuropathy seen in elderly populations. Another important factor is decreased production of nitric oxide locally in the stomach in response to food, which is considered the major reason for the age-related decline in adaptive relaxation. With the decrease in adaptive relaxation, food fills the antrum more quickly, resulting in earlier antral stretch and early satiety.

D. CCK. In addition, circulating levels of the satiating hormone CCK increase with aging. Studies have shown that older subjects have more CCK levels in their small intestine compared with younger age groups. CCK also has a greater satiating effect when administered to older

persons. CCK is released in response to fat in the meals, and these findings explain the decline in the fat calories ingested as a person ages.

E. **Leptin.** Leptin is a peptide hormone produced by the adipose cell. It decreases food intake and increases metabolic rate. With aging, leptin levels increase in men and decline in women. This increase in leptin level in men is associated with the age-related decline in testosterone, and testosterone administration to older men has been shown to decrease leptin levels. Men have a more dramatic decrease in food intake with aging than women, and the testosterone–leptin interaction appears to explain this difference.

F. **Neuropeptides.** Rodent studies have suggested that aging results in the alterations in the levels or responsiveness of a number of central orexigenic neuropeptides involved in food intake, including the endogenous κ opioid and neuropeptide Y. The expression of both neuropeptide Y and its receptors in the hypothalamus is decreased in studies of older rats, which impacts its role as a mediator of leptin's effects in the central nervous system.

G. **Cytokines.** Not only do cytokines produce anorexia, they also lead to muscle wasting (cachexia) and a reduction in circulating albumin levels. The cytokines most active in this regard are TNF-α, IL-2, IL-6, and ciliary neurotrophic factor. Older persons suffer multiple inflammatory conditions that result in cytokine elaboration. Certainly, cytokines appear to play a major role in the anorexia seen in frail sick older persons. Studies have shown that aging is associated with increased levels of cortisol and catecholamines, which, in turn, also lead to increased cytokine activity in this population.

H. **Ghrelin.** Ghrelin, a peptide hormone produced by gastric mucosa, is a ligand for the GH receptor. It exerts its effects by stimulating the release of neuropeptide Y from the arcuate nucleus, which, in turn, leads to increased appetite. Ghrelin stimulates the release of GH and regulates energy balance and adipose tissue metabolism. Studies have shown that ghrelin also inhibits the production of inflammatory cytokines. Acyl ghrelin levels decline with aging, and data that older individuals have impaired secretion of ghrelin in response to nutritional deficiencies exist, which could possibly contribute to decreased food intake.

I. **Glucagon-like peptide-1 (GLP-1).** GLP-1 is secreted from gut endocrine cells and mediates its effects by vagal afferent signals from

the liver to slow gastric emptying. Some studies have shown a possible role of glucagon in satiation associated with older age, particularly in postmenopausal women. Peripheral administration of GLP-1 has been shown to suppress food intake and increase satiety. In diabetics, glucagon administration has been shown to decrease appetite and increase satiety.

J. Treatable causes of weight loss. Besides cancer, numerous treatable conditions result in anorexia and subsequent weight loss. Depression is considered the most common condition leading to weight loss in the elderly, with this cause representing 30% to 36% in community and nursing home settings. Polypharmacy is the second most common cause of pathologic anorexia. Metabolic causes include hyperthyroidism, Addison disease, pheochromocytoma, and hyperparathyroidism. Other chronic medical conditions, including rheumatoid arthritis, AIDS-related cachexia, temporal arteritis, malabsorption syndromes, *Helicobacter pylori* infection, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), alcoholism, and infections, can contribute to unintentional weight loss. Therapeutic diets may p. 966p. 967result in excessive weight loss and malnutrition if their effects are not carefully monitored. Other conditions such as bad oral hygiene and poor dentition play an important role in malnutrition in the elderly. Table 77-4 provides a simple mnemonic as a reminder of the treatable causes of weight loss in older persons.

TABLE 77-4 MEALS-ON-WHEELS Mnemonic as an Easy Method to Screen for Causes of Weight Loss in Older Persons

Medications (e.g., digoxin, theophylline, and cimetidine)
Emotional (e.g., depression)
Alcoholism, elder abuse, and anorexia tardive
Late-life paranoia
Swallowing problems
Oral factors
Nosocomial infections (e.g., tuberculosis)
Wandering and other dementia-related factors
Hyperthyroidism, hypercalcemia, and hypoadrenalism
Enteral problems (e.g., gluten enteropathy)
Eating problems

Low-salt, low-cholesterol, and other therapeutic diets
Stones (cholecystitis)

K. Anorexia treatment. The key components of treatment include identification and management of the underlying cause, followed by administration of oral liquid calorie supplements between meals with correction of vitamin and mineral deficiencies, especially vitamin D, folate, and calcium. A meta-analysis has demonstrated their efficacy at increasing food intake and producing weight gain. More aggressive measures such as tube feeding are considered in cases of severe malnutrition and disorders that cause difficulty in swallowing and digestion. A number of orexigenic agents have also been used to increase food intake, including megace, dronabinol, and anabolic steroids, although the effects have been disappointing. Megestrol acetate, a mixed progestagen–corticosteroid–testosterone, was found to decrease cytokine levels and increase food intake in older individuals, especially those with cancer-related cachexia. Unfortunately, the weight gain achieved is mostly fat rather than muscle, and secondary adrenal insufficiency as a potential side effect is a cause for concern. Dronabinol, a tetrahydrocannabinol, leads to a small weight gain by stimulating appetite and improving taste, anxiety levels, and sleep. Although originally it was thought that GH might improve outcomes in persons with malnutrition, Takata et al. suggested that in critically ill, severely malnourished patients, the use of GH increased mortality. In cachexia related to chronic medical conditions such as COPD, CHF, and end-stage renal disease, ghrelin injections have been shown to be effective in increasing weight. Some studies have shown the benefit of mirtazapine, an antidepressant, in improving appetite and causing weight gain in patients with underlying depression and weight loss.

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78 Neuroendocrine (APUD) Syndromes

Adrian Langleben

I. INTRODUCTION

Although the term APUD tumors is still recognized, at this time these tumors are most usually classified and discussed under the category of the **"neuroendocrine tumors" (NETs).** The pathologic classification of these tumors, as well as the understanding of their associated genetic and clinical features, continues to evolve.

II. GENERAL PRINCIPLES

The APUD cell, a term coined by Pearse in 1968, constitutes a family of neurosecretory cells that are widely distributed throughout the body. These cells display electron-dense granules on ultrastructural microscopy and contain neuron-specific enolase, characteristics that persist as malignant degeneration occurs. These cells share a common synthetic pathway for hormone production, from which the acronym **APUD** has been derived. This includes the capacity for **amine precursor uptake and subsequent decarboxylation**, resulting in the synthesis of bioactive amines or polypeptide hormones. This classification remains valid, even though subsequent experimental evidence has challenged the notion of a common embryologic origin, that is, the neural crest for the APUD cells, as originally proposed by Pearse. Current oncologic literature refers to these cells as "neuroendocrine" (NE) and to the tumors that are produced as NETs or neuroendocrine carcinoma (NEC).

A. Location. NE cells are found in:

1. The central and peripheral NE system (from the hypothalamus and pituitary to the peripheral autonomic ganglia and adrenal medulla)
2. The gastrointestinal tract (from the pharynx to the anus)
3. The pulmonary mucosa

B. The **function** of the NE cells is the NE regulation of normal homeostatic mechanisms, including vasomotor tone, as well as carbohydrate, calcium, and electrolyte metabolism. Each NE cell

normally synthesizes, stores, and secretes its single amine or polypeptide and is responsive to its environment for stimulation or suppression.

C. Classification. Three classes of hormones are produced or regulated by NE cells: **(1)** the amines (produced by NE cells), **(2)** the polypeptides (produced by NE cells), and **(3)** the steroids (produced by the mesodermal adrenal cortex and the gonads). Steroids are not NE cell products but are involved in the NE syndromes because they are responsive to the trophic actions of the NE polypeptides. The specific hormones in the first two categories are listed in Table 78-1.

Hyperplasia or neoplasms of cells that produce these hormones are called **APUDomas**, a term first used by Szijj in 1969 to describe a medullary carcinoma of the thyroid that was secreting adrenocorticotropic hormone (ACTH).

Depending on the location of the tumor and the specific hormone produced, an APUDoma may be characterized as either entopic or ectopic:

1. **Entopic (orthoendocrine).** The NE cell in its normal location produces excessive amounts of its native hormone. For example, a *β*-cell adenoma of the pancreas oversecretes insulin.
2. **Ectopic (paraendocrine).** Polypeptides and occasionally amines are produced by tumors, usually malignant, that are located in areas that do not normally p. 970p. 971produce that humoral substance. The term **ectopic** is sometimes used to describe embryologically misplaced adenomas such as mediastinal parathyroid adenomas or pheochromocytomas of a sympathetic ganglion. In such instances, the secretion is entopic, but the tumor tissue is embryologically misplaced. The true ectopic syndromes arise from the tumors of either endocrine glands or organs not considered endocrine that, when malignant, hypersecrete polypeptide hormones that are not native to that gland or tissue. For example:
   - **a.** An islet-cell malignancy producing the **Zollinger–Ellison syndrome** by elaboration of a high-molecular-weight prohormone of gastrin, not native to the pancreas.
   - **b.** An oat cell carcinoma of the lung hypersecreting the prohormone of ACTH, resulting in **Cushing syndrome.**

TABLE 78-1 NEC Cell Hormones

I. Amines
1. Catecholamines
   - **a.** Epinephrine
   - **b.** Norepinephrine
   - **c.** Dopamine
2. Serotonin
3. Histamine
4. Thyroxine
5. Acetylcholine

II. Polypeptides
1. Hypothalamic and pituitary tropic hormones
   - **a.** Adrenocorticotropic hormone
   - **b.** Prolactin
   - **c.** Growth hormone
   - **d.** Melanocyte-stimulating hormone
   - **e.** Thyroid-stimulating hormone
   - **f.** Somatostatin
2. Thyrocalcitonin
3. Parathyroid hormone
4. Gastropancreatic hormones
   - **a.** Gastrin
   - **b.** Secretin
   - **c.** Cholecystokinin-pancreozymin
   - **d.** Gastric inhibitory peptide
   - **e.** Substance P
   - **f.** Insulin
   - **g.** Glucagon
   - **h.** Somatostatin
   - **i.** Human pancreatic polypeptide
   - **j.** Vasoactive intestinal polypeptide

NEC, neuroendocrine carcinoma.

D. Furthermore, it is recognized that there are large **differences** within this "large family," based upon the organ of origin, clinical manifestations, grade (i.e., well-differentiated NETs, as opposed to poorly differentiated NEC), and, increasingly different, treatment options.

E. The **origin** of these tumors has been postulated to be primitive cells that have stem cell features, as opposed to aberrant differentiation of more mature cells, which then give rise to these neoplasms. Well-differentiated neuroectodermal tumors morphologically p.

971p. 972resemble nonneoplastic NE cells. However, the poorly differentiated NECs are high-grade malignancies that exhibit only some features of NE differentiation.

F. The **well-differentiated and poorly differentiated NETs** are now felt to be two very distinct groups of neoplasms. Assessment of grade and assignment of proliferative index remain complex issues, but it is recognized that they are very important in the classification and the definition of aggressiveness of any particular tumor.

G. Biologic behavior differs greatly between these two categories of tumors, as do the therapeutic approaches; that is, surgery is the preferred modality for well-differentiated NETs, whereas poorly differentiated carcinomas do require systemic therapy.

Poorly differentiated NE cancers often arise in association with an epithelial component, but well-differentiated tumors rarely have such an epithelial component.

H. In addition, there are differences at the **molecular** level. The well-differentiated NETs lack alterations in genes such as RB-1 and TP53, alterations that are commonly found in poorly differentiated NECs.

I. The **biology** of these lesions also differs by site of origin, adding additional complexity to the management.

J. The **terminology** applied to the nomenclature of this large class of tumors, as well as the staging systems, remains in flux, with the American Joint Committee on Cancer being possibly the most comprehensive. In addition to the pathologic classification of these tumors, many of these tumors are also functional in terms of inappropriate secretion of bioamines or peptide hormones, which results in highly characteristic paraneoplastic syndromes.

K. The **annual incidence** of NETs has risen substantially during the past two decades, with much of the increase in incidence attributed to improvement in imaging technology. The annual incidence is approximately 5 cases per 100 000 people.

L. A large number of blood and urine biomarkers are useful for **diagnosis** and follow-up of these various tumors. MRI and CT scan provide complementary techniques for imaging of the abdominal cavity, chest, and liver. In addition, the family of agents that are used for functional imaging is expanding rapidly.

M. Significant advances have been made in the use of systemic **therapy** for control of symptoms produced by hormone hypersecretion.

Somatostatin analogs can control systemic symptoms to a significant degree in approximately 70% of patients. The use of **interferon** for this purpose has been largely supplanted by these molecules, which are highly effective and less toxic than interferon. Additional compounds, such as small-molecule inhibitors of **tryptophan hydroxylase**, are under investigation.

Significant advances have also been made in the use of systemic therapy, of various types, for the actual control of tumor growth and progression.

Somatostatin analogs inhibit the growth of well-differentiated NETs. Tumor cell proliferation and invasion and angiogenesis are blocked, and apoptosis is induced. Clinically, very significant prolongation of time to progression has been achieved in two prospective randomized trials, establishing long-acting somatostatin analogs as a treatment of choice for well-differentiated, moderately differentiated, metastatic neuroectodermal tumors.

Several randomized trials have **not documented clinical benefit with the use of interferon** in the first line of therapy. Accordingly, the use of interferon remains somewhat controversial, and currently its use is reserved for second line, after a lack of response with somatostatin analogs.

The **mammalian target of rapamycin (mTOR) pathway** is a downstream mediator of several growth factor pathways that are active in neuroectodermal tumors. Overactivation of this pathway has been documented. Everolimus is an inhibitor of this pathway that is approved for the treatment of neuroectodermal tumors on the basis of improvements in progression-free survival.

Neuroectodermal tumors are highly vascularized. Accordingly, inhibitors of tumor angiogenesis have been studied to assess the therapeutic response and clinical benefit. **Bevacizumab** was shown to slightly improve progression-free survival compared with interferon, but the time to treatment failure was significantly longer

p. 972p. 973with the Bevacizumab arm. Oral small-molecule receptor tyrosine kinase inhibitors, such as **sunitinib**, are approved on the basis of the ability to delay tumor progression, compared with placebo. Median progression-free survival was significantly increased, with a clinical benefit clearly seen.

Streptozocin-based combination chemotherapy remains

the best studied, with response rates up to approximately 30%. Many other additional chemotherapeutic agents have been studied, without significant clinical benefit. **Platinum-based regimens** are reserved for very poorly differentiated neuroectodermal carcinomas, with variable response rates, usually not of long clinical duration.

Peptide receptor radionuclide therapy combines the radionuclide with the somatostatin analog, thus targeting delivery to the somatostatin receptor on the tumors. Response rates as high as 30% are reported, but these are early studies. Additional studies are ongoing.

The rising incidence of neuroectodermal tumors of all grades poses an unmet clinical need, in domains of improved diagnostics and improved therapies.

III. NEUROENDOCRINE TUMOR (APUDoma) SYNDROMES

This (Table 78-2) may be categorized as follows.

A. Entopic

1. Gastrointestinal tract

a. Carcinoid. First described by Obendorfer in 1907, this tumor is the most frequently encountered one of the NEC system. The incidence of carcinoid tumors is estimated to be approximately 1.5 cases per 100 000 of the general population (about 2 500 cases per year in the United States). Carcinoid tumors have been identified throughout the gastrointestinal tract, including the esophagus, stomach, duodenum, jejunum, ileum, Meckel diverticulum, appendix, colon, rectum, bile ducts, pancreas, and liver. They have also been found in the larynx, thymus, lung, breast, ovary, urethra, and testis.

i. The secretory product of the tumor is primarily 5-hydroxytryptamine (serotonin), although there are other hormones reportedly elaborated by this tumor, including bradykinin, hydroxytryptophan, prostaglandins, substance P, neurokinin A, thyrocalcitonin, pancreatic polypeptide, calcitonin gene–related peptide, vasoactive intestinal polypeptide (VIP), and histamine.

ii. Symptoms associated with the classic carcinoid syndrome (which occur in <10% of patients with carcinoid tumors) include the following.

a) Flushing (see Chapter 87) (found in 49% of

symptomatic patients; a pellagra-like eruption in severe cases). This symptom is usually attributed to the effects of secreted bradykinin, hydroxytryptophan, and prostaglandins. It is occasionally responsive to a combination of the H_1 blocker diphenhydramine and the H_2 blocker cimetidine. Niacin may partially alleviate the pellagra-like eruption.

b) Diarrhea (found in 83% of symptomatic patients) is attributed to the effects of serotonin, prostaglandin, and bradykinin. It may respond to the serotonin antagonists cyproheptadine or methysergide.

c) Bronchospasm (found in 6% of symptomatic patients) is attributed to bradykinin, histamine, and prostaglandins, and may also be responsive to methysergide.

The following are all attributed to the effects of serotonin:

d) Coronary artery spasm leading to angina pectoris

e) Endocardial fibrosis

f) Arthropathy

g) Glucose intolerance

h) Hypotension

Only 7% to 10% of patients with carcinoid tumors, but up to 45% of those with liver metastases, have been reported to exhibit any of the above symptoms of the carcinoid syndrome. This observation has been attributed to the short half-life of serotonin (<1 minute) and the very high hepatic extraction of this chemical from the circulation.

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TABLE 78-2 APUDoma Syndromes

Tumor type	Clinical syndrome	Site	Hormone(s)
Entopic			
Carcinoid	Flushing/diarrhea/wheezing	Midforegut	Serotonin

		Pancreas/foregut adrenal medulla	
Insulinoma	Hypoglycemia	Pancreas/uterus retroperitoneal liver	Insulin, IGF
Pancreatic glucagonoma	Dermatitis/dementia Diabetes/DVT	Pancreas	Glucagon
Gastrinoma	Ulcer disease	Stomach Duodenum	Gastrin
Somatostatinoma	Diabetes/steatorrhea, cholelithiasis	Pancreas	Somatostatin
Anterior pituitary adenoma	Cushing syndrome Hyperpigmentation Acromegaly, gigantism Galactorrhea	Anterior pituitary gland	ACTH MSH GH Prolactin
Medullary carcinoma	Diarrhea	Thyroid gland	Calcitonin Prostaglandin
Pheochromocytoma	Hypertension	Adrenal medulla	Epinephrine
Ganglioneuroma	Abdominal mass	Sympathetic ganglia	Norepinephrine
Neuroblastoma			
Bronchogenic carcinoma Carcinoid of bronchus or gut Epithelial cancer of thymus Islet-cell tumor of pancreas Medullary cancer of thyroid Pheochromocytoma	Cushing syndrome	Lung Bronchus or gut Thymus Pancreas Thyroid Adrenal medulla	ACTH
Gastrinoma	Zollinger–Ellison syndrome	Pancreas	Gastrin
VIPoma	Watery diarrhea Hypokalemia Alkalosis	Pancreas	VIP

ACTH, adrenocorticotropic hormone, corticotropin; APUD, amine precursor uptake and decarboxylation; DVT, deep venous thrombosis; GH, growth hormone, somatotropin; IGF, insulin-like growth factor; MSH, melanocyte-stimulating hormone; VIP, vasoactive intestinal polypeptide.

iii. **Diagnosis** of a nonfunctioning carcinoid tumor is by biopsy and histologic section. Patients with functioning carcinoid tumors may be diagnosed by measuring the 24-hour urine excretion of 5-hydroxyindoleacetic acid. A value

>9 mg per 24 hours in a patient without malabsorption, or >30 mg per 24 hours in a patient with malabsorption, is reported as diagnostic.

iv. **Treatment** of choice is surgical excision of the primary tumor and, when possible, of the hepatic or nodal metastases, because this tumor generally grows at an indolent pace. When symptomatic metastases cannot be removed, palliative therapy with the long-acting analog of somatostatin p. 974p. 975(octreotide acetate, Sandostatin) has been of reported benefit both for symptom control and occasionally for actual reduction of tumor burden. A review of 300 patients with carcinoid tumors treated with interferon-α for a median of 2.5 years concluded that this agent has significant antitumor effects in 70% to 80% of patients, as manifested by biochemical control and inhibition of tumor growth. Tumor progression generally occurred within 3 to 9 months after cessation of the drug. However, other studies have questioned the efficacy of interferon-α. Traditional single-agent and combination chemotherapy have only modest activity. However, targeted therapy with sunitinib has shown very high rates of "clinical benefit" and prolonged stable disease. Furthermore, imatinib, an inhibitor of the platelet-derived growth-factor receptor, has recently been shown to produce a high rate of disease stabilization.

Until recently, the median 5-year survival rate for all cases of carcinoid tumors was 82%, increasing to 94% if the tumor was localized and falling to 64% with regional lymph node involvement, and to 18% with the presence of distant metastases. It remains to be seen if the new targeted therapies will improve these statistics.

b. **Insulinoma.** This tumor usually arises from the β cells of the islets of Langerhans. This tumor, which accounts for >75% of functional islet-cell tumors, is usually benign and may be a solitary lesion, but in 10% of cases it is a part of a multiple endocrine neoplasia (MEN) syndrome.

i. **Symptoms** are the result of hypoglycemia from excessive or inappropriate insulin secretion.

ii. **Diagnosis** is by radioimmunoassay (RIA) of plasma insulin level, which is generally high or high normal.
iii. **Treatment,** ideally, consists of surgical removal of the tumor, if possible. Resection or radiofrequency ablation of metastatic lesions should be considered when necessary. If the tumor is malignant and cannot be completely excised, hypoglycemic symptoms may be controlled with diazoxide, corticosteroids, or the long-acting analog of somatostatin (**Sandostatin**). Conventional chemotherapy has only modest activity, but sunitanib has been specifically associated with a high clinical benefit in this histology.

c. **Pancreatic glucagonoma** is usually the result of a malignant tumor of the *α* cells of the islets of Langerhans. From 60% to 85% of patients have metastatic disease at the time of diagnosis, even though the growth rate tends to be slow.
i. The **clinical picture** is a characteristic rash in a diabetic patient. The rash, called **necrolytic erythema migrans**, consists of superficial epidermal blistering, central healing, and peripheral spreading with a defined edge. The erythema may occur anywhere but has a predilection for the lower abdomen and areas of chafing, such as the groin or thighs. Glossitis, anemia, thromboembolic phenomena, and weight loss have been reported as well.
ii. **Diagnosis** is by RIA of **elevated plasma glucagon.** Plasma insulin is also often elevated as a compensatory reaction. The tumor may be localized by pancreatic angiography.
iii. **Treatment** of this catabolic syndrome is surgical **excision** when possible. Selective intra-arterial **streptozotocin** infusion for symptomatic liver metastases may be of benefit. Symptom control and reduction of glucagon levels has been reported using the long-acting analog of somatostatin (**Sandostatin**). Specific data evaluating the efficacy of the targeted tyrosine kinase and mTOR inhibitors in this histology are not yet available. However, in a preliminary study, **everolimus**, an effective inhibitor of the mTOR, achieved clinical benefit in 86% of patients with low-grade islet-cell tumors.

d. **Gastrinoma** is a result of G- (gastrin-secreting) cell

hyperplasia or carcinoma in the stomach or duodenum. The inappropriate hypergastrinism is stimulated by an ingested meal and is not affected by secretin stimulation. The possibility p. 975p. 976of the gastrinoma syndrome should be entertained in all patients with ulcer disease and in those with unexplained secretory diarrhea.

i. The **clinical picture** varies from an almost asymptomatic duodenal ulceration to acute perforation of a jejunal ulcer. This clinical picture may be indistinguishable from that due to a pancreatic gastrinoma and is, therefore, termed **pseudo-Zollinger–Ellison syndrome**.

ii. **Treatment.** The ulcerative symptoms usually respond completely to surgical antrectomy. Alternative therapies include **omeprazole**, a benzimidazole that suppresses gastric acid secretion by inhibiting the sodium-potassium ATPase of the parietal cell, and the long-acting analog of somatostatin (octreotide acetate, **Sandostatin**).

e. **Somatostatinoma.** Somatostatin, first identified as a polypeptide of the hypothalamus, is an inhibitor of the release of somatotropin (growth hormone) from the anterior pituitary. It is also present entopically in the D cells of the pancreas, from where it inhibits the release of insulin and glucagon. The tumor responsible for this syndrome is usually a malignant pancreatic neoplasm, with 83% of patients reported to have metastatic disease at the time of diagnosis.

i. **Signs and symptoms** of this syndrome include:
   a) Mild diabetes mellitus
   b) Steatorrhea (usually with dyspepsia and diarrhea)
   c) Gallstones
   d) Anemia
   e) Weight loss

ii. **Diagnosis** is confirmed when plasma levels of somatostatin are elevated, whereas those of insulin and glucagon are depressed, distinguishing this APUDoma from a glucagonoma.

iii. **Treatment** is surgical removal of the tumor, if possible.

Streptozotocin may help shrink symptomatic metastases.

2. **Anterior pituitary gland**
   a. **Clinical features**
      i. ACTH overproduction leads to Cushing syndrome.
      ii. Melanocyte-stimulating hormone overproduction leads to hyperpigmentation.
      iii. Growth-hormone overproduction leads to acromegaly or gigantism.
      iv. Prolactin overproduction leads to galactorrhea.
   b. **Treatment** for all the above is ablation of the pituitary gland by irradiation or surgery, followed by appropriate replacement therapy.
3. **Thyroid gland.** Medullary carcinoma of the thyroid produces calcitonin, which causes no symptoms, and prostaglandin, which often is responsible for diarrhea.
   a. **Treatment** is total thyroidectomy and removal of all involved lymph nodes.
   b. This tumor may be a solitary lesion or a part of MEN type 2.
4. **Adrenal medulla and other sympathetic ganglia.** These tumors range from the relatively well-differentiated and benign pheochromocytoma (which may be a solitary lesion or a part of MEN), ganglioneuroma, and paraganglioma to the highly malignant neuroblastoma.

B. Ectopic

1. **Cushing syndrome**
   a. This is the **most frequently encountered ectopic NEC syndrome**, and it is usually a result of one of the following:
      i. Bronchogenic carcinoma (most often of the small-cell type)
      ii. Carcinoid tumors of the bronchus or the gut
      iii. Epithelial carcinoma of the thymus
      iv. Islet-cell tumors of the pancreas
      v. Medullary carcinoma of the thyroid
      vi. Pheochromocytoma
      vii. Cushing syndrome has been reported as well in primary malignancies of the ovary, liver, and breast. Interestingly, in 1928, Brown reported clinical

stigmata of adrenal cortical overactivity in a patient with cancer of the lung, four years before Cushing described this symptom complex to which his name has been appended.

b. Symptoms include:

i. Hypokalemia, often with associated alkalosis
ii. Hyperglycemia
iii. Hypertension
iv. Hirsutism
v. Edema
vi. Profound muscle weakness and atrophy

The other features seen in pituitary Cushing syndrome or exogenous corticosteroid excess, such as centripetal obesity, cutaneous striae, moon facies, buffalo hump, and increased pigmentation, are less common, and are reported to be more common in the relatively indolent carcinoids, thymomas, and pheochromocytomas.

c. Diagnosis begins by thinking about the possibility in the appropriate clinical setting. When the previously described features are present, a plasma ACTH >200 pg/mL is highly suggestive of ectopic ACTH production. The simplest biochemical approach is to obtain an 8 AM and a 6 PM cortisol level (in ectopic ACTH syndromes, these are usually >40 μg/mL, showing loss of the diurnal variation), followed by an 8 AM cortisol and ACTH level after 2 mg of dexamethasone given every 6 hours for 8 doses (48 hours). In 95% of cases of ectopic hormone production, the ACTH and cortisol levels will not suppress (i.e., will not fall to at most 60% of the prior values). If results of these studies are consistent with ectopic ACTH production, a careful evaluation for a tumor should be undertaken and continued until the source of ACTH overproduction has been identified.

d. Treatment should be directed at eradicating the primary tumor when possible, using surgery, radiotherapy, and/or chemotherapy as determined by the histologic characteristics and location of the primary tumor. If treatment directed at the primary tumor fails, drugs that inhibit adrenal corticoid production may be tried, including aminoglutethimide,

metyrapone, or mitotane. In rare cases of chronic ectopic ACTH excess and indolent tumors, bilateral adrenalectomy may be considered.

2. **Zollinger–Ellison syndrome (pancreatic gastrinoma).** In 1955, Zollinger and Ellison described two patients with fulminant peptic ulcer disease and non-β islet-cell tumors of the pancreas. The gastrin produced by these pancreatic tumors is believed to arise from the pancreatic D cell. Most of the tumors are multifocal within the pancreas, and though approximately 25% are benign adenomas, 60% to 75% are malignant and have metastasized by the time of diagnosis. About 30% to 50% of patients belong to kindreds with a history of MEN syndromes.
   a. **Symptoms** include:
      i. Severe peptic ulcer disease manifested usually by pain. The ulcers are commonly multiple, often recurrent, and frequently located in atypical sites.
      ii. Diarrhea, which may precede the ulcer symptoms or which may be the dominant feature of presentation in 15% to 20% of cases.
   b. **Diagnosis** is by RIA for circulating gastrin levels that are 10 times greater than normal. In 60% to 70% of patients, the tumor cannot be localized radiographically in the absence of metastases. The use of selective venous catheterization in association with a provocative stimulus, such as secretin, may provide accurate localization of the tumor. In **30% to 50% of patients, associated MEN syndromes coexist.**
   c. **Treatment** includes parietal cell receptor blockade with cimetidine, ranitidine, or omeprazole and complete extirpation of the tumor if possible. If surgical removal of the gastrinoma is not possible, antrectomy or total gastrectomy may be required.

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3. **VIPoma (WDHA syndrome, also called pancreatic cholera).** The responsible hormonal agent is a VIP that is normally secreted by both the small and large intestinal mucosa cells, and, in this case, ectopically secreted by δ cells, usually located in the body and tail of the pancreas. This syndrome has also been seen in patients with bronchogenic carcinoma and neuroblastoma.

a. **Symptoms** typically include the following (and make up the acronym for WDHA syndrome):
   i. **W**atery **d**iarrhea, with a volume of 6 to 8 L/day
   ii. **H**ypokalemia
   iii. **A**lkalosis

b. Treatment is surgical excision, if possible, of both the primary and metastases. Some reports have implicated prostaglandins in the pathogenesis of this syndrome, and indomethacin, an inhibitor of prostaglandin synthesis, has sometimes been of benefit. Symptoms may also be controlled with the long-acting analog of somatostatin (octreotide acetate, Sandostatin).

C. MEN syndromes (see Chapter 79). The endocrinopathies, whether entopic or ectopic, may occur in combinations sufficiently often to be designated MEN syndromes. These associations are usually genetic and transmitted as an autosomal dominant trait. The pathologic changes of dysplasia range from hyperplasia to malignant neoplasia. The endocrinopathies may present in a synchronous fashion with simultaneous aberrant endocrine manifestations or, more commonly, in a metachronous fashion in which one component of MEN precedes the others by several years. There are now **three well-established genetic associations of MEN.**

1. **MEN1.** Initially described by Wermer, this syndrome is composed of three component endocrinopathy sites: parathyroid, anterior pituitary, and pancreatic islet cells. A genetic defect, allelic loss in the 11q12–11q13 region, has been linked to this disorder.
   a. **Parathyroid.** Usually hyperplasia leading to elevated parathyroid hormone levels.
   b. **Anterior pituitary**
      i. Increased prolactin leading to lactation and amenorrhea in the female
      ii. Increased human growth hormone leading to acromegaly
      iii. Increased ACTH–melanocyte-stimulating hormone leading to Cushing syndrome and/or hyperpigmentation
      iv. Increased thyroid-stimulating immunoglobulin leading to hyperthyroidism
      v. Increased gonadotropins leading to feminizing or masculinizing syndromes
   c. **Pancreatic islet cells**
      i. Ectopic hypergastrinemia with Zollinger–Ellison syndrome

ii. Ectopic release of VIP with WDHA syndrome
iii. Ectopic ACTH leading to Cushing syndrome
iv. Ectopic parathyroid hormone leading to hyperparathyroidism
v. Entopic hyperinsulinism
vi. Entopic hyperglucagonism
vii. Entopic release of human pancreatic polypeptide. This peptide, which by itself is identified with no clinical syndrome, has pharmacologic and, presumably, physiologic actions that appear to be antagonistic to cholecystokinin-pancreozymin (i.e., it relaxes gallbladder contractions and inhibits exocrine pancreatic enzyme release). It is deficient in patients with obesity and with cystic fibrosis of the pancreas, and is excessively elaborated in response to a meal in MEN1 patients. Most importantly, it has been found to be an excellent marker in the fasting state of MEN1 patients with islet-cell tumors.

2. **MEN2A.** Initially described by Sipple, this syndrome is also composed of three endocrinopathy components: medullary carcinoma of the thyroid, adrenal pheochromocytoma, and secondary parathyroid hyperplasia.
   a. **Medullary carcinoma of the thyroid** is usually present in both lobes of the thyroid gland and consists of microscopic, nonpalpable tumors. A diagnostic histologic feature is the presence of **amyloid** in the thyroid carcinoma, which is reported to contain the prohormone of thyrocalcitonin. This tumor may also elaborate ectopic ACTH and prostaglandins.

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   b. **Adrenal pheochromocytoma** is bilateral in 70% of cases and is seldom malignant. Satellite lesions may be present in the sympathetic ganglia, ranging from the mediastinum to the urinary bladder. It is important to **exclude pheochromocytoma before operating on medullary thyroid carcinoma**, because general anesthesia administered to patients with untreated pheochromocytomas may lead to hypertensive crisis and death.
   c. **Secondary parathyroid hyperplasia** with elevated circulating parathormone levels usually disappears when the

medullary carcinoma of the thyroid (with an associated increase in circulating thyrocalcitonin) is resected.

3. **MEN2B**
   a. This syndrome, originally described by Schimke et al., is similar to MEN2A. In addition to the medullary carcinoma of the thyroid and pheochromocytomas seen in the latter syndrome, these patients are often found to have:
      i. Multiple mucosal neuromas of lips, mouth, and tongue
      ii. Marfanoid habitus
      iii. Prominent jaw
      iv. Pectus excavatum

      In contrast to MEN2A, hyperparathyroidism is rare in MEN2B. As well, medullary thyroid carcinoma tends to develop in younger MEN2B patients, and often pursues a more aggressive course.
   b. **Management** of the thyroid and adrenal components of this syndrome is surgical, as it is for type 2A. Bilateral adrenal resection and total thyroidectomy with central node dissection are recommended. Activating mutations of the RET protooncogene have been found in sporadic as well as MEN2-related medullary thyroid cancer. Recently, targeted therapy with small-molecule tyrosine kinase inhibitors that inhibit RET signaling has been shown to be active in medullary thyroid cancer.

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79 Multiple Endocrine Neoplasia Syndromes

Vidya Aluri and Joseph S. Dillon

I. INTRODUCTION

The term “multiple endocrine neoplasia” (MEN) refers to a group of syndromes manifested by multiple endocrine abnormalities, neoplasms (frequently malignant), and other tissue dysplasias. Different syndromes are characterized by the specific organ involved, associated features, and genetic mutations (Table 79-1). Besides the “core” group of endocrine tumors that define each syndrome, there are additional tumors and nontumor manifestations associated with each syndrome, and variations are common. Syndromes may be diagnosed on the basis of the occurrence of two or more syndrome-specific tumors in an individual, the occurrence of a syndromic tumor in a person with a first-degree relative with MEN, or the occurrence of a germline mutation in a syndrome-specific gene in a person with or without any known tumors.

Currently described syndromes include MEN1 (related to mutations in the MEN1 gene), MEN2 (including MEN2A, MEN2B, and variants related to mutations in the RET gene), and, more recently, MEN4 (related to mutations of CDKN1B). These disorders are autosomal dominant and highly penetrant, although tumors are frequently asynchronous in expression. De novo mutations (new diagnosis of MEN without a family history) occur in about 10% of individuals with MEN1 and up to 50% in individuals with MEN2.

Mutational analysis of the MEN1 or RET genes is recommended for index cases, first-degree relatives of patients with MEN-associated tumor, or patients with suspicion for MEN (e.g., polyglandular hyperparathyroidism before 40 years of age, recurrent hyperparathyroidism, and MEN-associated tumor). Presumably, a similar approach is appropriate for mutations of CDKN1B, although this is less well understood.

A. MEN1

MEN1 is clinically defined as the cooccurrence of tumors of the

parathyroids, endocrine pancreas, and anterior pituitary. Other features can include tumors of the adrenal cortex and carcinoid tumors. MEN1 is caused by inactivating mutations in the MEN1 gene which encodes the tumor suppressor menin. Over 1 500 mutations have been identified throughout the coding region of the MEN1 gene. Genomic

p. 981p. 982mutations are not found in truly sporadic endocrine tumors. Importantly, specific MEN1 genetic mutations are not strongly associated with specific features of the syndrome, unlike in MEN2.

TABLE 79-1 Features of MEN1 and MEN2

Syndrome	Organs involved	Other features	Gene
MEN1	PT, pancreas, pituitary	Carcinoid, adrenal cortex tumor, meningioma, facial angiofibroma, collagenoma, lipoma	MEN1
MEN2A	T, adrenal medulla, PT	Lichen amyloidosis, Hirschsprung	RET
MEN2B	T, adrenal medulla	Marfan, mucosal neuroma, Hirschsprung	RET

MEN1, multiple endocrine neoplasia type 1; MEN2A, multiple endocrine neoplasia type 2a; MEN2B, multiple endocrine neoplasia type 2b; PT, parathyroid; T, thyroid (medullary carcinoma).

1. **Hyperparathyroidism** occurs in over 90% of patients and is the **most common presenting feature** with MEN1. At diagnosis, or over time, all four glands will become adenomatous, leading to frequent recurrence of hyperparathyroidism after initially successful subtotal parathyroidectomy. Hypercalcemia, renal stones, and osteopenia can be seen, as with sporadic hyperparathyroidism. The parathyroid tumors of MEN1 are diagnosed at younger ages unlike sporadic tumors, a common feature with all tumors of MEN syndromes.
2. **Pituitary tumors** can occur in over 50% of these patients and are the first manifestation in 10% to 25%. Tumors may be functional (prolactin, GH, or ACTH secreting) or nonfunctional. They can also be associated with pituitary hypofunction from mechanical

damage to the gland. Macroadenomas are more common in MEN1 than in sporadic cases (about 80% vs. 60%). Clinically silent lesions are detected only by imaging (CT and MR) performed in patients suspected of having MEN1. Note that acromegaly and Cushing syndrome can also be caused by ectopic secretion from foregut carcinoid tumors in MEN1 patients.

3. **Pancreatic tumors** occur in 40% to 80% of patients with MEN1. These are usually multicentric and may be of β- or other islet-cell origin. They can be associated with hypergastrinemia (Zollinger–Ellison syndrome), causing severe peptic ulcer disease. Tumors may be nonfunctional or functional (secreting insulin, glucagon, vasoactive intestinal polypeptide [VIP], and somatostatin). They may present with characteristic clinical features: insulinoma with recurrent hypoglycemia; glucagonoma with diarrhea, venous thrombosis, and skin rash; and VIPoma with watery diarrhea.
4. **MEN1: other features**

   About 40% of patients have adrenal adenomas or hyperplasia that are generally nonfunctional and detected incidentally. About 10% of patients have thyroid disorders, including benign or malignant, nonmedullary tumors. Other neuroendocrine tumors, generally foregut (thymus, bronchial, or stomach) carcinoids, develop in one third of patients. There is also an increased prevalence of lipomas, facial angiofibromas, collagenomas, meningiomas, and tumors of the testes and nerve sheath.
5. **MEN1: evaluation and screening**

   MEN1 tumors are rare before the age of 10 years but can develop at any age, peaking between the second and fourth decades. Once an index case has been diagnosed, they should be offered genetic testing for MEN1 gene mutations. Subsequently, all first-degree relatives should be tested for this mutation. Once an individual has been shown to have the genetic mutation, annual screening should be instituted according to available Clinical Practice Guidelines. Testing should include the following:

   Parathyroid: Serum calcium, parathyroid hormone (PTH).

   Pituitary: Serum prolactin, insulin-like growth factor 1, Cushing screen (dexamethasone suppression test, 24-hour urine cortisol, or 11 P.M. salivary cortisol), pituitary CT or MRI to detect early or silent lesions.

Pancreatic: Fasting plasma gastrin, glucagon, VIP, pancreatic polypeptide, chromogranin A, insulin and glucose. Imaging of pancreas and duodenum by MR, CT, or endoscopic ultrasound. If negative, proceed with ordering selective venous catheterization, somatostatin receptor nuclear imaging (e.g., Octreoscan).

6. MEN1: treatment

Treatment is directed to the individual tumors with added complications because of the multicentricity of the lesions. For pancreatic lesions, surgical resection is performed for lesions greater than 2 cm (smaller lesions have low metastatic risk) or those causing secretory syndromes, for example, an insulinoma with hypoglycemia. Total pancreatectomy should be avoided, if possible, because of a high morbidity. Management of hyperparathyroidism is generally a 3.5-gland resection with autotransplantation of the remaining gland to an accessible location, for example, forearm. Prolactinoma can generally be medically managed with p. 982p. 983dopamine agonists, for example, cabergoline. Neurosurgical resection (preferably by transsphenoidal route) for tumors with other secretory phenotypes remains the first choice, although there are medications available to inhibit ACTH or GH secretion (e.g., somatostatin analogs) or to block GH or the cortisol effect (e.g., pegvisomant or mifepristone).

B. MEN2 and associated syndromes

MEN2 and related syndromes are caused by activating mutations in the RET protooncogene, which encodes a tyrosine kinase receptor. Over 50 mutations of RET, clustered into 7 exons of the gene, are linked to MEN2-associated syndromes. MEN2A is caused by mutations in exons 10 and 11, most commonly at codon 634. MEN2B involves mutations in exons 13 to 16. Characteristic clinical features are strongly associated with specific mutations. For example, 98% of families with MEN2A have RET mutations in exons 10 or 11, whereas 95% of MEN2B are associated with a single mutation in exon 16. Specific RET mutations are associated with more aggressive tumors. This close genotype–phenotype linkage can guide screening and therapy decisions. RET germline mutation testing has replaced calcitonin testing as the basis for case diagnosis in MEN2 families.

1. MEN2A

MEN2A is characterized by medullary thyroid cancer (MTC) in more than 90% of patients, pheochromocytoma in 50% to 70%, and parathyroid hyperplasia in 20% to 30%.

a. **MTC** is usually multicentric. Transformation of C cells proceeds from normal histology, through C cell hyperplasia, microscopic MTC, and finally, macroscopic MTC. These tumors are the most common presentation of MEN2, although up to 75% of MTC are sporadic. MTC produces calcitonin, CEA, and occasionally other hormones (e.g., ACTH causing ectopic Cushing syndrome, or serotonin). Increased calcitonin does not lead to hypocalcemia or other known biologic effects. Calcitonin and CEA are excellent tumor markers as the levels correlate with tumor burden. Elevated calcitonin levels at 6 months after surgery suggests persistent disease.

b. **Pheochromocytomas** are frequently bilateral and may be intraadrenal or extraadrenal. They may present with sustained or intermittent hypertension. They appear in the third or fourth decade of life. Undiagnosed pheochromocytoma can cause significant morbidity. Thus, in patients with MEN2 or with apparently isolated MTC, it is critical to rule out this tumor before any interventional procedure.

c. **Hyperparathyroidism** secondary to hyperplasia occurs in 20% to 30% of the cases with a mean age of onset at 36 years. The hypercalcemia is usually mild and 85% of the patients are asymptomatic.

d. **MEN 2A: other features**

   MEN2A may be associated with Hirschsprung disease as an uncommon variant presenting in childhood with mega colon or obstructive symptoms. MEN2A may be associated with cutaneous lichen amyloidosis in approximately 10%, characterized by a pruritic rash on the upper back.

e. **Familial MTC (FMTC)** is characterized by MTC, without pheochromocytoma or hyperparathyroidism, and with a family history of the isolated MTC. Although not a multiple endocrine disorder, it is caused by specific RET mutations and accounts for 15% of hereditary MTC. It is crucial to rule out other features of MEN in such patients to correctly establish this diagnosis. It has a later age of onset and a less aggressive clinical course compared with MTC in MEN2A or B.

f. MEN2B

MEN2B (previously named MEN3) is characterized by MTC (over 95%), pheochromocytoma (33%), and mucosal neuromas (over 95%). Neuromas are seen on the lips, eyelids, and tongue, producing the characteristic “lumpy lips” appearance. Also frequently noticed are marfanoid habitus, hyperplastic corneal nerves, and gastrointestinal ganglioneuromatosis and megacolon-producing motility disorders or severe constipation. Gastrointestinal features may be manifested in infancy as the first sign of MEN2B. Hyperparathyroidism is uncommon (<5%).

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g. MEN2: evaluation and screening

Genetic testing for specific RET mutations should be performed in index cases, first-degree relatives, and those suspected of having MEN2. The goal is early identification and intervention on MEN2-related disorders, and for counseling about risk of disease transmission. MEN2 tumors, particularly MTC, can occur before the age of 10 years, but the peak in incidence is between the second and fourth decades. Once an individual has been shown to have the genetic mutation, annual screening should be instituted for the features of the disease according to available Clinical Practice Guidelines. Specific screening may be modified by knowledge of the specific genetic mutation in RET. Testing should include the following:

MTC: Plasma calcitonin, CEA. If calcitonin and CEA are normal for 5 years after thyroidectomy, no further studies are needed.

Pheochromocytoma: Plasma-free metanephrines or 24-hour urinary catecholamines or metanephrines. Imaging may include: abdominal CT or MR, flourodeoxyglucose positron emission tomography (FDG PET), or Iodine-125 meta-iodobenzylguanidine scan. Screening should begin on diagnosis of MTC or at prophylactic thyroidectomy (5 to 7 years).

Parathyroid hyperplasia: Serum calcium and PTH

h. MEN2: treatment

Cure rates are low when MEN2 patients have palpable MTC lesions. Total thyroidectomy, based on RET mutation prior to

the development of clinically detectable disease, offers the best chance for cure. Risk stratification, based on the predicted clinical behavior of MTC-related to specific RET mutations, can guide the timing of prophylactic thyroidectomy. Metastatic MTC is currently not curable. Palliative external beam radiation, tyrosine kinase inhibitors, and chemotherapy have been used. Parathyroid hyperplasia is treated surgically, if present, at the time of thyroidectomy.

If a pheochromocytoma is present, it should be resected prior to surgery for MTC. Bilateral adrenalectomy and adrenocortical sparing surgery should be considered because of the high risk of bilateral disease and morbidity of postoperative hypoadrenalism. Adequate preoperative alpha blockade, to allow for blood pressure control and blood volume expansion, followed by beta blockade, is important before resection of pheochromocytoma.

C. MEN4

Up to 5% of MEN2 and 25% of MEN1 patients do not have mutations in RET or MEN1, respectively, suggesting that mutations of other genes are causing their disease. MEN4 has clinical manifestations similar to those of MEN1 and is related to mutations in the CDKN1B gene, encoding a cell cycle regulator protein. Reported cases with CDKN1B mutation are as yet too few to be clear on what the core clinical manifestations are. Patients have presented with pituitary, parathyroid, carcinoid, thyroid (papillary), and adrenal cortex tumors. Mutations in other genes are likely to be discovered because there are individuals with MEN syndromes without evidence of RET, MEN1, or CDKN1B mutations.

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80 Radiology, Nuclear Medicine, and Endocrinology

Sing-Yung Wu

I. IMAGING MODALITIES RELATED TO ENDOCRINE DISEASE

A. Radiologic (nonisotopic). Adrenal, thyroid (<1.5 cm in diameter and nonpalpable), and pituitary "incidentaloma" found by computed tomography (CT)/ultrasonography (US)/magnetic resonance imaging (MRI) for unrelated problems are often benign, nonfunctioning lesions, such as adenomas or cysts.

Radiation dose from a full-body CT scan is 1 000 mrem (10 mSv) as compared to a chest x-ray, which is 10 mrem. These doses should have a perspective with a US average annual natural exposure of 310 mrem and the lowest dose for a statistical risk of cancer, 5 000 mrem. A positron emission tomography (PET)–CT study may have a radiation dose of 2 500 mrem. (A lower-dose CT reduces the exposure dose.)

1. **MRI** is the first choice for imaging of pituitary and parasellar lesions without radiation exposure. A gadolinium-based agent has been used as an MRI-contrast agent. Dynamic scan may be obtained at 20- to 30-second intervals.

   Patient preparation: None.

   MRI is contraindicated in patients with an indwelling metal prosthesis or pacemaker or claustrophobia. **Caution:** The use of gadolinium-containing contrast agents in patients with renal or liver dysfunction has been associated with nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy.

2. **Multislice CT** is the first choice for imaging adrenal and abdominal endocrine lesions. Patients are often given both oral and IV iodine-containing contrast.

   Patient preparation: NPO after midnight.

   Caution: CT with contrast is contraindicated in patients who

are allergic to iodine-containing agents and those whose serum creatinine is >1.5 mg/dL (or estimated glomerular filtration rate < 30 mL/min/1.73 m^2). However, elderly patients at risk of developing iodine-induced thyroid dysfunction (nodular goiter, positive thyroid antibodies, and/or a history of prior iodine-induced subclinical or clinical hyperthyroidism) should be closely monitored after they receive iodinated contrast media.

3. **PET–CT** combines complementary modalities, thereby allowing precise structural and functional characterization of a variety of endocrine conditions.
4. **US** provides excellent and reproducible anatomic images for thyroid, parathyroid, and neighboring structures without ionizing radiation exposure. **Doppler US** is useful for evaluating tissue vascularity. (**Power Doppler US**, after injection of a contrast agent, is an increasingly used procedure for differentiating benign and malignant tumors.) US can be used to guide fine-needle aspiration for cytologic diagnosis of an endocrine/thyroid/adrenal nodule. In the long-term follow-up of differentiated thyroid carcinoma (DTC), cervical US is the imaging of choice for evaluating recurrence in the thyroid bed and central/lateral cervical nodal compartments. **Endoscopic or intraoperative US** may be useful in making an early diagnosis of pancreatic/abdominal endocrine tumors but requires the use of conscious sedation and may evaluate only a part of the organ (e.g., pancreas). **Venography (phlebography)** is usually accompanied by venous sampling to determine hormonal output from a gland (e.g., adrenal, parathyroid) or a suspected area of functional metastatic lesion. Venous samples are usually obtained before injection of the contrast agent.

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5. **Intra-arterial angiography (arteriography)** has been largely replaced by multislice CT angiography (CTA) or magnetic resonance angiography.
6. **Planar x-ray radiography** is useful in screening for bone age, bone disease, sellar size, and tumor metastases (lytic lesions).
7. **Dual x-ray absorptiometry** is today's established standard for measuring bone mineral density to evaluate osteoporosis.

B. Isotopic

1. **Radioactive iodine.** Radioactive iodine uptake (RAIU) and imaging reveals the functional status of thyroid tissue, including nodules, ectopic tissue, and metastatic foci. The sodium/iodide symporter mediates iodide uptakes.
   a. **Iodine 131 (^{131}I)** is reserved for thyroid cancer imaging and therapy, and for management of a hyperfunctioning thyroid gland or nodule.
   b. **Iodine 123 (^{123}I)** replaces other iodine isotopes for routine thyroid RAIU and scan because of its short half-life (13.3 hours) and low radiation dose to the patient (190 mrem).
   c. **Patient preparation**
      i. For a patient on **no** thyroid medication (either thyroid hormone or antithyroid) and who has not received iodine-containing agents (e.g., kelp, amiodarone, and betadine) recently, no patient preparation is needed.
      ii. For a thyroid cancer patient on a suppressive dose of **thyroxine (T_4)**, stop the T_4, which has a half-life ($T_{1/2}$) of 6 to 8 days, for 3 to 4 weeks, or stop the T_4 and switch to **triiodothyronine (T_3)** (25 μg two or three times a day; T_3 has a shorter $T_{1/2}$ of about 1 day) for 2 to 4 weeks, then stop the T_3 for 2 weeks. Both methods of preparation can achieve serum thyroid-stimulating hormone (TSH) levels >30 mU/L in >90% of patients. It is also good practice to get a blood sample for thyroglobulin (Tg) measurement before giving the ^{131}I dose. Tg measurement is important to monitor patients for residual or recurrent disease. To provide better quality of life and avoid the morbidity of hypothyroidism that is often associated with thyroid hormone withdrawal, recombinant human TSH (rhTSH) (Thyrogen) is available for clinical use. Patients are given 10 U (0.9 mg) of rhTSH, two doses 24 hours apart. Twenty-four hours after the second dose, 1 to 3 mCi of ^{131}I ("stunning" may occur with doses of 5 to 10 mCi) is administered orally, and a total-body scan is obtained 48 hours later. To avoid possible "stunning," I-123 total-body scan may be performed for pediatric patients, even though

this is controversial in nature. I-123 (no β radiation and more optimal energy for imaging) total-body scan may be performed for pediatric patients for lower radiation dose (rad/mCi) as compared to I-131 (0.09 vs. 0.81 rad/mCi, respectively). The use of I-123 to lower the rate of stunning has been reported.

iii. For a hyperthyroid patient on **antithyroid medication**, such as methimazole (MMI) or propylthiouracil (PTU), stop the MMI or PTU for 3 days and then do the uptake and scan; give a treatment dose of ^{131}I if indicated. After administration of ^{131}I (for Graves disease or toxic nodular goiter), MMI or PTU can be resumed in 48 hours.

iv. For a patient who has received a large dose of iodine (e.g., water-soluble CT radiocontrast agent), one should usually wait for 1 to 2 months for an accurate RAIU study, ^{131}I total-body scan, or ablative treatment for thyroid cancer, especially in older patients with reduced renal function.

2. **^{99m}Tc-MIBI (methoxy-isobutyl-isonitrile).** Preoperative localization of an abnormal parathyroid gland (2 to 3 hours delay and/or ^{123}I substrate imaging) can reduce operative time, postoperative morbidity, and the need for repeat surgery. No patient preparation is needed.

3. **Iodocholesterol (^{131}I-labeled 6-iodomethyl-19-norcholesterol, NP-59)** for adrenocortical imaging in Cushing disease, cortisol-producing adenoma, and primary aldosteronism.

   Patient preparation: One drop saturated solution of potassium iodide or Lugol solution PO, t.i.d. started 1 day before imaging and continued throughout p. 986p. 987the study. For a suppression scan, patients receive 2 mg of dexamethasone PO q6h beginning 2 to 3 days before injection of NP-59. The medication is continued until imaging is completed.

4. **MIBG (^{131}I- or ^{123}I-metaiodobenzylguanidine)** for adrenomedullary imaging in pheochromocytoma, neural crest tumors (paragangliomas), carcinoid, and medullary thyroid carcinoma. **^{131}I-MIBG** may be used for palliative therapy.

   Patient preparation: Same as with iodocholesterol (see Section I.B.3).

5. **Indium 111 (^{111}In) octreotide scan.** Somatostatin (SS) analog is used to show neural crest tumors with predominantly subtypes 2 and 5, including pheochromocytoma, carcinoid, paraganglioma, medullary thyroid carcinoma, islet-cell tumor, and gastrinoma. If available, one should also consider receptor imaging other than SS.

   Patient preparation: Discontinue somatostatin analog therapy 1 week before study. Administration of a laxative may be considered.

6. **Fluorodeoxyglucose (^{18}FDG) PET/CT or single photon emission computed tomography (SPECT)/CT.** FDG PET or SPECT imaging in combination with multislice CT provides anatomic and metabolic information; it may be helpful in detecting ^{131}I-negative/Tg-positive thyroid carcinoma and evaluating its prognosis, as well as in characterizing a variety of endocrine tumors.

   Patient preparation: Fasting for 4 to 6 hours (check serum glucose, <150 mg/dL).

7. **Other isotopic scans.** Isotope bone scan is extremely useful in Paget bone disease to determine disease location and activity.
   Patient preparation: None.

II. ENDOCRINE DISORDERS

Table 80-1 lists recommended multitechnique imaging approaches for various endocrine disorders.

A. Pituitary abnormalities

1. **Functional adenoma** is usually a microadenoma (<10 mm), a growth hormone–secreting adenoma (acromegaly), an adrenocorticotropic hormone (ACTH)–secreting adenoma (Cushing disease), or a prolactinoma. Imaging modalities are MRI (may use dynamic to increase the detection rate) and CT (thin-section). Localization of microadenomas within the pituitary gland demands highest standards of imaging technique and interpretation. The diagnosis is made on clinical and laboratory grounds.
2. **Nonfunctional adenoma** is often a macroadenoma. Imaging modalities are MRI and CT. MRI has distinct advantages over CT in the delineation of the extent of a macroadenoma. Cavernous sinus involvement and basilar skull invasion are shown best on

coronal and sagittal images.

3. **Hypopituitarism.** MRI is used for delineation of common anatomic abnormalities in patients with hypopituitarism that may be the result of developmental, toxic, hypoxic, or traumatic etiologic factors.

B. Adrenal abnormalities. Thin-section CT is the imaging technique of choice for the initial evaluation in adults; US is used in children to avoid radiation exposure.

1. **Cushing syndrome.** Clinical and biochemical studies usually first establish the diagnosis of ACTH-dependent Cushing syndrome (80%, MRI of the pituitary is the first choice) or adrenal tumor (20%). Imaging techniques are used to determine on which side an adrenal tumor is located. Imaging modalities include the following:
   a. **CT** to determine the location and size of the lesions.
   b. **MRI** to assess the size and extent of a pituitary lesion.
   c. **Iodocholesterol scan (NP-59)** may be used to differentiate **ACTH-dependent cortical hyperplasia** and **ACTH-independent adenoma** with dexamethasone suppression protocol.
   d. **PET-CT** helps to determine whether ACTH-independent adenoma, hyperplasia, and carcinoma (and metastasis) are visualized concordantly.

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TABLE 80-1 Optimal Imaging Modalities in the Management of Endocrine Disorders

Disorder	Isotopic							Nonisotopic			
	^{131}I	^{123}I	PET/CT	MIBI	Octre	MIBG	Chol	US	CT	MRI	Venogram
Functional adenoma (acromegaly, prolactinoma)									2	1	
Nonfunctional adenoma									2	1	
Cushing disease			4				3		1	2	
Conn syndrome							3		1		2
Pheochromocytoma			3		2	2			1		
Congenital adrenal hyperplasia			3					2	1		
Addison disease									1	2	
Adrenocortical carcinoma			3						1	2	
Carcinoid					2	3			1		
Paraganglioma					2	3			1		
Graves disease	2[a]	1									
Nodules		2						1[b]			
Thyroiditis											
Subacute		1									
Painless		1									
Congenital hypothyroidism		1[c]									
Carcinoma, Differentiated Thyroid	1		2	3							
Adenoma, Parathyroid				2				1			3
Insulinoma			1[d]		4			3[e]	1[d]	2	
Glucagonoma			1[d]		4			3[e]	1[d]	2	
Gastrinoma			1[d]		4			3[e]	1[d]	2	
Islet-cell tumor			1[d]					3[e]	1[d]	2	
Struma ovarii	1	1							2	2	

Numbers indicate order of preference for administration of tests.
[a]Treatment with ^{131}I.
[b]Fine-needle aspiration can be done concurrently.
[c]RAIU and perchlorate discharge test.
[d]PET may be combined with CT as PET/CT fusion imaging.
[e]Endoscopic ultrasound may be extremely helpful for insulinoma in pancreatic head.
CT, computed tomography (may be combined with an angiography, CTA); MIBG, metaiodobenzylguanidine; MIBI, methoxy methylpropyl isonitrile; MRI, magnetic resonance imaging; PET, positron emission tomography; US, ultrasonography; Chol, iodocholesterol scan; Octre, octreotide scan.

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2. **Primary aldosteronism (Conn syndrome).** After biochemical documentation of primary aldosteronism, the next step is to localize the lesion and determine whether one or both adrenals are affected. Imaging modalities include the following:
   a. **CT,** thin-section, to differentiate a unilateral adenoma (80% of cases) from bilateral hyperplasia. One difficulty is that there is a 2% to 8% incidence of a small nonfunctioning adrenal adenoma in the general population. MRI is an alternate imaging modality to characterize the adenoma.
   b. **Venous sampling.** Technical difficulties and complications, such as rupture of the adrenal veins, should also be considered.
   c. **Iodocholesterol scanning** is useful if the patient is on a suppression protocol.
3. **Pheochromocytoma (see Chapter 18)**. The diagnosis must be first made clinically and biochemically. About 85% of pheochromocytomas arise in the adrenal medulla, and 15% are found in extramedullary sites. Imaging modalities include the following:
   a. **CT** has been the imaging modality of choice and has an accuracy of 85% to 95% for adrenal masses equal or greater

than 1 cm. The use of IV low-osmolar CT contrast is generally safe (from inducing hypertensive crisis). **MRI** is an alternative to CT. Both have high sensitivity in detecting sporadic tumors and pheochromocytoma in MEN 2.

b. **^{111}In-Octreotide or ^{131}I-MIBG** is useful if CT findings are equivocal or if recurrent or metastatic disease is suspected. ^{131}I-MIBG is more sensitive than CT or MRI for diagnosing adrenal medullary hyperplasia (a precursor) and also has been used to treat patients with unresectable or metastatic pheochromocytomas. Overall, octreotide and MIBG scanning score similarly with respect to the diagnosis of pheochromocytoma, both having a specificity of 88%.

PET–CT using ^{18}F-DOPA or fluorodopamine PET may be helpful in detecting occult pheochromocytomas.

4. **Congenital adrenal hyperplasia.** The differential diagnosis includes ovarian neoplasia, polycystic ovarian disease, and autonomous adrenal tumors. Imaging modalities include the following:
   a. **CT.** Hyperplasia or tumor can be detected.
   b. **US** may be used to delineate adrenal masses in children and thin adults.
5. **Addison disease.** A biochemical distinction between pituitary and adrenal causes must be established first. Imaging modalities include CT, which is valuable in distinguishing certain specific adrenal causes (e.g., dense calcification from previous granulomatous disease, hemorrhage, and metastasis) from idiopathic adrenal atrophy.
6. **Adrenocortical carcinoma.** This is a rare malignant neoplasm with prevalence of 12 in 1 million. The CT findings are not specific. The differential diagnosis includes metastasis, lymphoma, adenoma, and granulomatous infection. MRI may be useful in differentiating benign adenoma from malignancy. In this respect, ^{18}FDG PET/CT or MTO (^{11}C-metomidate) may also be helpful to identify additional unsuspected lesions.

C. Neural crest tumors (other than pheochromocytoma). These include paragangliomas, neuroblastoma, and carcinoid tumors. CT or MRI is sensitive in the initial diagnosis and follow-up. ^{111}In-octreotide, ^{131}I-MIBG, or PET/CT may be used in demonstrating

metastatic lesions.

D. Thyroid

1. **Graves disease.** Diffuse enlargement of the thyroid gland, characteristic eye signs, suppressed TSH, increased serum-free thyroxine, and elevated RAIU usually confirm the diagnosis.
   a. **^{123}I.** An elevated uptake in the face of elevated serum T_3/T_4 is important evidence to differentiate Graves disease from other entities such as thyroiditis (subacute, painless, or postpartum) and iodine-induced (amiodarone-induced, type 1) or factitious thyrotoxicosis. Imaging is important in Graves disease only when toxic nodular goiter is in the differential diagnosis.
   b. **^{131}I** is used for therapy.

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2. **Thyroid nodule**
   a. **US** is used to determine whether a palpated nodule is part of a focal, multifocal, or diffuse disease process; whether that nodule is solid, cystic, or calcified; as well as to document and follow-up the size. Fine-needle aspiration (US-guided, if necessary) is often used to make a cytologic diagnosis in cases involving a solitary hypofunctioning nodule.
   b. **Radioactive iodine (^{123}I)** provides a true physiologic picture of the thyroid tissue because it determines the functional status of the nodule (cold, warm, or hot). ^{131}I is used for the management of toxic nodular goiter.
   c. **CT** is not generally used as a first-line imaging modality in this field, but it can provide valuable data detailing extrathyroid tumor extension and invasion of malignant thyroid nodules; it is particularly effective in the areas of the superior mediastinum and the cervical lymph nodes.
3. **Thyroiditis.** RAIU with ^{123}I is useful in determining different phases of subacute, painless, and postpartum thyroiditis. In the acute phase, when the patient has elevated T_3 and T_4, the RAIU is characteristically suppressed. In the recovery phase, the RAIU can rise transiently to even above normal. Occasionally, patients with Hashimoto thyroiditis and a relatively high RAIU need a perchlorate discharge test to document a defect in organification if antithyroid antibodies are negative.

4. **Dyshormonogenesis.** RAIU and perchlorate discharge tests are used to detect dyshormonogenesis, including an organification defect.
5. **Carcinoma.** Treatment of DTC involves a postablative ^{131}I total-body scan and therapy with 30 to 200 mCi of oral ^{131}I. In the long-term follow-up of DTC, cervical **US** to evaluate the thyroid bed and central/lateral compartments should be performed 6 to 12 months after surgery and then periodically depending on the patient's risk for recurrent disease and Tg status. **FDG PET** is used in posttherapy ^{131}I scan–negative patients and may have prognostic value. When a patient is classified as refractory to RAI, there is no indication for further RAI treatment (a strong recommendation by American Thyroid Association). The management of such RAI-refractory DTC includes other modalities such as external beam radiation, surgery, systemic chemotherapy, and newer targeted therapies. An encapsulated follicular variant of papillary thyroid carcinoma has recently been reclassified as noninvasive follicular thyroid neoplasms with papillary-like nuclear features with very low risk of adverse outcome. This entity should be managed with lobectomy and without RAI ablation.

E. Parathyroid. Once the diagnosis of primary hyperparathyroidism is established, localization of a parathyroid adenoma may be helpful to the surgeon.

1. **US** provides correct preoperative localization of 60% to 70% in new cases where the parathyroid glands are close to the thyroid gland, but it is less reliable in identifying ectopic glands in the mediastinum.
2. **^{99m}Tc-MIBI scans** have 83% sensitivity and specificity and compare favorably with ultrasound and MRI.
3. **Venography with selected venous sampling** technique is used after other noninvasive procedures have failed to locate an adenoma.

F. Insulinoma, gastrinoma, and glucagonoma. These three are the most common functioning pancreatic endocrine tumors. After the diagnosis is confirmed biochemically, radiographic localization includes pancreatic US and CT (with CTA) as well as venography with sampling in the case of glucagonoma. Endoscopic US may be helpful in the early diagnosis of insulinoma in the pancreatic head. The

advantages of CT over endoscopic US include a lack of invasiveness, less operator dependence, and improved detection of liver metastasis. SS receptor scintigraphy (gastrinoma, in particular) and PET/CT are also noninvasive methods.

G. Ovarian teratoma. Modalities to detect struma ovarii, or a thyroxine-producing teratoma, include RAIU and CT scanning.

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III. CONCLUSION

The advancement in structural and functional characterization (multislice CT, CTA, MRI, and PET/CT) discussed in this chapter has altered the way we manage endocrine disease to a large extent. In addition, the use of these techniques has either eliminated unnecessary endocrine surgery or resulted in greater postoperative success.

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81 Surgery for Endocrine Disorders

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I. THYROID NODULES AND THYROID CANCER

A. General principles

About 4% of people in the United States have thyroid nodules, yet according to the Surveillance, Epidemiology, and End Results Program, 135 persons, worldwide, per million per year develop clinical thyroid cancer and 5 persons per million per year die from this tumor. As a recent article in *The New England Journal of Medicine* (NEJM) shows, although the rate of thyroid cancer is rapidly rising in the Western world, the mortality rate remains low. Well-differentiated thyroid cancers generally have an indolent and favorable course, especially in patients <55 years of age. However, some thyroid cancers are lethal. A selective approach must, therefore, be used in determining whether a patient will benefit from aggressive surgical and adjuvant treatment or observation.

1. Factors suggesting that a thyroid nodule is benign are the following:
   - **a.** Multinodular goiter (MNG) (risk of cancer in MNG is unclear, between 5% and 35%)
   - **b.** Diffuse goiter
   - **c.** Family history of benign goiter
   - **d.** Increased thyroid-stimulating hormone (TSH)
   - **e.** Cystic lesion
   - **f.** Benign cytology by aspiration biopsy
2. Factors suggesting that a thyroid nodule might be malignant are the following:
   - **a.** History of irradiation to the head and neck (the a and b list of irradiation risks following)
   - **b.** Family history of thyroid cancer, multiple endocrine neoplasia type 2 (MEN2; see Chapter 79), Gardner syndrome, Cowden disease, or Carney complex

c. History of familial nonmedullary thyroid cancer in self or family
d. History of thyroid cancer in other lobe (>1 cm in size)
e. Solitary
f. Growing nodule, although many benign nodules can grow
g. Hard nodule
h. Solid or mixed solid–cystic lesion
i. Palpable or sonographic suspicious ipsilateral lymph nodes
j. Ipsilateral vocal cord palsy
k. Suspicious appearance on ultrasonography, that is, microcalcifications vascularity, solid and irregular boarders
l. Suspicious or diagnostic cytology for cancer by aspiration biopsy.

New genetic testing can help determine the risk of malignancy in indeterminate cytology samples. Current options are Gene Expression Classifier, DNA analysis, and hybrid types.

i. About 13% of persons exposed to low-dose, therapeutic irradiation (6.5 to 3 000 rad calculated dose to thyroid gland) develop thyroid cancer. Parathyroid tumors, salivary gland tumors, and breast tumors are also more common in irradiated persons.
ii. About 40% of persons exposed to low-dose therapeutic radiation who also have a discrete thyroid nodule have thyroid cancer in the thyroid gland. In 60%, the discrete nodule is the cancer, and in 40%, the cancer is found elsewhere in the thyroid gland that is usually small and multicentric.

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iii. Most persons with thyroid nodules are euthyroid with a normal serum TSH level. TSH levels are increased in hypothyroidism and decreased in hyperthyroidism.
iv. Benign thyroid nodules are colloid and involutional nodules, adenomas, cysts, and focal thyroiditis.
v. Malignant thyroid tumors are papillary, mixed papillary–follicular, follicular variant of papillary thyroid cancer, and follicular thyroid cancer, Hürthle cell cancer, medullary cancer, undifferentiated or anaplastic thyroid cancer,

lymphosarcoma, teratoma, squamous cell cancer, and secondary or metastatic tumors. There are also multiple variants of papillary thyroid cancer such as Tall cell or hobnail, portending a worse prognosis. Follicular and Hurthle cell lesions can be either benign adenomas or malignant carcinomas and must be removed to analyze the tumor capsule to determine malignancy (Table 81-1). In these follicular or hurthle cell lesions, molecular analysis can be helpful to determine risk of malignancy.

B. Evaluation of the nodule

Patients with clinically solitary thyroid nodules or a discrete or growing nodule in an MNG should be evaluated by a sensitive TSH test, ultrasound examination of the thyroid and cervical nodes, and percutaneous aspiration cytology. Lesions measuring >1.5 which are not benign on ultrasound (ATA Guidelines 2015) such as containing microcalcifications should be further investigated. Lesions of any size with associated suspicious lymphadenopathy should be evaluated further. If a lesion is malignant by cytologic examination, the tumor should be removed. There is an emerging body of evidence to recommend hemithyroidectomy for smaller tumors, specifically microcarcinomas, and those between 1 and 4 cm in size. If a lesion is benign, it can be safely followed; and if it is a follicular neoplasm, and the TSH level is suppressed, a radioactive iodine scan is recommended. If the follicular neoplasm is “hot” by scanning, it can be followed; if it is “cold” and >2 cm, it should usually be removed. Fine-needle aspiration (FNA) is less helpful in hyperthyroidism (hot nodules or graves) because hypertrophy of the gland will often cause false-positive indeterminate results. Operative treatment may be best for hyperthyroid patients with nodules because definitive management would yield both diagnosis and treatment. Risk of **malignancy in hot nodules is about 1%**. FNA is also less effective in patients with a history of irradiation, a family history of thyroid cancer, or very large tumors. In such patients, thyroidectomy is usually recommended.

C. Management

Thyroid nodules that are growing, that occur in patients with a family history of thyroid cancer or who have been irradiated, that are unusually hard on palpation, larger than 15 mm, or that are suspicious on ultrasound examination or diagnostic of cancer by aspiration biopsy cytology should usually be surgically removed by thyroid lobectomy

or total thyroidectomy.

TABLE 81-1 Genetic Regions Associated with Familial Nonmedullary Thyroid Cancer

Gene	Location
MNG1	14q31
TCO	19q13.2
fPTC/PRN	1q21
NMTC1	2q21
FTEN	8p23.1-p22
	1q21, 6q22
FOXE1	9q22.33
Telomere telomerase complex	

Adapted from Mazeh H, Sippel R. Familial nonmedullary thyroid carcinoma. *Thyroid* 2013;23(9):1049–1058.

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1. **MNGs** should be evaluated by ultrasound, and any suspicious area or nodule in a nodular goiter should be biopsied by a fine needle (23 gauge) for cytology. The new American Thyroid Association (ATA) guidelines recommend clinician performed ultrasound as a good method for quantitating nodule size, suspicious nodules for cancer, and adjacent lymphadenopathy. Blood thyroglobulin levels usually correlate with goiter size; however, the utility of this test for detecting cancer in the context of benign MNG has not been proven.
2. **Solitary nodule.** If the lesion is benign by aspiration biopsy cytology, some clinicians recommend treatment with enough thyroxine (T_4) to suppress TSH but keep triiodothyronine (T_3) and T_4 levels in the normal range. Evidence from multiple randomized trials looking at populations in iodine-sufficient populations suggest that only up to one fourth of nodules shrink 50% with suppression. Lesions suspected of malignancy should be removed with the entire lobe of the thyroid gland. In general, thyroid suppression is not used in the Western world because diagnostic surgery provides both a definitive answer and treatment. The new ATA recommends thyroid lobectomy for many cancers (low-risk

tumors <4 cm), and this can be done very safely. Current data show that patients have similar oncologic outcomes with lobectomy versus total thyroidectomy. Most patients can avoid long-term full thyroid hormone replacement. In addition, risks to hypoparathyroidism are negated and recurrent laryngeal nerve is minimized by operating on only one lobe. This idea has been reflected in the new ATA and National Comprehensive Cancer Network (NCCN) guidelines.

3. **Irradiated patients.** All palpable nodules in these patients should be removed because of the increased risk of cancer (~40%). Treatment should be total thyroidectomy for biopsy proven PTC. A benign biopsy may not help avoid surgery because the false negative rate of cancer in a nodule of an irradiation thyroid gland is as high as 10% to 20%. In patients with a unilateral thyroid nodule that is small, the surgeon may elect to either follow or do a lobectomy if it is an indeterminate nodule or benign. FNA is often helpful.
4. **Familial thyroid cancer.** All family members of patients with familial medullary thyroid cancer should have an *RET* oncogene test. *RET* oncogene–positive patients warrant a prophylactic total thyroidectomy often as a child. Depending on the particular RET Codon mutation, family members may need more aggressive treatment, and other family members should be screened. These patients need to be screened for pheochromocytoma and hyperparathyroidism (HPT). Patients with a family history of familial nonmedullary thyroid cancer are also at an increased risk of thyroid cancer and should have a careful physical and ultrasound examination.
5. **Surgical treatment.** There is considerable controversy concerning the extent of surgery necessary for patients with suspicious thyroid nodules. The minimal operation for any lesion that may be cancer, except for small lesions in the isthmus, is a total thyroid lobectomy on the side with the nodule. Excisional biopsy is an acceptable treatment for lesions in the isthmus, but in general excisional biopsy should be discouraged. Total thyroidectomy should be performed only on patients with medullary thyroid cancer and traditionally those with differentiated thyroid cancer when it can be performed with minimal morbidity (<2% rate of hypoparathyroidism or recurrent laryngeal nerve

injury). The historic advantages of total thyroidectomy are that it **(1)** results in removal of all thyroid cancer within the thyroid gland, **(2)** allows use of radioactive iodine to identify and ablate micrometastases, **(3)** allows use of blood thyroglobulin levels as a sensitive indicator of persistent disease, **(4)** reduces local recurrence and improves survival rate, and **(5)** reduces the risk of change from a differentiated thyroid cancer to an undifferentiated thyroid cancer.

Recent literature using a large database is still undecided on its use for surveillance after thyroid lobectomy in cancer <4 cm in size. There is a growing body of literature supporting the utility of Tg as a tumor marker after lobectomy. Although classic follow-up of Tg at undetectable levels after total thyroidectomy is not possible, trends and absolute values are instead used after lobectomy. p. 994p. 995Long-term prospective studies are needed to evaluate this shift in treatment recommendations.

Patients with clinically palpable, cervical, or ultrasound-positive lymphadenopathy should be treated by a modified radical neck dissection (preserving the sternocleidomastoid muscle, spinal accessory nerve, and internal jugular vein) on the side of lymphatic metastases. Therapeutic dosing (usually 100 mCu) of adjuvant radioactive iodine therapy is usually used after this operation.

6. **Postsurgical treatment.** TSH suppression and RAI have classically been used to treat differentiated thyroid cancer. Current evidence supports de-escallation of treatment. Given the current recommendation to treat low-risk DTC with surgical lobectomy, RAI is not appropriate. Further, TSH target of 2.0 has been proposed in the most recent ATA but evidence for suppression is lacking. Patients with ATA moderate or high-risk lesions are treated with RAI and TSH suppression. In these **external beam radiation** is used in patients with invasive or metastatic thyroid cancer that fails to take up radioactive iodine, and with gross residual disease after surgery. It can also be employed in undifferentiated thyroid carcinomas or unresectable medullary thyroid carcinomas. Chemotherapy is palliative in some patients with recurrent unresectable thyroid cancer or with undifferentiated thyroid cancer and is usually used in conjunction with external beam radiation.

Systemic therapy using tyrosine kinase inhibitors has shown good results at prolonging years of life in the case of unresectable metastatic disease. Currently, Vandetanib and **Cobozantinib** are being used with good results in those with **widely metastatic medullary thyroid cancer**. For well-differentiated thyroid cancer, in addition to the off-label use of Sorafenib and a new drug called **Lenvatinib** are being used for those patients with thyroid cancer refractory to all other treatments. There has been some evidence showing use of these therapies sensitize thyroid cancer to RAI uptake. Studies have shown that these drugs do increase survival, although some patients have prohibitive side effects including GI symptoms and rash.

7. **Follow-up evaluation**
   - **a.** Perform semi-annual or annual ultrasound examination of the neck for lymph node metastases or recurrent thyroid bed masses. In patients followed after lonbectomy, new suspicious thyroid nodules should be evaluated.
   - **b.** Serum thyroglobulin levels should be monitored. Current trends indicate that there is less utilization of TSH stimulation; however, Tg sensitivity is increased after withdrawal of thyroid hormone or after recombinant TSH (Thyrogen). If TSH level is increased after total thyroidectomy, a thyroid ultrasound examination is recommended to rule out recurrent/persistent cancer. Caution should be taken while using high-sensitivity Tg as well as during evaluation for presence of Tg antibodies. For patients with medullary thyroid cancer, serum calcitonin levels should be obtained, as should a carcinoembryonic antigen level, and *RET* oncogene testing if concern for MEN2. Patients with medullary thyroid cancer should also be screened for a pheochromocytoma and HPT prior to any operation.
   - **c.** A sensitive TSH between 6 and 8 weeks after initiation of thyroid hormone or postop after lobectomy should be obtained to ascertain whether the patient is receiving enough thyroid hormone or need supplementation.
   - **d.** A radioactive iodine scan may be recommended after thyroidectomy for patients with invasive tumors or for patients with distant metastases who have been treated by total thyroidectomy. The patient should discontinue T_3 (Cytomel, 50

to 75 μg/day) for 2 weeks or T_4 (125 to 200 μg/day) for 6 weeks prior to scanning, so that serum TSH levels will be elevated. Patients should receive a low-iodine diet for 2 weeks and can also be scanned after receiving recombinant TSH. Recombinant TSH or THYROGEN© is given as an intramuscular injection daily for 2 days (0.9 mg) prior to radioactive iodine treatment or scan as an alternative to withdrawal method. Either withdrawal or Thyrogen may be used to elevate the TSH prior to RAI treatment; p. 995p. 996however, for more widespread thyroid cancer, many endocrinologists prefer the withdrawal method.

e. CT or MRI may be employed in a high-risk patient with the likelihood of systemic disease. The ATA recommends cross sectional imaging when lymphadenopathy bulky or less differentiated disease is suspected. There has been evidence suggesting that CT may be more sensitive and specific than U/S, especially for lymph node disease in the lateral neck or posterior central neck. Depending on the radiology expertise at your center, cross-sectional imaging may be a more accurate staging test. A positron emission tomography (PET) scan is recommended for patients with signs of undifferentiated thyroid cancer, namely those who are thyroglobulin-negative but have other signs of disease progression by ultrasound or CT scan.

8. Factors predicting prognosis. Differentiated thyroid cancers (papillary, mixed papillary–follicular, follicular, and Hürthle cell) generally have a favorable prognosis. The AJCC has recently changed staging whereby all patients <55 years old without distant metastatic disease are considered stage I with a negligible chance of mortality.

II. HYPERTHYROIDISM (see Chapter 38)

A. General principles

See Chapter 38.

B. Differential diagnosis

See Chapter 38.

1. Management

Graves disease (autoimmune-mediated hyperthyroidism usually with a diffuse goiter) and Plummer (hyperfunctioning/toxic

nodular goiter because of one or more “hot nodules”) may be treated by antithyroid drugs, radioactive iodine, or subtotal or total thyroidectomy. Patients may be treated with antithyroid medication or managed definitively with radioactive iodine or surgery. Patients with ophthalmologic manifestations of Graves wishing to become pregnant in the short term or with suspicious thyroid nodules are better treated with surgery. All patients should be prepared with antithyroid medications prior to definitive treatment, and some surgeons use Lugol solution for 10 days for potential effects on bleeding and postoperative hypocalcemia.

2. **Drug therapy with antithyroid drugs.** See Chapter 38.
3. **Radioactive iodine (^{131}I).** See Chapter 38.
4. **Subtotal/near-total or total thyroidectomy**
   - **a.** This is the treatment of choice for young patients (children and pregnant women) who are not readily controlled by antithyroid medications, for patients with large diffuse or nodular goiters with low radioactive iodine uptake, for patients with coexisting suspicious or malignant thyroid nodules, for patients with exophthalmos, and for those who can not take antithyroid hormone.
   - **b.** Preparation for surgery includes maintaining the patient euthyroid by continuing antithyroid medications and some surgeons add potassium iodide solution or Lugol solution (3 drops twice a day) for 10 days prior to thyroidectomy. Parathyroid hormone, calcium, and vitamin D should also be measured preoperatively both for detection of concurrent HPT and vitamin D deficiency and for baseline levels to monitor any hypocalcemia that can develop postoperatively.
   - **c.** Coexisting thyroid nodules should be investigated by fine-needle biopsy if surgery is not planned. This may guide the patient to choose surgery over a nonoperative option.
   - **d.** Complications of thyroidectomy include a low (1%) incidence of hypoparathyroidism or injury to the recurrent laryngeal nerve with permanent hoarseness.
   - **e.** If subtotal thyroidectomy is employed, the thyroid remnant should range from 4 to 8 g. For children, smaller remnants are required to avoid recurrence. Many surgeons today prefer total or near-total thyroidectomy because it avoids recurrence and may help patients with Graves ophthalmopathy.

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5. **Special situations**
   - **a. Thyroid storm (hyperthyroid crisis).** See Chapter 38.
   - **b. Severe exophthalmos.** See Chapter 38.
   - **c. Hyperthyroidism in pregnancy.** See Chapter 38.

III. OTHER THYROID DISORDERS

A. Thyroiditis

See Chapter 37.

B. Ectopic thyroid

Aberrant placement of thyroid tissue occurs because of the failure of normal migration of the thyroid during embryologic development. It results in development of a sublingual thyroid or thyroglossal duct cyst (midline cyst) anywhere from the foramen cecum at the base of the tongue to the normal position of the thyroid. Thyroglossal duct cysts must be occasionally removed for cosmetic or diagnostic reasons or for avoiding infection. About 1% of these cysts contain papillary or squamous cell carcinoma. Occasionally, it is difficult to differentiate histologically between a thyroid rest and a metastatic thyroid cancer. Thyroid rests are situated in the midline, whereas laterally located thyroid tissue in lymph nodes (lateral aberrant thyroid) represents metastatic thyroid cancer.

IV. HYPERCALCEMIA AND HPT

A. General principles (Table 81-2)

See Chapters 31 and 33.

TABLE 81-2 Differential Diagnosis of Hypercalcemia

Malignancy
- Solid
  - Metastatic to bone
  - Secretion of PTH-like protein
- Hematogenous
  - Myeloma, leukemia, lymphoma

Endocrine
- Hyperparathyroidism (plus malignancy account for 90% of all hypercalcemic cases)
- Other endocrine
  - Hyperthyroidism, hypothyroidism, hypoadrenalism, acromegaly, and VIPoma

Increased intake

- Calcium and alkali (milk–alkali syndrome)
- Vitamin D or A
- Thiazides
- Lithium
- Estrogen

Granulomatous disorders

- Sarcoidosis
- Tuberculosis
- Berylliosis

Other disorders

- Benign familial hypocalciuric hypercalcemia
- Immobilization
- Error or artifact
- Idiopathic hypercalcemia of infancy
- Acute renal failure with rhabdomyolysis

PTH, parathyroid hormone; VIP, vasoactive intestinal polypeptide.

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B. Clinical manifestations and associated conditions

See Chapters 31 and 33.

C. Diagnosis (Table 81-3)

See Chapters 31 and 33.

D. Management

1. **Surgical management—selection of patients for parathyroidectomy.** There is general agreement that patients with symptomatic HPT, those <50 years old, and those with a serum calcium level 1 mg/dL above the upper limit of normal should be treated with parathyroidectomy. Because “asymptomatic patients” with primary HPT receive the same metabolic benefits of parathyroidectomy as symptomatic patients do, many people believe that these patients should also be treated by parathyroidectomy. However, operative treatment is not urgent, and in all patients, the diagnoses must be certain. Patients who are pregnant and have primary HPT should be treated surgically during the second trimester. Those with hypercalcemic crisis should be treated surgically as soon as the diagnosis is confirmed and appropriately hydrated.

   The most recent guidelines for the management of asymptomatic HPT recommend more extensive evaluation of the

skeletal and renal systems and monitoring of these systems when surgery is not pursued.

2. **Medical management of hypercalcemia.** See Chapters 31 and 33.
3. **Localization.** There are many modalities for preoperative localization of parathyroid adenomas. The gold standard of localization is the intraoperative four-gland exploration yielding up to 98% cure rates. Most modalities used in the US endocrine surgery units include the Ultrasound and SESTAMIBI/CT. The multiphase CT is also seeing its use increase, specifically as a single p. 998p. 999preoperative test. Other modalities are usually reserved for nonlocalizable or recurrent parathyroid disease and these include MRI, PET, fine-needle aspirates and interventional venous sampling.

TABLE 81-3 **Laboratory Tests for Hypercalcemia or Possible Hyperparathyroidism (Bold Tests Routine)**

General tests (serum)
Calcium
Phosphorus
Parathyroid hormone
25-Dihydroxyvitamin D
Chloride
pH
Alkaline phosphatase
Protein electrophoresis
Uric acid
Creatinine
Hematocrit
Other tests
Urinalysis
24-hr urinary calcium
Chest radiography
Renal ultrasound
Specialized tests
Hydrocortisone suppression test
1,25-Dihydroxyvitamin D
Nephrogenous cyclic AMP
Tubular resorption of phosphorus

Industrial-grade hand films Bone biopsy **Bone Density Test (DEXA)**
AMP, adenosine monophosphate; DEXA, dual-energy x-ray absorptiometry.

The main factors that determine how successful a center is at localizing parathyroid disease likely rests more with the center's familiarity and specialization with a certain tool than with the tool itself. An ultrasound performed by a surgeon is becoming more common in the current endocrine surgery practice as well as the multidisciplinary patient-centered approach for each patient with parathyroid disease.

4. Operative approach and pathology

a. Many surgeons recommend bilateral neck exploration and identification of the abnormal and normal parathyroid glands, but most endocrine surgeons today recommend a focused approach often directed by sestamibi and ultrasound localization in patients with sporadic HPT. In this scenario, the surgeon will employ intraoperative PTH to decrease chances of recurrent/persistent disease.

i. A solitary adenoma occurs in 85% of patients with sporadic primary HPT. Today, surgeons usually perform a unilateral or focal exploration and determine whether the PTH level falls by 50% within 10 minutes following removal of the parathyroid tumor (Miami Criteria). This suggests a successful operation over 96% of the time.

ii. When all glands are hyperplastic (12% of all patients with primary HPT), a subtotal parathyroidectomy is done, leaving about 50 mg (the size of a normal parathyroid gland) of the smallest and most accessible parathyroid gland. In such patients, there may be considerable variation in size of the parathyroid gland.

iii. When there is more than one abnormal parathyroid gland and several normal-appearing parathyroid glands (4% of all patients with primary HPT), all abnormal glands should be removed and normal glands biopsied and marked with a clip in case reoperation is required.

iv. Total parathyroidectomy and parathyroid

autotransplantation has been recommended by some experts for patients with familial HPT, MEN1, or primary or secondary hyperplasia. We prefer a subtotal parathyroid resection in such patients, leaving approximately a 50-mg remnant of the most normal parathyroid gland. We reserve total parathyroidectomy and autotransplantation for patients with recurrent or persistent HPT or for children with neonatal HPT.

v. Pregnant patients, with severe hypercalcemia, should be operated upon during the second trimester of pregnancy.

vi. When a parathyroid tumor invades its surrounding structures, parathyroid carcinoma must be suspected. This parathyroid gland should be removed along with contiguous structures. These structures may include the thyroid lobe and adjacent lymph node level. Parathyroid cancer should be considered in any patient with profound hypercalcemia and a palpable parathyroid gland.

b. The possible **complications** of parathyroidectomy include hemorrhage, vocal cord dysfunction, postoperative hypocalcemia, infection, and, very rarely, hypomagnesemia. These complications should occur in <2% of patients. Patients with more severe HPT and with extensive bone disease are more likely to develop hypocalcemia following parathyroidectomy because of “bone hunger” (influx of calcium and phosphorus into the metabolically active bone).

c. The **benefits** of parathyroidectomy include metabolic cure. The International Workshop for the Management of Asymptomatic Hyperparathyroidism recommends surgery for most patients with a diagnosis of primary hyperparathyroidism. Renal stones and osteoporosis usually improves after surgery, and nonspecific symptoms such as fatigue, arthralgias, bone pain, and weakness improves in up to 50% of patients.

V. SECONDARY HPT

A. General principles

Secondary HPT occurs most often in patients with chronic renal failure, but may develop from any condition that causes hypocalcemia, such as malabsorption after bariatric surgery.

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1. Secondary HPT in patients with chronic renal failure can usually be prevented by good **medical treatment**, including **(1)** a low-phosphorus diet and binding phosphorus with calcium carbonate or aluminum hydroxide (Alucaps with meals); **(2)** maintaining a positive calcium balance with supplemental calcium intake and high calcium concentration (3.5 mEq/L) in dialysate; **(3)** treating with 1,25-dihydroxyvitamin D (Rocaltrol, 0.25 to 1.0 μg PO b.i.d.); and **(4)** treating with cinacalcet HCI (Senispar, 60 mg PO b.i.d.), which reduces PTH and the product of calcium × phosphate (CaXP).
2. **Indications for surgical treatment** include **(1)** a calcium × phosphorus product of 70 or greater, **(2)** progressing renal osteodystrophy with bone pain, **(3)** severe pruritus, **(4)** soft-tissue calcification, **(5)** a calcium level >11.0 mg/dL with a markedly increased PTH level, **(6)** calciphylaxis, and **(7)** persistent severely elevated calcium and PTH after renal transplant.

B. Surgical management

1. **Surgical treatment** includes the following:
   a. **Dialysis** 1 day before operation to correct electrolyte abnormalities and to lower potassium level.
   b. **Subtotal parathyroidectomy**, leaving 50 to 60 mg of an accessible, histologically confirmed hyperplastic parathyroid gland (preferred); or total parathyroidectomy and autotransplantation of 15 1-mm pieces to individual muscle pockets in the forearm. The upper thymus situated cephalad to the innominate should be removed in these patients, because as many as 15% of persons will have a fifth hyperplastic parathyroid gland.
2. **Postoperatively**, these patients are prone to develop tetany because of “hungry bones” and a small parathyroid remnant. They should be treated with 1,25-dihydroxyvitamin D (0.25 to 1.0 μg PO b.i.d.) and calcium supplementation.
3. **Complications** include hemorrhage, hypoparathyroidism, recurrent laryngeal nerve injury, infection, and hyperkalemia with respiratory arrest. All these complications are rare except for hypocalcemia.
4. The **prognosis** after successful parathyroidectomy is good. Bone

pain and pruritus usually disappear, and patients develop an improved state of well-being. However, patients' calcium balance must be corrected by vitamin D supplementation or else the secondary HPT will recur. Some patients with secondary HPT also develop bone pain and have a low-turnover type of osteomalacia, which may be caused or aggravated by aluminum toxicity. The PTH values in these patients, though increased because of renal failure, are generally much lower than in patients with osteitis fibrosa cystica.

VI. ADRENALS

A. General principles

Clinically important functioning and nonfunctioning adrenal tumors are rare and arise from the cortex, causing hyperaldosteronism or Cushing syndrome, or from the adrenal medulla or other chromaffin cells in the sympathetic nervous system, causing pheochromocytomas. Adrenal tumors may secrete one or more hormones. Nonfunctioning adrenal tumors are identified in around 5% of cross-sectional imaging done for unrelated reasons. These incidentalomas need to be worked up for biochemical functionality. If these adrenal tumors are asymptomatic, nonfunctional, homogeneous with a smooth capsule, and <4 cm in diameter, they can be followed. CT should be repeated in 6 months.

Adrenalectomy is recommended for functioning adrenal tumors, whether benign or malignant, for growing or enlarging tumors, for complex tumors, and for nonfunctioning adrenal tumors 4 cm and larger and for those with any concerning features on imaging.

B. Primary hyperaldosteronism

1. **Diagnosis**
   - **a. Clinical manifestations.** See Chapter 17.
   - **b. Laboratory tests.** See Chapter 17.
2. **Differentiating between adenoma and hyperplasia.** See Chapter 17.

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3. **Treatment**
   - **a. Medical. Spironolactone**, a competitive aldosterone antagonist, or **amiloride**, a potassium-sparing diuretic, will normalize blood pressure and correct the hypokalemia. Either of

these medications is the treatment of choice for patients with adrenocortical hyperplasia and for preparing patients with adrenocortical adenomas or carcinomas for operation. In patients with mild biochemical abnormalities and symptoms, potassium supplementation (8 g potassium chloride daily) and sodium restriction can correct the electrolyte abnormalities.

b. Surgical

i. Once the patient has been prepared medically for the operative procedure, laparoscopic adrenalectomy is the treatment of choice. Today, laparoscopic surgeons may approach the adrenal gland anteriorly or intraabdominally, or posteriorly through the retroperitoneal space. The posterior 12th-rib or laparotomy open approach is used when an experienced laparoscopic surgeon is not available.

ii. In patients with bilateral hyperplasia causing hyperaldosteronism, total or subtotal adrenalectomy (leaving 30% of the adrenal gland) for patients with hyperplasia is controversial, because few patients become normotensive. Therefore, most of these patients are treated medically.

c. Postoperative care

i. Most patients require only the usual postoperative care and can leave the hospital 24 hours or less after a laparoscopic adrenalectomy for an aldosteronoma. Postoperative plasma aldosterone level should be checked on postoperative day 1. Potassium supplementation should be discontinued.

ii. A few patients will require supplemental saline because of transient (1 day to 1 month) aldosterone deficiency. Fludrocortisone (50 to 100 μg/day PO) may also be needed especially in situations where bilateral adrenalectomy is performed.

iii. Glucocorticoids are rarely required if only one gland is removed, but a high unexplained fever, hypotension not responsive to fluids or profound weakness warrants obtaining a plasma cortisol level to rule out Addisonian crisis and the need for immediate glucocorticoid treatment.

4. **Prognosis.** The response rate to adrenalectomy can usually be predicted by the preoperative response to spironolactone. Young, slim female patients with a relatively short period of hypertension

have the best response. Blood pressure decreases in ~80% of patients, although this may take several months, and virtually all patients become normokalemic. In patients with hyperplasia, some degree of hypertension normally remains, but the hypokalemia is usually corrected.

C. Hyperadrenocorticism (Fig. 81-1)

See Chapter 17.

1. **Diagnosis and differential diagnosis.** See Chapter 17.
   a. **Clinical manifestations.** See Chapter 17.
      i. **Symptoms.** See Chapter 17.
      ii. **Physical findings.** See Chapter 17.
   b. **Laboratory tests.** See Chapter 17.
2. **Complications.** See Chapter 17.
3. **Treatment**
   a. **Medical treatment.** Temporary control of Cushing syndrome can be accomplished with ketoconazole, metyrapone, and aminoglutethimide, which inhibit steroid production, and with 1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane (mitotane), which is toxic to the adrenal cortex. Mitotane with steroid replacement and documentation of mitotane levels have been used for patients with adrenocortical carcinomas.
   b. **Surgical treatment**
      i. Cushing disease is managed by transsphenoidal hypophysectomy with microsurgical excision of the pituitary adenoma or with pituitary irradiation. Excision of the pituitary adenoma results in rapid relief of symptoms, although ACTH deficiency is common. The clinical response to irradiation takes longer (up to 18 months) and frequently results in panhypopituitarism.

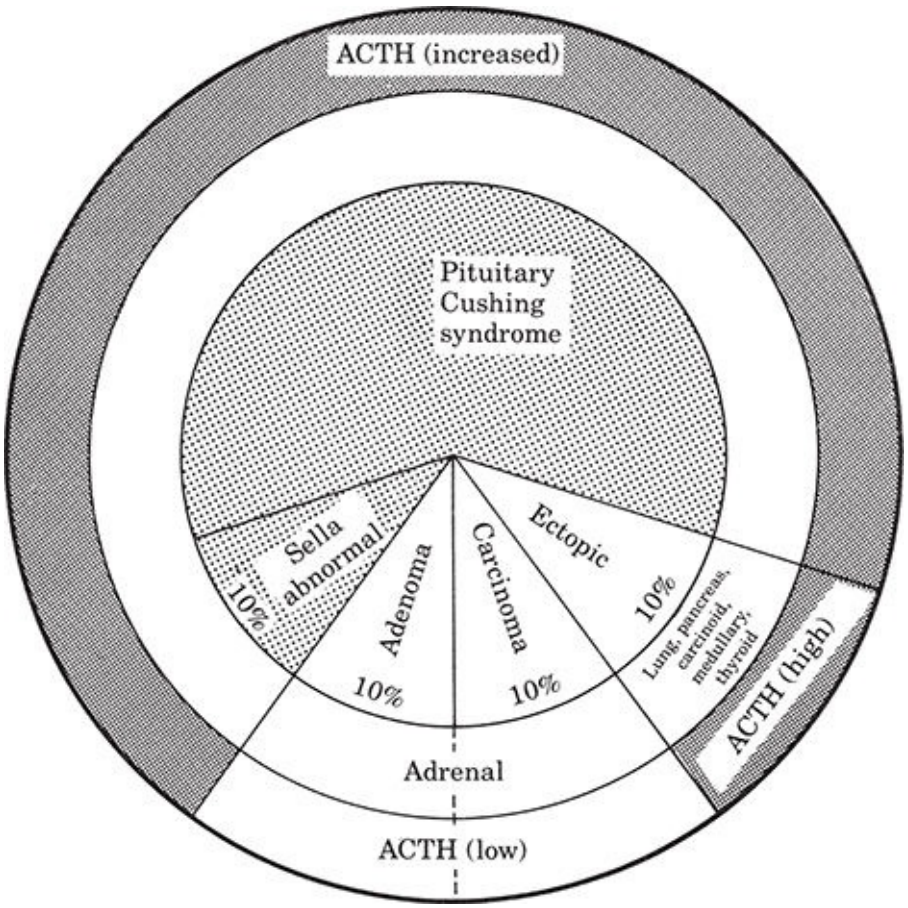

Figure 81-1. Approximate distribution and adrenocorticotropic hormone levels in patients with Cushing syndrome. (Modified from Welbourn RB. Some aspects of adrenal surgery. *Br J Surg* 1980;67:723.)

ii. Laparoscopic adrenalectomy is the treatment of choice for patients with benign-appearing adrenal tumors and for some with pituitary Cushing syndrome who fail to respond to pituitary irradiation or microsurgery. Before operation, hypokalemia and other electrolyte abnormalities should be corrected and diabetes mellitus controlled.

a) Postoperative care. Patients with Cushing disease who undergo bilateral adrenalectomy must have permanent cortisol replacement. Those with unilateral adrenalectomy for Cushing syndrome or subclinical cushing syndrome may take postoperative replacement prophylactically or may undergo an ACTH stimulation test on postoperative day 1 to determine if there is a requirement for exogenous steroids. In general, if steroids are needed, a stress dose of at least 50 mg to 25

mg BID pf hydrocortisone should be given in the immediate postoperative period. In patients with bilateral adrenalectomy, it is important to supplement mineralocorticoid, and there is a need for lifelong steroid supplementation. In those with unilateral adrenalectomy, cortisol requirements should be assessed periodically by the endocrinology team to determine when steroid replacement can cease. It can often take months for patients with a suppressed adrenal gland to recover from the condition of their steroid replacement safely. Postoperative complications include p. 1002p. 1003wound infection, wound dehiscence, peptic ulceration with bleeding, and pulmonary problems.

b) The **prognosis** in patients after removal of an adrenal adenoma and after treatment of pituitary Cushing syndrome is generally excellent. Hypoadrenocorticism and panhypopituitarism occur after total adrenalectomy and pituitary ablation, respectively, and these patients require lifelong corticosteroid replacement, which must be increased in times of stress. **Nelson syndrome**, which causes hyperpigmentation, headaches, exophthalmos, and blindness because of growth of the pituitary tumor, develops in 20% of patients after total bilateral adrenalectomy. When Cushing syndrome is the result of adrenocortical carcinoma, the prognosis is grave. Palliation with **mitotane**, started soon after adrenalectomy, is helpful in approximately 20% of patients.

D. Pheochromocytomas

Pheochromocytomas (see Chapter 18) are tumors of the adrenal medulla and chromaffin tissues elsewhere in the body and account for 0.1% to 0.2% of all cases of hypertension. Ten percent of these catecholamine-producing tumors are malignant, 10% are bilateral, and 10% are found in extraadrenal sites. They occur sporadically, in association with Sipple syndrome (medullary carcinoma of the thyroid, HPT, and ganglioneuromatosis) and in association with the

neurocutaneous syndromes (neurofibromatosis, von Hippel–Lindau disease—MEN2, Sturge–Weber disease, and tuberous sclerosis). Children and patients with familial syndromes are more likely to have multiple pheochromocytomas. Previously, it was thought that only a small fraction of these tumors were familial in nature, but recent genetic linkage studies show that more than one third of pheochromocytomas have a hereditary component. The gene encoding the succinate dehydrogenase complex is the most recent gene to be implicated in this disease.

1. **Diagnosis.** See Chapter 18.
2. **Treatment.** See Chapter 18.
   - **a.** Medical treatment includes:
     - **i.** Upon diagnosis, it is important to block the excess catecholamines with an *α*-adrenergic–blocking agent. Although there is no unanimously accepted preoperative *α*-blockade protocol, we use doxazocin but other agents are commonly used including prosazocin and phenoxybenzamine. Orthostatic hypotension and rhinitis tend to be the most common side effects with phenoxybenzamine. Phentolamine has also been used.
     - **ii.** **Nitroprusside** (0.01% IV infusion) is the drug of choice for managing intraoperative hypertension. Nitroprusside has replaced phentolamine because of its shorter duration of action and because it has no direct cardiac-stimulating effects.
     - **iii.** Restoration of blood volume preoperatively by forced hydration while the patient is being treated with *α* blockade is essential to avoid hypotension upon removal of the tumor.
     - **iv.** **Propranolol** (Inderal, 5 to 40 mg PO q6h), a *β*-blocker, is used for the management of tachycardia and arrhythmias, but only after treatment with *α* blockade has been started.
   - **b. Operative treatment**
     - **i.** Careful intraoperative monitoring (central venous pressure, arterial pressure, and electrocardiographic monitoring) in a well-hydrated patient treated with *α* blockade for at least 10 days is the initial step.
     - **ii.** A laparoscopic approach is recommended when tumors are <6 cm. These tumors sometimes may be multiple and in

ectopic sites, so preoperative localization tests are indicated.

iii. Avoid hypotension after removal of the tumor by ensuring that the patient is well hydrated prior to operation and is adequately blocked.

iv. **Complications** include sequelae of hypertension (stroke, renal failure, and myocardial infarction), arrhythmias, hypotension, bleeding, and hypoglycemia.

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3. **Prognosis.** The results of surgery are excellent for benign lesions, with an operative mortality rate of <1%. About 95% of patients with paroxysmal hypertension and 65% of those with sustained preoperative hypertension become normotensive. Malignant pheochromocytoma has a poor prognosis. Treatment with phenoxybenzamine and metyrosine (Demser), as well as with external irradiation or with ^{131}I-MIBG, sometimes gives effective palliation.

VII. VIRILIZATION AND FEMINIZATION

A. General principles

1. **Diagnosis and differential diagnosis.** See Chapters 25, 28, and 29.
2. **Treatment.** See Chapters 25, 28, and 29.
   a. Congenital adrenal hyperplasia
   b. Tumor
3. **Course.** See Chapters 25, 28, and 29.

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82

Surgical Management of Pediatric Endocrine Diseases

Anna Kundel and Omar Bellorin-Marin

I. SURGICAL MANAGEMENT OF THYROID DISEASE IN CHILDREN

A. Thyroid cancer in children

Benign cervical lymphadenopathy is one of the most common causes for consultation during childhood. When present, a thorough neck exam must be performed focusing in the midline. In approximately 2% of the cases, a solitary thyroid nodule will be present. Thyroid nodules in children are more likely to be malignant when compared with the risk of malignancy in thyroid nodules of an adult. Therefore, although most of the time nodules represent a benign condition, malignancy must be ruled out.

Compared with adults, epithelial-derived well-differentiated thyroid cancer (DTC), which includes papillary and follicular thyroid cancer (FTC), tends to present with advanced disease: lymph node involvement, pulmonary disease, and extrathyroidal extension. This increases the operative morbidity and recurrence rate that may result in lifelong disability. The incidence of DTC is low with an annual rate of 0.54 cases per 100 000 persons. In children less than 10 years old, the incidence of DTC is 1 per 1 000 000. The incidence increases with age: in children from 10 to 14 years, it is 1 per 200 000, whereas in children from 15 to 19 years old, the incidence reaches one in 75 000. The female to male ratio is 4:1 after puberty with a 1:1 ratio in the prepuberty ages.

The thyroid cancer types in children are papillary thyroid carcinoma (PTC) 60%, follicular variant of PTC 23%, FTC 10%, and medullary thyroid cancer (MTC) 5%. Of the well DTCs, **PTC represents the most common thyroid cancer in the pediatric population**, accounting for 1.4% of new childhood

malignancies. PTC has an excellent prognosis when diagnosed and treated in the early stages with a low cancer-specific mortality.

There are several major differences between PTC and FTC. PTC is more likely to be bilateral and multifocal, and in the majority of pediatric cases, metastasizes to regional lymph nodes. FTC may be less aggressive than PTC and is generally associated with less advanced disease. FTC is usually unifocal; it rarely involves regional lymph nodes, but hematogenously metastasizes to lung and bone. As FTC is rare in children, current guidelines are more focused on the management of PTC in children.

B. Thyroid nodule

Recently, the American Thyroid Association (ATA) published the **latest guidelines** in the management of thyroid nodules and cancer in children on the basis of expert recommendations.

1. The pediatric patient is defined as a patient ≤18 years.
2. The evaluation and treatment of thyroid nodules in children (Fig. 82-1) should be the same as in adults with some exceptions:
   - **a.** Ultrasound (US) features and clinical picture (risk factors) should be used rather than size alone to identify nodules that require fine-needle aspiration (FNA). This is especially important for nodules under 1 cm because **small size does not necessarily correlate to a lower risk of cancer in children**.
   - **b.** All FNAs in children should be performed under US guidance by expert hands. If a worrisome nodule is noted, a thorough US of the cervical lymph nodes should be done.
   - **c.** FNA of a hyperfunctioning nodule in a child is not warranted but should be surgically removed. For autonomous thyroid nodules, the recommended approach is surgical resection, as opposed to medical therapy.

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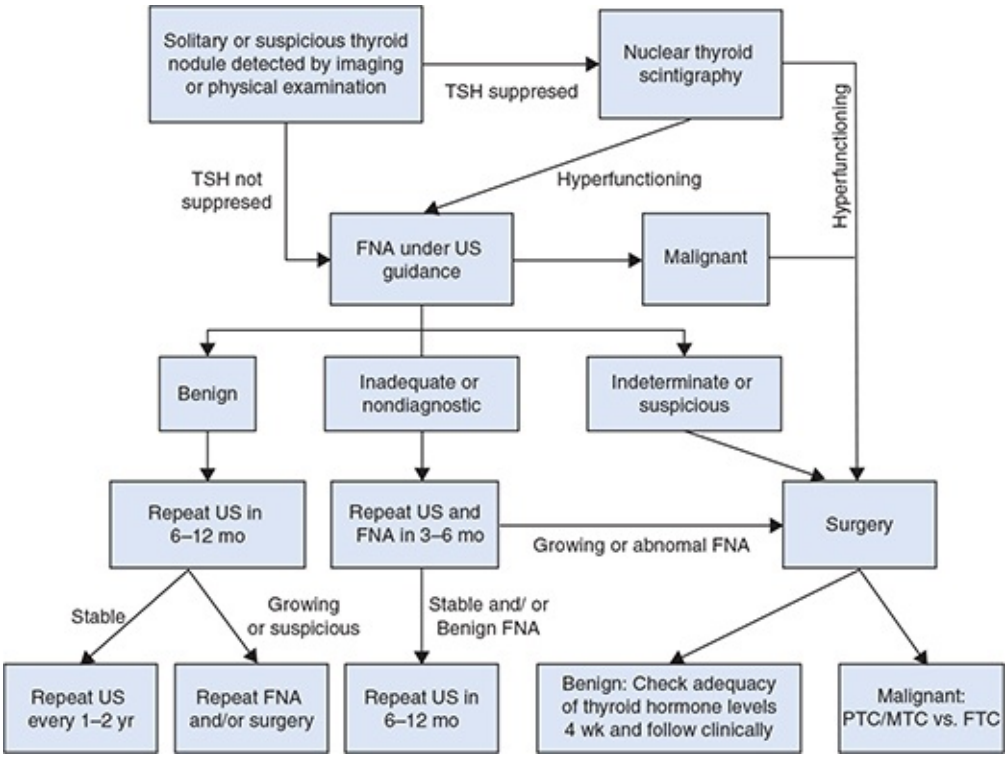

Figure 82-1. Workup of thyroid nodules in children. FNA, fine-needle aspiration; FTC, follicular thyroid cancer; MTC, medullary thyroid cancer; PTC, papillary thyroid carcinoma; TSH, thyroidstimulating hormone; US, ultrasonography. (From Francis GL, Waguespack SG, Bauer AJ, et al. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2015;25(7):716–759.)

d. A diffusely infiltrative form of PTC may occur in children and should be considered in a clinically suspicious gland (diffuse enlargement of a lobe or gland and/or associated with lymphadenopathy). Microcalcifications may be seen on US, and FNA should, therefore, be performed.

e. Surgical excision with lobectomy with isthmusectomy is favored over repeat FNA for most nodules with indeterminate, Bethesda III/IV, cytology.

C. Surgical management

Pediatric thyroid surgery should be performed in a hospital with a full pediatric care department including endocrinology, intensive care, radiology, nuclear medicine, anesthesia, and most importantly, a high-volume thyroid surgeon. Studies have implied that a surgeon should perform at least 30 or more cervical endocrine procedures annually especially if compartment-focused lymph node resection is indicated. High volume reduces the incidence of complications, hospital stay, and

costs.

D. Benign nodule

1. A benign FNA should prompt follow-up with a repeat US at 6 months and another at 1 year to document stability. Repeat FNA should be done if the nodule grows or develops suspicious features.
2. Surgical management should be offered if the patient exhibits compressive symptoms or if the patient prefers surgery for cosmetic reasons.
3. Surgery should be considered in nodules >4 cm or in patients with significant clinical concern or risk factors for cancer.

E. PTC

1. A thorough US of the neck evaluating cervical lymph node basins should be performed preoperatively and any worrisome lymph node biopsied. Further p. 1006p. 1007imaging workup with CT or MRI should be obtained in cases with large fixed tumors, bulky nodal disease, or vocal cord paralysis to aid in surgical planning.
2. For the majority of children, total thyroidectomy is recommended. An increased incidence of bilateral and multifocal disease has been noted in children. A total thyroidectomy has been correlated with decrease persistence and recurrence of disease.
3. Central lymph node dissection (CND) is recommended for patients with malignant cytology and clinical evidence, either on preoperative workup or on intraoperative lymph node involvement. To reduce the local recurrence and complications, CND should be performed only by an experienced surgeon. A formal lymph node dissection is recommended rather than “berry picking” resection. Prophylactic CND should be selectively considered on the basis of tumor size, focality, intraoperative findings, and surgeon experience.
4. Cytologic confirmation of positive lateral lymph node disease is recommended prior to surgery. No routine prophylactic lateral lymph node dissection (level II to V, lymph nodes located lateral to the carotid artery) is recommended.
5. Radioactive I^{131} therapy should be decided on a case-by-case basis, taking into account potential long-term side effects.

6. Postoperative follow-up consists of serial US of the neck and measurement of Tg antibody every 6 months for at least the first 5 years. Thereafter, follow-up should be individualized.
7. Recurrent or persistent disease noted grossly on imaging or on clinical examination (macroscopic disease >1 cm) should prompt an expert surgical consult.

F. FTC

1. An FNA with indeterminate results warrants lobectomy and isthmusectomy as surgical management in a child where there is a possibility of follicular neoplasm.
2. Intraoperative frozen section can be considered; however, it is not routinely recommended because the diagnosis of cancer rests on capsular and lymphovascular invasion usually not identified on frozen section.
3. With a minimally invasive FTC, size <4 cm and less than 3 vessels invaded, lobectomy alone may be sufficient.
4. If more than three areas of vascular invasions are identified or if the tumor is >4 cm, total thyroidectomy and postoperative RAI therapy is recommended because of the higher risk of distant disease.
5. FTC diagnosed in childhood may be a red flag for a hereditary cancer syndrome. **Cowden syndrome** is caused by autosomal dominant germline mutation in PTEN gene and is associated with an increased risk of nonmalignant tumors as well as breast and endometrial cancers. Therefore, testing for PTEN germline mutation should be considered in children with diagnosed FTCMTC.

G. MTC

1. MTC in children is associated with familial MTC and multiple endocrine neoplasia (MEN) types 2A and 2B in one third of the cases (see Chapter 79). Sporadic MTC is rarely seen in childhood.
2. Children with MEN2A should undergo total thyroidectomy before 5 years, and those with MEN2B should have a total thyroidectomy in the early few years of life.
3. All children who have a germline RET mutation should undergo surgery regardless of the calcitonin levels. The goal is to prevent development of invasive MTC.
4. All children with MTC should be **tested for pheochromocytoma before undergoing thyroidectomy**.

5. Total thyroidectomy with prophylactic central neck dissection (level VI) should be performed. But in MEN2A patients, it may be omitted if calcitonin is <40 pg/mL and if there is no evidence of lymph node metastasis on preoperative imaging. Near-total or subtotal thyroidectomy where a small part of the thyroid, usually posteriorly, is left in place in order to preserve nerve and parathyroid function is not recommended. This is because the c-cells (origin of medullary cancer) are posteriorly located within the thyroid gland.

p. 1007p. 1008

6. Lateral neck dissection should be performed only when a patient is diagnosed with preoperative FNA. No prophylactic lateral neck dissection is advised because there is no survival benefit, but may cause morbidity from nerve injury during surgery.
7. Follow-up should consist of serial US of the neck, calcitonin levels, and carcinoembryonic antigen (CEA) levels.

II. SURGICAL MANAGEMENT OF PARATHYROID DISEASE IN CHILDREN

A. Hyperparathyroidism (HPTH) (see Chapter 41)

1. HPTH in children manifests with symptoms related to hypercalcemia or is suspected when it is incidentally found in routine laboratory studies. In general, children may present with more severe hypercalcemia-related symptomatology than adults do.
2. Differential diagnosis of hypercalcemia in children is broad and must be taken into consideration during the initial assessment (Table 82-1).
   a. Primary HPTH
3. Incidence of primary HPTH in children is 2 to 5 per 100 000.
4. Most childhood HPTH, if no family history or nephrolithiasis is present, is possibly due to single-gland disease.
5. Localization studies include ultrasonography, ^{99m}Tc-sestamibi scan, single-photon emission computed tomography (SPECT), MRI and/or CT scan.
6. Therefore, if preoperative localization is successful, surgery consists of directed gland excision with **intraoperative measurement of PTH**. A drop of more than 50% and into the

normal range confirms successful resection.

7. If PTH remains elevated or if preoperative localization was unsuccessful or the nature of the disease indicates hyperplasia, a four-gland exploration should be performed. This exploration includes one of the following three approaches:
   a. Resection of only visible enlarged glands
   b. Three-and-a-half parathyroidectomy
   c. Total four-gland resection with autografting.
8. HPTH in **MEN1** patients is a result of all-gland hyperplasia. Supernumerary gland is more likely in this population. Four-gland exploration with cervical thymectomy should be performed.
9. Patients with **MEN2A** seem to have milder forms of HPTH as compared to those with MEN1 and may be asymptomatic. It is now preferred to remove only the enlarged parathyroid glands as long as there is an associated intraoperative PTH drop consistent with normal function.

TABLE 82-1 Causes of Hypercalcemia in Children

Endocrine

- Primary hyperparathyroidism
- Secondary hyperparathyroidism
- Tertiary hyperparathyroidism
- Thyrocoxicosis
- Familial hypocalciuric hypercalcemia
- Neonatal severe hyperparathyroidism
- Ectopic parathyroid hormone production

Other

- Granulomatous disease
- Pharmacologic
- Immobilization
- Subcutaneous fat necrosis

From Hannah GP, Michael AS. Childhood diseases of the thyroid and parathyroid glands. In: *Pediatric Surgery*. 7th ed. Philadelphia, PA: Saunders; 2012.

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10. In the setting of hyperplasia, autotransplantation is recommended to be performed outside of the neck (forearm).

a. Both **secondary** and **tertiary** HPTH are commonly related to renal disease and affect all four glands. Medical management is the first line of treatment, and it consists of dietary modifications, dialysis, vitamin D, and/or phosphate binders. When required, surgical management can be attempted, and this consists of subtotal parathyroidectomy or total parathyroidectomy with autotransplantation.

B. Parathyroid carcinoma

Parathyroid carcinoma is exceedingly rare in children with only case reports published in the literature. Metastatic disease is often found in initial diagnosis. Typical presentation is a neck mass with hypercalcemia reported to be 3 to 10 times normal. Treatment includes hypercalcemia control, followed by surgical excision if appropriate. Recommended surgical approach includes enbloc hemithyroidectomy, parathyroidectomy, and lymph node dissection. Long-term survival (90%) can be achieved if there is complete resection. Incomplete resection precludes a recurrence rate of 50%.

III. SURGICAL MANAGEMENT OF ENDOCRINE PANCREATIC DISEASE IN CHILDREN

A. Hyperinsulinism (HI)

1. Background
   a. Congenital HI is a rare disease in children with an incidence of 1.4 in 50 000 live births.
   b. HI is the most common cause of persistent hypoglycemia leading to seizures and brain damage in neonates.
   c. Two spectrums of disease have been genetically evidenced: localized disease (focal, localized lesions) and diffuse disease (unable to identify focal disease).
   d. Most common endocrine tumor of the pancreas in children; usually benign (90%).
   e. Solitary (80%) in children with >4 years.
   f. Insulin-secreting tumors (MEN1 related) are rare in children and are usually expressed after the first decade of life.
2. Diagnosis:
   a. Clinical manifestation related to hypoglycemia: seizures, lethargy, and apnea
   b. Fasting hypoglycemia (glucose <50 mg/dL)
   c. Inappropriately elevated plasma insulin (>2 μU/mL)

d. Low-plasma β-hydroxybutyrate (<2 mmol/L)

e. Low-free fatty acids (<1.5 mmol/L)

f. Inappropriate glycemic response to IV glucagon at the end of the 72-hour fast (>30 mg/dL rise in serum glucose level). In normal subjects, glycogen stores are depleted after a prolonged fast to prevent hypoglycemic symptoms. Because insulin promotes storage of glycogen, **patients with insulinoma have an abundance of glycogen even when fasting**. Therefore, when glucagon (a potent glycogenolytic) is given at the end of a fast, patients with insulinoma will have a vigorous increase in glucose levels as compared to a weak response in normal subjects. This is usually done if other tests are borderline.

g. **C peptide** measurement should be done to rule out factitious hyperinsulinemia.

3. Imaging studies

a. US, MRI, CT, contrast angiography, and radiolabeled octreotide scans have all been largely unsuccessful in identifying multiple lesions.

b. Imaging studies are most useful when a focal nodular lesion is the cause of HI.

c. Arterial stimulation with venous sampling:

i. Requires glucose levels to be maintained between 60 and 80 mg/dL during the procedure

ii. Selective stimulation of the pancreas with intraarterial calcium with simultaneous venous insulin measurement

a) Gastroduodenal artery: pancreatic head

b) Superior mesenteric artery: uncinated process and neck

c) Splenic artery: pancreatic body and tail

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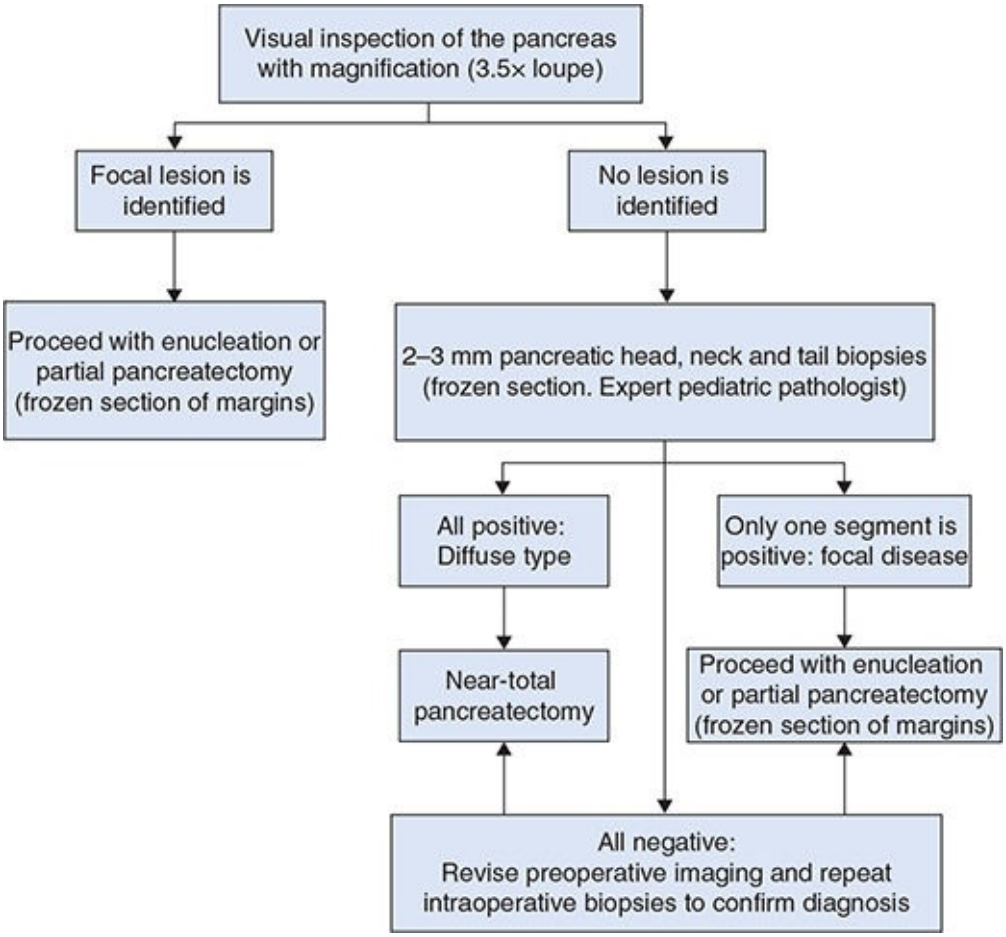

Figure 82-2. Surgical management of hyperinsulinism in children. (Adapted from Adzick NS. The pancreas. In: *Pediatric Surgery*. 7th ed. Philadelphia, PA: Saunders; 2012; Lovvorn HN III, Nance ML, Ferry RJ Jr, et al. Congenital hyperinsulinism and the surgeon: lessons learned over 35 years. *J Pediatr Surg* 1999;34(5):786–792; discussion 792–793.)

iii. An immediate rise in insulin from selective stimulation in only one artery suggests focal HI. Insulin rise in all three pancreatic segments suggests diffuse type.

d. Transhepatic portal venous catheterization and selective sampling of the pancreatic veins

i. Requires glucose levels to be maintained at 50 mg/dL during the procedure

ii. Pancreatic venous insulin levels are compared to plasma levels of insulin simultaneously drawn.

4. Surgical management

a. The surgical approach consists of enucleation when insulinoma is identified.

b. Intraoperative US is useful in identifying insulinomas.

c. If the tumor is difficult to localize or diffuse disease is present, the algorithm described in Figure 82-2 should be followed.
d. The type of pancreatic resection depends on the location of the hyperfunctioning cells.

B. Other hormonally active tumors

1. Gastrinoma
   a. The second most common pancreatic islet cell tumor
   b. The most common pancreatic tumor related to MEN1

p. 1010p. 1011

   c. Localized in the gastrinoma triangle: superiorly by confluence of cystic and common bile duct, medially junction of the neck and body of pancreas, and inferiorly second portion of duodenum.
   d. Commonly **malignant**, multicentric, and metastatic at diagnosis in children
   e. Suspected after multiple episodes of peptic ulcer disease and elevated gastrin level (>500 pg/mL) in the absence of proton pump inhibitors (PPIs)
   f. Paradoxical **elevation of gastrin levels after secretin administration is diagnostic**. This test is done to differentiate gastrinoma from other sources of hypergastrinemia (e.g., G-cell hyperplasia, retained antrum). Secretin inhibits gastric G-cells but stimulates gastrin production for gastrinoma cells. Hence, secretin stimulation will elicit an increase in gastrin levels in patients with gastrinoma and suppress production in others.
   g. Localizing imaging studies include CT, EUS, percutaneous transhepatic portal vein sample, octreotide scan, and intraoperative US.
   h. Medical treatment with H_2 blockers, PPI, and somatostatin should generally be avoided in the long term because of the inhibitory effect in growth hormone secretion.
   i. Surgical excision is warranted if a solitary tumor is found. For residual tumor, failure in medical treatment, or metastatic disease, total gastrectomy may be required, but it is very rare with the current available medical management.
2. VIPoma

a. Extremely rare in children with only a few cases reported in the literature
b. Malignant in up to 50%
c. Patients have profuse watery secretory diarrhea associated with hypokalemia and hypochlorhydria, dehydration, metabolic acidosis, and acute renal failure.
d. Medical therapy includes streptozotocin and somatostatin.
e. Surgical excision of the tumor is recommended whenever possible.

IV. SURGICAL MANAGEMENT OF ADRENAL DISEASE IN CHILDREN

A. Pheochromocytoma (see Chapter 18)

1. Uncommon in children with an incidence of 1 in 500 000 children. Ten percent to 20% of pheochromocytomas in children are familial:
   a. MEN2 (A and B): up to 50% will develop pheochromocytoma
   b. Von Hippel–Lindau disease: 20% chance of pheochromocytoma
   c. Others: Neurofibromatosis type 1, Carney triad, and SDH mutations.
2. In children, they are frequently bilateral (24% to 70%) compared with adults (10%).
3. There is higher prevalence of extraadrenal location in children.
4. Higher predominance in males
5. Variable rate of malignancy has been reported in the literature (up to 47%).
6. Risk factors for malignant disease are:
   a. Extraadrenal paraganglioma
   b. Sporadic
   c. Tumor size >6 cm
      i. Symptoms:
         a) Average age at presentation is 11 years.
         b) Common symptoms are headaches, visual disturbance, palpitations, polyuria, polydypsia, sweating, nausea, and weight loss.
         c) **Sustained hypertension is a landmark sign** found in the initial assessment (70% to 90%), as opposed to paroxysmal hypertension found in adults.
         d) Other causes of primary hypertension in children must

also be ruled out: renal abnormalities, renal artery disease, coarctation of the aorta, etc.

ii. Diagnosis

a) The best diagnostic test consists of a 24-hour measurement of catecholamines, metanephrine, and vanillylmandelic acid.

b) Plasma catecholamines can also be measured but with high incidence of false positives because of normal adrenergic response (anxious, restless child), a common finding in children.

p. 1011p. 1012

c) Plasma catecholamine levels >2 000 pg/mL are diagnostic. Levels between 500 and 1 000 pg/mL are suspicious and need further testing.

iii. Imaging studies

a) US avoids radiation and may be good for differentiating solid lesions from cystic lesions and for evaluating vasculature. It is not useful for localizing small or multifocal lesions and may not be used for evaluating extraadrenal locations.

b) CT scan has better resolution and sensitivity. Disadvantages include the need for IV contrast material and exposure to ionized radiation. **In younger children, it is less accurate** due to the absence of retroperitoneal fat.

c) MRI has good resolution and sensitivity. Phechromocytomas demonstrate low signal intensity on T1-weighted images, enhance with gadolinium-diethylenetriaminepentaacetic acid, and have an intense signal on T2 weighted images. MRI has the disadvantage of requiring sedation or general anesthesia because of the length of the study on a patient who may have not been receiving blocking agents.

d) ^{131}I-labeled metaiodobenzylguanidine scanning is a technique where a norepinephrine-like isotope accumulates where norepinephrine is taken up allowing for tumor detection. This technique is useful for

evaluating extraadrenal tumors (paragangliomas), metastatic disease, or recurrence.

B. Surgical treatment

1. **Preoperative biopsy is not indicated** and may be detrimental to the patient.
2. Intraoperative hypertension may be induced by tumor manipulation. Postoperative hypotension and cardiac arrest may result because of an abrupt fall in catecholamine levels. Therefore, **preoperative patient preparation** is the key to a safe surgical intervention.
   a. *α*-**Adrenergic blockers** (phenoxybenzamine and phentolamine) should be **started 1 to 2 weeks** before the procedure and the dose titrated up to achieve normal to slightly orthostatic blood pressure.
   b. *β*-**Blockers** may be used for reflex tachycardia only after the patient is adequately *α*-blocked.
   c. Several days prior to surgery, **volume repletion with salt** loading should be initiated to counteract the postoperative hypotension resulting from vasodilation.
   d. Fluctuation in intraoperative blood pressure is expected during anesthesia induction, intubation, tumor dissection and manipulation, and vein ligation.
3. Surgical treatment is excision of the adrenal or extraadrenal mass (paraganglioma):
   a. Laparoscopic adrenalectomy is preferred: transperitoneal or retroperitoneal approach.
   b. Open adrenalectomy should be considered for larger or malignant tumors.
   c. For patients with bilateral pheochromocytomas, a cortical sparing adrenolectomy is an option. However, this carries a higher risk for pheochromocytoma recurrence.
4. Postoperatively, patients need to be monitored for hypovolemia and hypoglycemia.
5. Because of the possibility of recurrent ad malignant transformation, long-term biochemical follow-up with selective imaging are needed.

C. Cushing syndrome

1. Cushing syndrome is rare in the pediatric population, with an incidence of 2 to 5 per 1 million children. It occurs more

frequently in young women (female to male ration is 9:1) and is usually the result of exogenous hormones. The most common endogenous cause of the syndrome is Cushing disease secondary to pituitary adenoma.

2. In patients <6 years, the most common cause of Cushing syndrome is an adrenal tumor; 60% to 80% will be adrenocortical carcinomas.
3. Other adrenal causes of Cushing syndrome are nodular adrenal hyperplasia, primary pigmented adrenocortical nodular disease associated with Carney complex, bilateral macronodular adrenal hyperplasia associated with McCune Albright syndrome, and massive macronodular adrenal hyperplasia.
4. A virilizing syndrome is often present in the setting of an adrenocortical tumor. Approximately 30% of such patients also have Cushing syndrome.

p. 1012p. 1013

5. Classification
    a. ACTH-dependent type: ectopic ACTH secretion and pituitary tumor (Cushing disease)
    b. ACTH-independent type: exogenous, adrenal nodular hyperplasia, adenoma, and adenocarcinoma.
        i. Symptoms
            a) In children, Cushing syndrome manifests by weight gain, long bone growth retardation, and frequent skin manifestations.
            b) Other symptoms include hypertension, osteoporosis, menstrual irregularity, and glucose intolerance. Psychiatric manifestations are rare.
        ii. Diagnosis
            a) Tests used to confirm the diagnosis:
                1) 24-hour urinary free cortisol test (98% sensitivity)
                2) Midnight plasma cortisol or late-night salivary cortisol
                3) Low-dose dexamethasone suppression test: 1 mg (0.3 mg/m^2 in children) of dexamethasone given at night. Morning cortisol level >5 μg/dL (unsuppressed) is consisted with Cushing syndrome.

b) Once Cushing syndrome is confirmed, the cause of hypercortisolism must be identified (Fig. 82-3).

iii. Surgical treatment

a) Surgical treatment is summarized in Figure 82-3.

b) In patients with a pituitary ACTH-producing tumor, screening for medullary cancer of the thyroid (serum calcitonin levels) and pheochromocytoma (24-hour urine cathecholamines) must be performed. If an ectopic ACTH-producing tumor is not localized or is unresectable, the patient should undergo bilateral adrenalectomy.

c) **Adrenalectomy** is the treatment of choice for an isolated unilateral tumor. The procedure is often done using a laparoscopic technique (for small lesions) or an open incision (for larger lesions).

d) Adrenocortical carcinoma requires enblock resection with thorough evaluation for metastatic disease. Tumor debulking in unresectable cases plays a role in symptom control. **Mitotane** may also be used when complete surgical resection is not achievable.

e) After unilateral adrenalectomy, the patient must be on steroid taper until the remaining adrenal gland recovers from suppression. Bilateral adrenalectomy requires lifelong glucocorticoid and mineralocorticoid replacement and is, thus, associated with considerable mortality.

D. Hyperaldosteronism

1. Primary hyperaldosteronism: Adrenal aldosterone-producing tumor (Conn syndrome) or bilateral adrenal hyperplasia

2. Secondary hyperaldosteronism: Overproduction of renin: cirrhosis, congestive heart failure, renin-producing tumor, and renal artery stenosis

3. The most common cause of primary hyperaldosteronism in the pediatric population is **bilateral adrenal hyperplasia**. There are only a few cases reported of aldosterone-producing adenoma.

a. Symptoms

i. Headache, fatigue, and weakness as a result of hypokalemia (the most common laboratory finding)

ii. Hypertension secondary to sodium and water retention

iii. Inadequate weight gain, nocturia, polyuria, and polydipsia.

b. Diagnosis
   i. Elevated plasma and urine aldosterone with decreased plasma renin
   ii. Plasma aldosterone:plasma renin activity (PRA) ratio of 35 (20 to 45) has 100% sensitivity and 92.3% specificity in diagnosing primary hyperaldosteronism
   iii. CT scan is recommended as the initial imaging study.
   iv. Adrenal vein sample (AVS) is useful in determining whether the source of the disease is bilateral or unilateral. If a single nodule is noted on CT, without any concern for bilateral disease, AVS may not be necessary before proceeding with the surgery.

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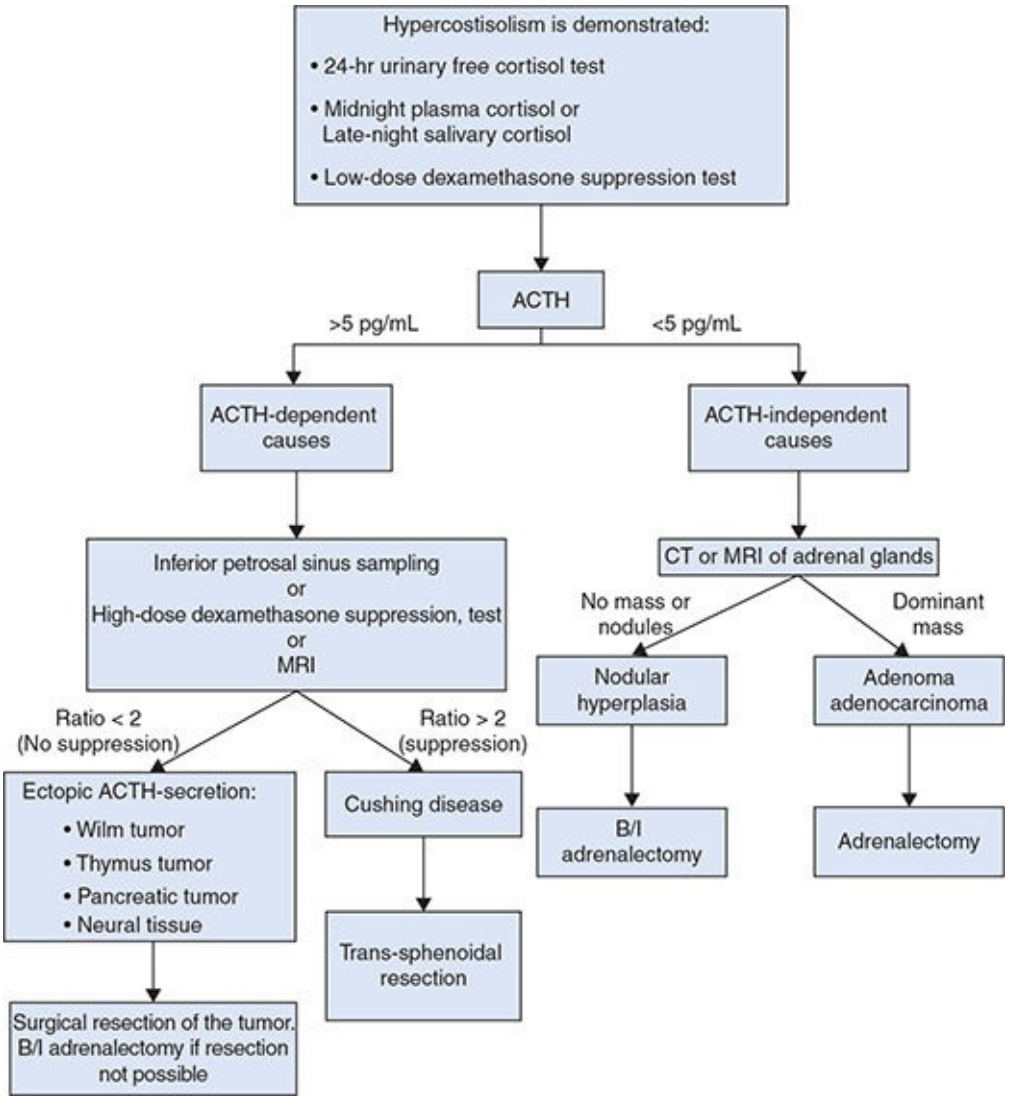

Figure 82-3. Algorithm for localization and treatment of hypercortisolism in children. (From Caty MG, Escobar MA Jr. Adrenal tumors. In: Coran AG, Adzick NS, Krummel TM, et al, eds. *Pediatric Surgery*. 7th ed. Philadelphia, PA: Elsevier Saunders; 2012:562.)

c. Treatment

i. The treatment of choice for bilateral adrenal hyperplasia is suppression therapy with mineralocorticoid receptor antagonist (spironolactone and eplerenone). Bilateral adrenalectomy should be avoided because of high morbidity of the resulting adrenal insufficiency.

ii. The treatment of unilateral disease is laparoscopic adrenalectomy.

iii. A summarized algorithm in the management of primary aldosteronism according to the latest guidelines of the

American endocrine society is depicted in Figure 82-4.

E. Incidental adrenal mass

An incidental adrenal mass discovered on CT scan performed for other reasons should be evaluated for function, especially a pheochromocytoma. Screening tests such as 24-hour urine cortisol and cathecholamines, serum potassium, plasma aldosterone concentration, and aldosterone/PRA ratio should be considered.

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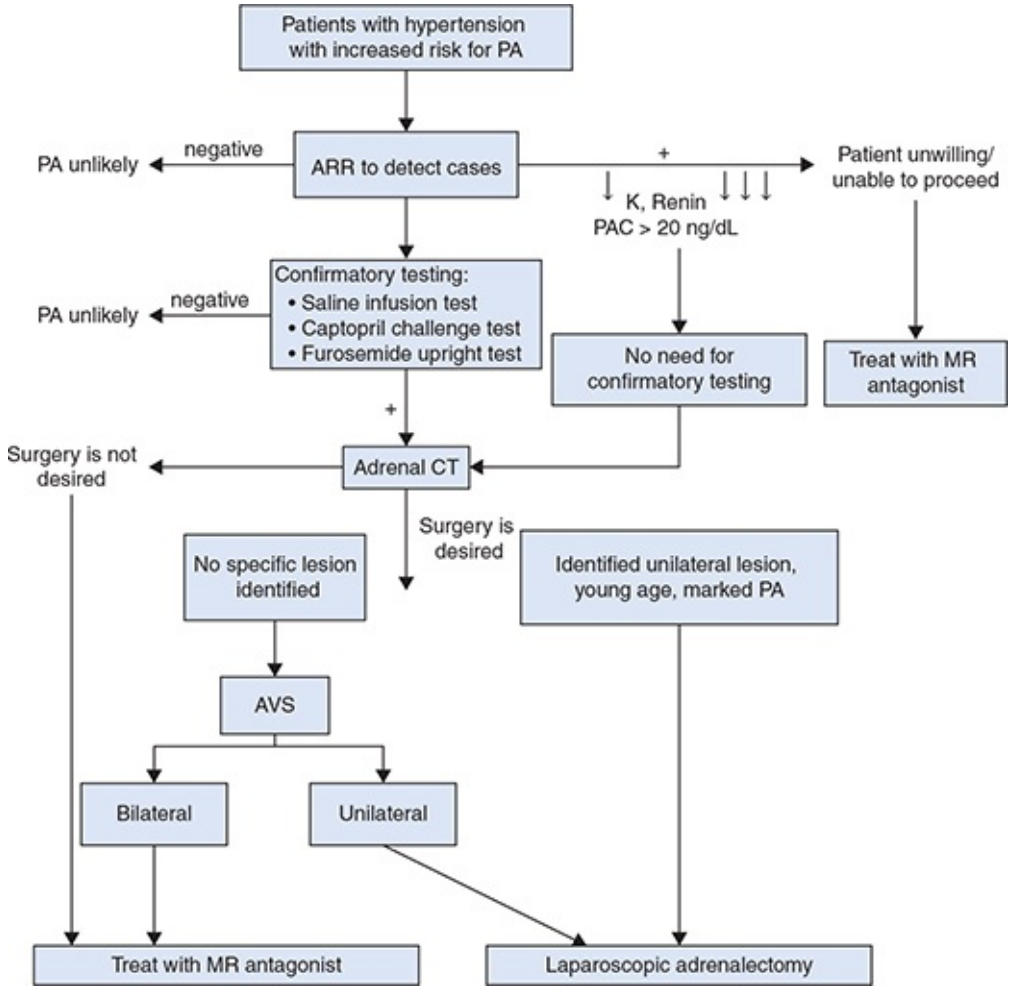

Figure 82-4. Algorithm for the evaluation and treatment of primary aldosteronism. ARR, aldosterone:renin ratio; MR, mineralocorticoid receptor; PA, primary aldosteronism; PAC, plasma aldosterone concentration. (From Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016;101(5):1889–1916.)

In the pediatric population, there are no established guidelines for

excision. Because of the high incidence of functional and malignant tumors in children, experts recommend adrenalectomy for all incidentally identified adrenal tumors.

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83 Biomarkers Used in the Screening, Diagnosis, Management, and Surveillance of Endocrine Cancers

Colin M. Court and Avital Harari

I. INTRODUCTION

Serum biomarkers are measurable substances present in the blood that provide clinically useful information. They are particularly important in endocrine cancers due to the secretion of peptide hormones and biogenic amines by these tumors.

Existing biomarkers for endocrine cancers differ from other commonly used tumor biomarkers, such as carcinoembryonic antigen, in that they are often a natural secretory product of the cell of origin. Because of their constitutive nature, the physiologic level of many of these biomarkers varies considerably in the general population, necessitating complex sampling and analysis parameters in order to have clinical utility.

Although established biomarkers for endocrine tumors are mostly hormone peptides, emerging biomarkers are increasingly diverse in origin; examples include circulating tumor cells (CTCs), serum cell–free DNA, (or microRNAs), and circulating exosomes. Increasingly, these emerging biomarkers are demonstrating clinical utility in answering important questions that existing biomarkers cannot.

In this chapter, the current utilization of biomarkers in endocrine cancers will be reviewed. Additionally, emerging biomarkers of potential clinical importance will be highlighted, especially when they may fill a hole in the current clinical framework.

II. GASTROENTEROHEPATIC NEUROENDOCRINE TUMORS

A. Overview

Although once considered to be a rare entity, neuroendocrine tumors (NETs) now comprise **2% of all malignancies**. This rise in prevalence has primarily been attributed to better imaging and biomarker studies for the diagnosis of NETs. Symptoms tend to be nonspecific at first in most cases, resulting in 60% of patients having metastases at the time of diagnosis. Broadly speaking, NETs can be divided into gastrointestinal NETs (**GI NETs, formerly known as carcinoid tumors**) and pancreatic NETs (pNETs), which include both functional and nonfunctional (NF-NETs) types. Additional information about NET epidemiology and treatment, including their relationship to genetic syndromes such as MEN I and II, is covered in **Chapter 79**.

Biomarkers are crucial to the initial diagnosis of NET tumors and are also used for prognosis and management decisions as detailed below. Additionally, for most NET tumors, surveillance for recurrent or persistent disease in malignant NETs generally follows the National Comprehensive Cancer Network (NCCN) guidelines. Biomarker levels are usually checked at 3 and 6 months and then every 6 to 12 months for up to 3 years. After this, they are checked only if they are clinically indicated.

B. GI NETs (Carcinoid tumors)

Carcinoid tumors are a diverse group of NETs that share similar pathologic characteristics and can be found throughout the GI tract. They are generally well-differentiated tumors and characteristically stain strongly for neuroendocrine markers. Eighty percent of carcinoid tumors are found in the GI tract, most commonly in the appendix. Most GI NETs are essentially nonfunctional due to the liver's ability to metabolize serotonin and other secretory products before they can reach the systemic circulation. Thus, liver or retroperitoneal metastases are generally required for the development of carcinoid syndrome symptoms. This manifests typically with periodic flushing, p. 1018p. 1019diarrhea, abdominal pain, and dyspepsia. Serotonin is rapidly metabolized by the liver. Thus, for GI NETs, first-pass metabolism by the liver is sufficient to clear all of the serotonin produced. Liver metastases secrete serotonin into the posthepatic

circulation, thus resulting in systemic circulation of the serotonin and the symptoms of carcinoid syndrome.

Serotonin: Because of the hypersecretion of serotonin found in almost all GI NETs, serotonin and its metabolites are the most well-studied biomarker in GI NETs. Serum serotonin levels vary widely between individuals and throughout the day, limiting its clinical utility. As a result, 24-hour urine ELISA of the serotonin metabolite 5-hydroxyindole acetic acid (**5-HIAA**) has been found to have the best sensitivity (70%) and specificity (90%) and is the **most frequently used assay in the diagnosis of Carcinoid Syndrome**.

C. Functional pNETs

There are over 17 different neuroendocrine cells in the GI tract and pancreas alone, but only a small number are definitively associated with a known tumor type. Functional NETs are classified on the basis of the secretion of endocrine biomarkers that manifest clinically as a set of pathognomonic symptoms. These clinically relevant hormones are the biomarker of choice for the diagnosis, management, and surveillance of functional tumors. The diagnosis of the most common functional NET tumors is outlined in Table 83-1. It is important to note, however, that many functional pNETs secrete more than one peptide. For example, 70% of gastrinomas secrete pancreatic polypeptide, and up to 30% secrete an additional functional hormone.

D. Nonfunctioning pNETs

Nonfunctional tumors (NF-NETs), which have no clinical symptoms related to hormone release, make up to 40% to 60% of all pNETs. Despite the absence of clinical symptoms, these tumors are by no means biochemically inactive. In fact, at least one general biomarker is elevated in 60% to 100% of all NET patients. These tumors are particularly **important in Multiple Endocrine Neoplasia Type I**, where many of the pancreatic neuroendocrine tumors that grow can be nonfunctional and multiple in number.

1. **Chromogranin A (CgA).** CgA is the best studied and most useful of the general NET biomarkers, and is the most commonly used clinically. The function of CgA is not fully understood; however, it is known to be involved in the biogenesis of p. 1019p. 1020secretory vesicles and dense core

secretory granules. **CgA is elevated in most endocrine cancers**. One study found elevated CgA in 100% of gastrinomas, 89% of pheochromocytomas, 80% of carcinoids, 69% of NF-NETs, and 50% of medullary thyroid cancers (MTCs).

TABLE 83-1 Functional Neuroendocrine Tumor Tumors

Tumor	Clinical features	Biomarkers
Gastrinoma	Peptic ulcer disease, diarrhea, epigastric pain	Fasting gastrin level, SST, PP
Insulinoma	Hypoglycemia	CgB, 72-hr fast and measurement of insulin, proinsulin, C-peptide, β-hydroxybutyrate
Glucagonoma	Weight loss, diabetes, diarrhea, NME	Fasting glucagon and glicentin level
VIPoma	WDHA: watery diarrhea, hypokalemia, achlorhydria	VIP level
Somatostatinoma	Diabetes, steatorrhea, cholelithiasis, weight loss	SLI

CgB, chromogranin B; NME, necrotizing migratory erythema; PP, pancreatic polypeptide; SLI, somatostatin-like immunoreactivity assay; SST, secretin stimulation test; VIP, vasoactive intestinal peptide.

The sensitivity of CgA in the diagnosis of NF-NETs ranges between 67% and 93%, mostly dependent upon which immunoassay is used. Its specificity ranges between 71.3% and 85.3%, but is as high as 100% in metastatic disease. In addition, the serum concentration correlates with tumor burden and biologic activity, which, in turn, correlates with prognosis in NF-NETs. CgA differentiates benign and malignant NF-NETs, with a sensitivity of 57% to 63.3% and specificity between 55.6% and 71.4%. Unfortunately, a number of non-NET conditions elevate CgA, limiting its clinical utility. These include proton pump inhibitor therapy, atrophic gastritis, liver disease, inflammatory bowel disease, chronic kidney disease, and sympathetic nervous system stimulation.

2. **Chromogranin B (CgB).** CgB has also been studied as a potential general biomarker. Like CgA, CgB is thought to be

involved in the production of hormones. CgB is involved in the maturation and release of secretory granules containing both catecholamines and hormones. CgB has been evaluated only in a few studies to date, primarily in rectal NETs, which often have normal CgA levels but elevated CgB levels. The CgB assay does have the distinct advantage of not being elevated by the benign conditions that affect the CgA assay.

3. **Pancreatic Polypeptide (PP).** PP is part of a family of secretory proteins that includes peptide YY (PYY) and neuropeptide Y (NPY). Normally secreted by cells of the pancreas, PP is elevated in the serum of 50% to 80% of all patients with pancreatic NF-NETs, and greater than 30% of all NETs. Although the physiologic functions of PYY and NPY are well known, no functional role for PP has been elucidated. Patients with PPomas do not demonstrate symptoms; however, IV injection of PP causes secretory diarrhea.

   PP levels rise rapidly following a test meal, so serum levels should be measured following a fast. Although elevated PP has poor specificity, it has found clinical use as an adjunct marker. The combination of CgA and PP has the highest sensitivity and specificity of any biomarker assay in the diagnosis of GEP-NETs, and is the most commonly used in clinical practice. The sensitivity of elevation of both CgA and PP in the diagnosis of all GEP-NETs is 96%, 95% for NF-pNETs, and 94% for all pNETs.

4. **Other potential biomarkers.** Numerous other emerging biomarkers have been studied in NETs and are summarized in Table 83-2. Although some of these have shown promise as potential biomarkers, most have not. None of them have been recommended for clinical use in the diagnosis, prognosis, or follow-up of NETs.

III. THYROID CANCER

A. Overview

Thyroid cancer is the most common endocrine malignancy. It is also the cancer with the highest increase in prevalence, with a 240% increase between 1972 and 2002. Currently, thyroglobulin (Tg) for differentiated thyroid cancer (DTC) and calcitonin for MTC are the only biomarkers in widespread use. Both are well established, and are used extensively for the clinical management of thyroid cancer.

Additionally, emerging biomarkers are addressing other clinical issues not addressed by currently available biomarkers.

B. Differentiated thyroid cancers

Because of the high rate of recurrence and metastases, regular follow-up and surveillance is required for all DTC patients after surgery, as outlined in **Chapters 39 and 81**. Numerous methods to detect recurrence have been used in the past, including whole-body scintigraphy, ultrasound, clinical exam, and biomarkers.

1. **Tg.** Tg is a 670-kDa glycoprotein made up of two identical subunits. Found exclusively in the follicles of the thyroid gland, its role is to act as a platform upon which thyroid hormone is built. Tg levels correlate to the amount of thyroid tissue present in the body and thus have utility only postoperatively. Tg levels p. 1020p. 1021 are currently used to monitor postthyroidectomy DTC patients. It is also used to diagnose the absence of the thyroid gland and congenital hypothyroidism.

TABLE 83-2 General and Emerging NET Biomarkers

Biomarker	Tumor type	Use	Available evidence[a]	Comments
CgA	All NETs	Dx, Prog, Malig, Re	+++	
CgB	All NETs	Dx	+ (++ rectal carcinoids)	
5-HIAA	GI NETs	Dx, Prog, Malig, Re	+++	
PP	All NETs	Dx, Prog, Re	++	"PPoma"
NSE	All NETs	Dx, Re	+ (++ CgA negative)	
hCG	All NETs	Dx, Malig	+	Elevated in malignant NETs
Pancreastatin	All NETs	Dx	+	Elevated in metastatic NETs
NKA	Midgut NETs	Dx, Prog	++	
Ghrelin	NF-NETs	Dx	++	"Ghrelinoma"
GLP1	NF-NETs	Dx	++	"GLP1oma"

[a]Available evidence is rated on a scale from 1 (+) to 3 (+++), with 1 representing biomarkers

with only small studies available and 3 representing a biomarker tested in clinical trials and that is currently widely used in practice.

5-HIAA, 5-hydroxyindole acetic acid; CgA, chromogranin A; CgB, chromogranin B; Dx, diagnosis; GLP1, glucagon-like peptide-1; hCG, human chorionic gonadotropin; Malig, malignancy; NF-NET, nonfunctional NET; NKA, neurokinin A; NSE, neuron-specific enolase; PP, pancreatic polypeptide; Prog, prognosis; Re, recurrence.

Currently, the gold standard for surveillance of DTC is Tg level combined with neck ultrasound. However, Tg levels are affected by thyroxine and TSH suppression therapy; thus, a stimulated Tg level is required in most patients. When combined with neck ultrasound, a recombinant human thyrotropin–stimulated Tg level has a sensitivity of 96.3% and a negative predictive value (NPV) of 99.5% for recurrence in patients without TgAbs.

2. **Tg antibodies (TgAbs).** Although Tg is the gold standard for most patients, 25% of DTC patients have antibodies to Tg. TgAbs interfere with the Tg assay, resulting in artificially low Tg levels. For the 25% of patients with TgAbs, Tg levels will generally not become detectable until late in the disease course, making it a poor test for recurrence. Some studies have shown that TgAbs titers may actually have some utility as a biomarker, as they tend to rise during recurrence. However, this is controversial and has been questioned in other studies. In one study, 22.6% of postresection patients had positive TgAbs, and 49% of them were positive for recurrence. Further studies of the utility of quantitative TgAbs titers are needed.
3. **TSH mRNA.** One emerging biomarker for patients with DTC is thyroid stimulation hormone receptor (TSHR) mRNA. For patients with an indeterminate fine-needle aspiration (FNA), a detectable serum TSHR mRNA increases the risk of thyroid cancer in that nodule to 90% to 96% from 30%, thus potentially altering surgical management. TSHR mRNA has also been studied in the surveillance of DTC. In one long-term follow-up, undetectable TSHR mRNA was predictive of no disease recurrence in 96% of patients at 24 months. Additionally, in the cohort of patients with TgAbs, detectable TSHR mRNA had a sensitivity of 67%, a specificity of 100%, and a positive predictive value (PPV) of 100% for recurrence.

p. 1021p. 1022

C. MTC

1. **Calcitonin.** Calcitonin is secreted almost exclusively from C cells, making it the most specific test for MTC. It is typically used both for initial diagnosis and for posttreatment surveillance. Its use in diagnosis has been controversial, although some studies have shown that its sensitivity is equivalent or better than that of FNA in the diagnosis of MTC. Calcitonin levels also correlate well with tumor burden. Lymph node metastases are typically found when initial calcitonin levels are between 10 and 40 pg/mL, whereas levels >400 pg/mL typically indicate distant metastases. Postoperatively, calcitonin is used for recurrence surveillance.

IV. PARATHYROID CARCINOMA

A. Overview

Parathyroid carcinoma is a very rare cancer and usually presents as a severe form of primary hyperparathyroidism. The diagnosis of parathyroid carcinoma is difficult to establish cytologically and requires pathologic evidence of local invasion and/or distant metastases at the time of diagnosis. A PET/CT scan is used in suspected cases to diagnose distant metastases. However, without evidence of distant metastases, the diagnosis and definitive treatment typically occurs during surgery. It is, therefore, important for clinicians to have a high index of suspicion for these tumors prior to surgery because the initial surgery is the best chance for cure. In almost all cases of parathyroid cancer, biomarkers are crucial for diagnosis and management.

Nonfunctional parathyroid carcinomas are rare, accounting for less than 10% of tumors. Unfortunately, no biomarker exists to suggest the possibility of malignancy in these tumors. Therefore, these nonfunctional tumors usually present in advanced stages.

B. Biomarkers

1. **Calcium and PTH.** Parathyroid carcinomas generally have higher levels of calcium than adenomas do, and account for a disproportionate number of parathyroid crises, with serum calcium levels often greater than 14 mg/dL. Because the only chance for cure of these patients is a complete surgical excision, it is important for physicians to have a high index of suspicion for this

diagnosis if a patient presents with calcium levels above 14 and a palpable mass. The serum PTH level is also significantly elevated, commonly 3 to 10 times the upper limit of normal. If a patient has these biochemistries, a metastatic workup, including imaging of the chest and abdomen, should be initiated prior to surgical treatment. Postoperative surveillance for recurrence in parathyroid cancer patients consists of biochemical testing for calcium and PTH levels as well as imaging at regular intervals. In nonfunctional parathyroid carcinoma, patients have normal serum calcium and PTH levels, and thus, these labs cannot be used for surveillance or diagnosis.

2. **Other biomarkers.** Several other biomarkers have been examined in parathyroid carcinoma. **Alkaline phosphatase** is abnormally **high in most parathyroid carcinomas**, whereas it is generally **normal in hyperparathyroidism**. The α and β subunits of hCG are often elevated in parathyroid carcinoma as well. hCG has been found to be elevated in numerous nontrophoblastic cancers, including bladder, renal, prostate, carcinoid, lung, breast, gynecologic and oral cancers as well as lymphoma. The mechanism is not known, but a hyperglycosylated form of hCG is most commonly associated with malignancy.

V. ADRENAL CANCERS

A. Overview

With the increased use of abdominal imaging in the recent past, adrenal neoplasms are becoming more common, occurring in up to 6% of the ambulatory population. In contrast, malignant adrenal tumors are extremely rare (1 to 2 cases per million). However, despite its rarity, the consequences of adrenal cancer are dire because patients typically die within months of diagnosis if diagnosed too late.

Malignant adrenal tumors, both adrenocortical carcinomas (ACC) and pheochromocytomas, secrete a variety of serum markers that are useful for the diagnosis and management of these cancers. Unfortunately, to date, there is no way to accurately p. 1022p. 1023predict malignancy in an adrenal nodule prior to resection unless there are definitive signs of metastases or local invasion. Not surprisingly, the differentiation of benign from malignant adrenal

tumors that have not yet metastasized represents the largest area of continued biomarker development. This is additionally due to the fact that preoperative biopsy of these tumors has not proven helpful for distinguishing malignancy and, in fact, increases the probability of tumor seeding and subsequent recurrence.

B. Adrenocortical carcinoma

Prior to resection, several criteria are used to determine the *likelihood* of malignancy in solitary nonfunctional adrenal tumors such as tumor size (>4 to 6 cm), hypersecretion of virilizing and/or steroid hormones, and heterogeneous patterns/irregular surfaces on imaging. Currently, there is no useful biomarker to predict malignancy in these tumors. Therefore, the diagnosis and treatment plan is based entirely on imaging characteristics such as size, metastases, recurrence, and local invasion.

Current imaging standards have good sensitivity but poor specificity. According to one recent meta-analysis, PET is the best modality for differentiating benign from malignant disease with a sensitivity of 97% and a specificity of 91%. However, not all PET-positive tumors are malignant.

1. Biomarkers

a. Functional markers. Approximately 60% to 70% of ACCs are functional, secreting a variety of hormones and hormone precursors. Of the functional cancers, 45% produce cortisol, 25% cosecrete cortisol and androgens, <10% secrete androgens alone, <10% secrete feminizing hormones, and <10% secrete aldosterone. Studies have shown that many ACCs overproduce hormones and hormone precursors but do not manifest symptoms because of inefficient hormone production. Thus, ACC is marked by early metastases and poor response to treatment, with 80% of patients having advanced disease at the time of diagnosis. If adrenal cancers are functional, their hormone secretion levels are used for surveillance of recurrence or treatment response.

b. Emerging biomarkers

i. Urinary steroid profiling. In patients with hormonally inactive ACC, high concentrations of steroid precursors like androstenedione or 17-hydroxyprogesterone are often seen, demonstrating the adrenocortical nature of the tumor. Studies have demonstrated that using urinary steroid

profiling with mass spectrometry, combined with subsequent machine learning analysis, has a sensitivity and specificity of 90% for detecting malignant adrenal tumors, which compares favorably with imaging for diagnosing ACC.

ii. **Inhibin-proαC.** Another potential biomarker in ACC is inhibin-proαC. The overall diagnostic sensitivity is 59%, and the NPV is 68%, in differentiating benign from malignant disease. The serum levels reflect tumor burden, and fall rapidly after surgery or mitotane therapy. Additionally, the combination of inhibin-proαC and DHEA-S has a PPV of 92% in the confirmation of malignancy.

iii. **CTCs.** Recently, circulating cell technology has been investigated as potentially distinguishing benign from malignant disease. In a pilot study of 24 patients, CTC detection was found in all adrenocortical cancers but in none of the adenomas.

C. Pheochromocytoma (see Chapter 18)

Pheochromocytomas are rare catecholamine-secreting tumors arising from chromaffin cells of the adrenal medulla. **Extraadrenal pheochromocytomas, referred to as paragangliomas**, occur in sympathetic ganglia in the organ of Zuckerkandl, the neck, the mediastinum, the abdomen, and even the pelvis. The diagnosis of these rare tumors is through a combination of biomarkers and imaging only, as biopsies are never performed if a pheochromocytoma is suspected because of the risk of massive catecholamine release and hypertensive crisis. Clinical features and management of pheochromocytomas and paragangliomas are covered extensively in **Chapter 18**.

It is estimated that 10% of pheochromocytomas and 15% to 35% of paragangliomas are malignant; however, similar to ACCs, determining malignancy is an p. 1023p. 1024area of uncertainty in pheochromocytoma because pathology alone is not sufficient. Once again, preoperative diagnosis relies only on the presence of metastasis or local invasion. Malignancy confers a poor prognosis, with 5-year survival as low as 20% to 50%. Following surgery, recurrence is rare, reportedly as low as 4.6% to 11.6%. Surveillance for recurrence is important for all pheochromocytomas.

1. **Metanephrines and catecholamines.** The initial screening

tests for pheochromocytoma are plasma-free metanephrines and/or urinary fractionated metanephrines, catecholamines, and vanillylmandelic acid. These tests measure metabolites of epinephrine and norepinephrine. The sensitivity and specificity of a 24-hour urine test in the diagnosis of pheochromocytoma is greater than 90% and is reported to be as high as 98%. Typically, urine or plasma metanephrines are used as the most important biomarker for recurrence, usually checked a few weeks after initial surgery and at least annually thereafter. Although current guidelines call for frequent imaging to rule out recurrence, recent research has shown that this may be unnecessary, recommending imaging only for patients who demonstrate abnormal biomarker levels.

2. **CgA.** The combination of plasma-free metanephrines and CgA has a reported diagnostic sensitivity of almost 100% for all pheochromocytomas. CgA also has utility as an indicator of malignancy and as a marker of response to treatment.
3. **Dopamine.** Although almost all pheochromocytomas secrete norepinephrine and epinephrine, there are case reports of tumors that secrete only dopamine. Therefore, dopamine is a useful adjuvant marker in cases where the diagnosis is uncertain. Additionally, dopamine has utility as a potential marker of malignant potential in pheochromocytoma.

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84 Autoimmune Endocrine Syndromes

George S. Eisenbarth and Marian Rewers

I. GENERAL PRINCIPLES

Immunoendocrinopathy syndromes include (in approximate order of prevalence) autoimmune polyendocrine syndrome type II (APS2), APS type I (APS1), immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX), antiinsulin receptor antibody syndrome, plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M-protein gammopathy, and skin changes (POEMS), and thymic tumors with associated endocrinopathy. APS1, APS2, and IPEX have major known genetic determinants and disease associations that allow physicians to suspect and screen for additional unrecognized illnesses in the patients or their family members. These syndromes are characterized by the presence of autoantibodies to multiple organs that usually precede clinical disease by months or years. Table 84-1 is a simple handout that can be given to APS2 patients with instructions to distribute it to their relatives.

A. APS2. Also known as Schmidt syndrome, APS2 is characterized by the classic triad of Addison disease, autoimmune thyroid disease (primary hypothyroidism or less frequently Graves disease), and type 1A (autoimmune) diabetes. Other illnesses seen in these patients include primary hypogonadism, pernicious anemia, alopecia, serositis, myasthenia gravis, celiac disease, and stiff-person syndrome. The initial clinical manifestation usually occurs in young adulthood, and there is a moderate female preponderance. Inheritance is polygenic, and there is a strong human leukocyte antigen (HLA) DR and DQ allele association, specifically DR4, DQB1*0302 (with DR4 most often DRB1*0404 for familial Addison disease) and DR3, DQB1*0201. HLA-DR3-associated illnesses such as celiac disease, dermatitis herpetiformis, Sjögren syndrome, selective IgA deficiency, juvenile dermatomyositis, and chronic active hepatitis can be a part of APS2 and increase the index of suspicion for autoimmune thyroid

disease and type 1A diabetes. Some authors subdivide APS2 into the following: **type II**, Addison with type 1A diabetes or autoimmune thyroiditis; **type III**, thyroid plus other autoimmune disease (not Addison or diabetes); and **type IV**, two or more other organ-specific autoimmune diseases.

B. APS1. Also known as APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy), this syndrome is characterized by the classic triad of hypoparathyroidism (80% of patients), Addison disease (70% of patients), and mucocutaneous candidiasis (90% of patients). Other autoimmune illnesses seen in these patients include primary hypothyroidism, type 1A diabetes, primary hypogonadism, chronic active hepatitis, pernicious anemia, malabsorption syndromes, keratopathy, vitiligo, and alopecia. In contrast to APS2, the onset is usually in infancy and early childhood. Inheritance is autosomal recessive with a single gene defect, mutation of the *AIRE* (autoimmune regulator) gene on chromosome 21q22.3. There is evidence that the *AIRE* gene controls negative selection of T lymphocytes within the thymus, and in particular, expression of a series of "peripheral" antigens such as insulin, which are organ-specific molecules of which very small amounts are expressed in the thymus. Thus, a leading hypothesis is that mutations of the *AIRE* gene contribute to many autoimmune disorders by allowing self-reactive T cells to more often escape from the thymus and cause disease. Many patients have autoantibodies that precede clinical symptoms. Importantly, nearly 100% of these patients have autoantibodies that react with interferon-α. Diagnosis is usually confirmed by sequencing of the *AIRE* p. 1025p. 1026gene, with several populations having an increased frequency of specific mutations, including Iranian, Jewish, and Finnish populations. Chronic candidiasis may develop into oral squamous cell carcinoma, and evidence of ectodermal changes includes hypoplastic dental enamel and pitted dystrophic nails.

TABLE 84-1 Associated Illnesses Found in Relatives

Illness	Signs and symptoms
Hypothyroidism	Fatigue, weight gain, feeling cold, constipation, dry skin, and hair loss. In children, also short stature and/or delayed puberty.

Hyperthyroidism	Weight loss, feeling warm and anxious, increased heart rate and blood pressure, hand tremor, and puffy or bulging eyes (exophthalmos)
Pernicious anemia	Fatigue and weakness, pallor, sensation of pins and needles, and fine-movement problems
Adrenal insufficiency	Skin darkening, weight loss, dizziness, nausea, weakness, craving salty foods, and low blood pressure
Testicular failure	Decreased libido and infertility
Ovarian failure	Decreased libido, hot flashes, decreased/absent menstrual periods, and infertility
Diabetes mellitus	Increased urination, increased thirst, and weight loss

C. IPEX. This syndrome often manifests in neonates with overwhelming autoimmunity, frequently leading to death associated with severe enteropathy. However, late-onset cases have also been reported in school children and adolescents. Mutations of the *FOXP3* gene inherited in an X-linked manner are causative. The *FOXP3* gene encodes a transcription factor that is essential for the development of a major subset of regulatory T lymphocytes. In the absence of these regulatory T lymphocytes, multiple autoimmune disorders develop, including neonatal diabetes with β-cell destruction and the presence of islet autoantibodies, for example to insulin or glutamic acid decarboxylase (GAD). Bone marrow transplantation can replace missing regulatory T lymphocytes and has been successfully used for this fatal disorder.

D. Antiinsulin receptor antibody syndrome. Also known as type B insulin resistance, this syndrome is characterized by marked insulin resistance, hyperglycemia, and acanthosis nigricans. Approximately one third of patients also have other autoimmune diseases, such as lupus erythematosus. Paradoxically, the antiinsulin receptor antibodies can have an agonist effect and lead to episodes of hypoglycemia.

E. POEMS syndrome. This syndrome is characterized by severe sensorimotor polyneuropathy, organomegaly (liver, spleen, and lymph nodes), endocrinopathy, monoclonal antibody production with bony lesions secondary to a plasma cell dyscrasia, and skin changes (hyperpigmentation, hypertrichosis, sclerosis, and Raynaud phenomenon). The endocrinopathies include hyperestrogenism leading to impotence and gynecomastia in men (79% of patients), amenorrhea (70% to 100% of patients), primary hypothyroidism (16% of patients),

and diabetes mellitus (16% of patients, and 32% with impaired glucose tolerance). Disease onset is in adulthood (fourth or fifth decade). It has a male predominance and is more common in the Japanese population. There is evidence of increased VEGF levels associated with the syndrome as well as response to therapy of the plasmacytoma and reports of response to auto–peripheral blood stem cell transplantation following chemotherapy.

F. Thymic tumors. Thymomas are associated with autoimmune disease in approximately 40% of patients. The most common autoimmune diseases include **myasthenia** gravis, red blood cell aplasia, and hypogammaglobulinemia. Occasionally, type 1A diabetes, Addison disease, autoimmune thyroid disease, and stiff-man syndrome have been reported.

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II. EVALUATION

A. As a general rule, a patient with one of the APS2 components is 10- to 100-fold more likely to develop an additional autoimmune disease than the general population. Approximately one in six relatives of patients with APS2 has an unsuspected illness, most commonly hypothyroidism. Therefore, a screening thyroid-stimulating hormone is recommended every 5 years for otherwise asymptomatic patients and their family members. Assays for 21-hydroxylase autoantibodies are 90% sensitive and have high positive predictive value for **Addison disease**.

B. Although autoantibodies can be disease-specific (e.g., antithyroglobulin antibody), they can also be involved in multiple diseases. Both **stiff-person syndrome** (a rare neurologic disorder involving painful muscle contractions of the neck, trunk, and limbs) and type 1A diabetes have in common the autoantibody to GAD. Approximately 30% of patients with stiff-person syndrome will develop type 1A diabetes, and they are also at increased risk for other APS2 diseases.

C. Patients with any APS2 disease should undergo regular focused history and physical examinations for potential associated diseases. In addition, evaluation for organ-specific autoantibodies or even HLA typing of families can be useful in the detection of individuals at highest risk. For example, one could predict the risk of developing

type 1A diabetes among first-degree relatives of diabetics using a combination of autoantibodies to insulin, GAD, and insulinoma-associated antigen (IA-2A). For relatives, who are positive for two or more autoantibodies, the 3- and 5-year risks of developing diabetes were 39% and 68%, respectively. Autoantibodies to zinc transporter 8 (ZnT8) can identify an additional 3% of future type 1A diabetes patients who are negative for the three major islet autoantibodies. Islet cell autoantibodies (ICAs) reflect predominantly autoantibodies to GAD, IA-2, and ZnT8 (Fig. 84-1).

D. Patients with type 1A diabetes or who have first-degree relatives with type 1A diabetes are also at higher risk for developing celiac disease, which often has subtle or unrecognized symptoms for a number of years. Tissue transglutaminase autoantibodies (IgA class) are highly sensitive and specific serologic markers of celiac disease and have replaced previously used tests for endomysial autoantibodies (Fig. 84-1). A positive transglutaminase autoantibody among at-risk asymptomatic children has a positive predictive value of 70% to 80% for intestinal villous atrophy if the level of transglutaminase antibodies is 10 times the 99th percentile of normal controls. Early initiation of a gluten-free diet in asymptomatic patients may reduce the risk of subsequently long-term complications, such as osteoporosis, miscarriage, or lymphoma.

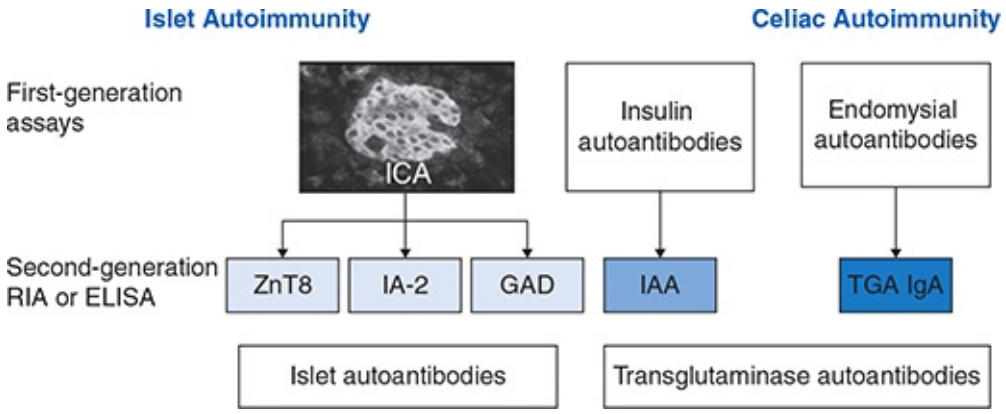

Figure 84-1. Serologic (autoantibody) tests used in screening for and clinical confirmation of diagnosis of type 1A diabetes and celiac disease. GAD, glutamic acid decarboxylase; IA-2, insulinoma-associated antigen; IAA, insulin autoantibodies; ICA, islet-cell autoantibody; RIA, radioimmunoassay; TGA IgA, transglutaminase autoantibodies; ZnT8, zinc transporter 8.

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E. The most common first presentation in APECED is persistent mucocutaneous candidiasis, with endocrine involvement developing in the subsequent several months to several years. The syndrome almost universally presents before 20 years of age. This is in contrast to candidiasis presenting in adults, which is frequently associated with thymoma or immunodeficiency. Siblings are at high risk for the component illnesses, and periodic evaluation for hypocalcemia, cortisol deficiency, and hepatic enzyme abnormalities is indicated. With identification of mutations of the AIRE gene, sequencing and identification of siblings with the mutation are now possible.

F. Antiinsulin receptor antibodies should be suspected in a patient with marked hyperinsulinemia (before insulin therapy), resistance to IV insulin on an IV tolerance test, and (rarely) fasting hypoglycemia. Specialized laboratories can directly quantitate the antireceptor antibodies to aid in the differential diagnosis.

G. Radiographic demonstration of a localized sclerotic bone lesion in a patient with other associated symptoms is strongly suggestive of POEMS syndrome.

H. Patients with aplastic anemia or myasthenia gravis with concurrent autoimmune endocrine disease should have a CT of the thorax to search for a thymoma. Transient remission of the syndrome often follows thymectomy.

III. MANAGEMENT

A. In patients with untreated Addison disease and hypothyroidism, steroids should be given prior to thyroxine (T_4) replacement to avoid precipitating an adrenal crisis. Thyroxine replacement increases the metabolism of the residual cortisol remaining in adrenal-insufficient patients, thereby worsening the insufficiency. Similarly, in patients with untreated Addison disease and diabetes, steroids should be given prior to insulin replacement to avoid severe hypoglycemia.

B. In addition to appropriate hormonal replacement therapy, patients with APECED-associated hepatitis should also be placed on immunosuppressive therapy. Given the adverse growth effects in children with chronic glucocorticoids, azathioprine may be preferred, but careful monitoring and specialized care is essential because cirrhosis is often preventable with appropriate therapy.

C. The clinical course of patients with antiinsulin receptor antibodies has been extremely varied, with some patients remitting, others developing

severe hypoglycemia, and others having no benefit from massive doses of IV insulin. No immunologic therapy is of proven efficacy.

D. Therapy of POEMS syndrome is initially directed at the plasmacytoma, which is quite responsive to radiotherapy or radiotherapy plus surgery. Avoid neurotoxic agents such as vincristine.

E. Surgical resection of thymic tumors can result in at least temporary remission of life-threatening-associated autoimmune diseases.

IV. FRONTIERS

Currently available autoantibody assays are sufficiently specific and sensitive to diagnose most autoimmune endocrine syndromes at an early stage. These tests are relatively inexpensive and should be applied to all patients with an autoimmune endocrinopathy and their relatives. Close follow-up of autoantibody positive asymptomatic persons is recommended because it has been shown to reduce morbidity and mortality with a diagnosis of disorders such as type 1A diabetes or Addison disease. Although hormone replacement remains the primary therapy, advances in immunogenetics show that immunomodulation can prevent progression to clinical disease. **Relatives of patients with type 1A diabetes can be screened for islet autoantibodies through Trialnet** (1-800-HALT-DM1) for potential entry into prevention studies. Similar to celiac disease, type 1A diabetes, autoimmune thyroid disease, and perhaps other autoimmune endocrinopathies are likely to have environmental triggers. The search for these triggers is the subject of intensive research and, if successful, may lead to primary prevention.

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85 Management of Some Hormone-Dependent Cancers with Analogs of Hypothalamic Hormones

Norman L. Block, Ferenc G. Rick, and Andrew V. Schally

I. PROSTATE CANCER

A. General principles

1. Carcinoma of the prostate is the most common noncutaneous malignancy and the second leading cause of cancer-related deaths among adult American men. In 2017, an estimated 26730 men in the United States died from prostate cancer and about 161000 new cases were discovered. Adenocarcinoma of the prostate is rare before 40 years of age; the incidence increases with advancing age. Men who have first-degree relatives with prostate cancer and African American men have a higher lifetime risk for developing the disease. Carcinoma of the prostate is androgen-dependent in approximately 70% of cases. Twenty percent to 30% of patients with prostate cancer already have metastatic disease when they are first diagnosed. A recent publication points out a significant association between diagnoses of thyroid and prostate cancers in the United States. (This is an epidemiologic study—the cause of the relationship is not known.)

B. Evaluation

1. **Screening tests** for prostate cancer offer the best chance for early diagnosis of organ-confined, potentially curable disease. The American Cancer Society currently recommends that both the prostate-specific antigen (PSA) blood test and digital rectal examination (DRE) be offered annually, beginning at 50 years of age, to men with a life expectancy of at least 10 years. In addition, the American Urologic Association currently recommends that

African American men and all men with a family history of prostate cancer have the screening tests initiated at 40 years of age. A recent recommendation by the United States Preventive Services Task Force to minimize the utilization of routine PSA screening has led to a 28% reduction in the number of new patients diagnosed as compared to prior years. The aim of this recommendation was to reduce the harm and side effects associated with prostate cancer detection and treatment. Although the recommendation minimizes such harm, it also minimizes the benefits.

2. **DRE.** DRE is routinely used for diagnosis and for evaluating the local extent of prostate cancer. The positive predictive value of DRE for prostate cancer is approximately 50% and varies relatively little with age. The predictive value of the DRE is enhanced by combination with the results of the PSA test.
3. **PSA.** The PSA and DRE are complementary in the detection of prostate cancer. It has been shown that PSA and DRE combined increase the rate of detection by 81% over DRE alone and 22% over PSA alone. **PSA levels >4.0 ng/mL are often considered suspicious of prostate cancer.** PSA is a glycoprotein produced by prostate cells and is specific to the prostate, but not to prostate cancer. Thus, PSA is not detected in the serum of 30% of patients with prostate cancer (**false negative**) and is found in increased concentrations in the serum of 20% of men who do not have prostate cancer (**false positive**). PSA levels can also be elevated in benign prostatic hyperplasia and for several weeks after acute prostatitis, transrectal needle biopsy, prostatic manipulation, prostate surgery, acute urine retention, catheters, bicycle riding, etc. PSA is more sensitive than the previously p. 1030p. 1031used prostatic acid phosphatase (PAP) for the detection of prostatic cancer and is also more useful in monitoring responses and recurrence after therapy.
4. **Transrectal ultrasound (TRUS) examination of the prostate.** TRUS is useful for detecting small lesions and for guiding biopsy procedures, but it is not recommended for screening. TRUS rarely detects cancer in the presence of both a normal DRE and PSA and should be reserved for further evaluation in patients who have abnormal results of DRE and/or

PSA-level testing.

5. **CT and/or MRI.** CT and MRI of the pelvis and/or the abdomen have been used extensively for staging prostate cancer; however, they cannot easily detect microscopic extension of cancer and are useful for evaluation only in patients with signs of advanced cancer.
6. **Radioisotope bone scan.** The bone scan is the most sensitive method for detection of osseous metastases. However, it is relatively nonspecific and, if equivocal, should be used in conjunction with roentgenography, such as thin-slice CT scanning with bone windows. A bone window is a CT algorithm that selects the gray scale of the scan, as visualized, to enhance anatomic structures with the density of bone. The bone scan may show an increase in uptake of radionuclide during a positive therapeutic response. This is presumably due to increased uptake by healing areas of bone. In this situation, disease worsening may be excluded by attention to clinical responses such as PSA levels, weight and/or appetite gain, and pain status.
7. **Pelvic lymphadenectomy.** Pelvic lymph node metastases are often asymptomatic and are uncommonly visualized even with the most sophisticated radiologic imaging modalities. Guidelines have been developed for assessing the probabilities of a patient having nodal metastases on the basis of a combination of clinical tumor stage, PSA, and biopsy Gleason grade. Such information allows a further staging of pelvic lymphadenectomy to be selectively performed in those patients in whom this procedure is likely to influence management decisions.

C. Management of prostate cancer

The treatment of prostate cancer is based on the patient's clinical stage of disease. Clinical stage is usually assigned to the patient with prostate cancer in accordance with the TNM classification system (primary tumor, regional nodes, and metastasis).

1. **Clinically localized prostate cancer.** Optimal therapy for patients with clinically localized prostate cancer still remains to be determined. The options for management of patients with clinically localized prostate cancer (stage T1 to T2N0M0) include watchful waiting, radical prostatectomy, external-beam irradiation, brachytherapy, and hormonal therapy. Watchful waiting can be offered to patients with a life expectancy of <10 years presenting

with small and well-differentiated cancers. Radical prostatectomy, external-beam irradiation, and brachytherapy are recommended for those patients who have a life expectancy of >10 years. These modalities of treatment may be associated with urinary and sexual dysfunction.

a. **Clinical course.** Recurrence of prostate cancer after local therapy is becoming a significant medical problem. Tumor grade, pathologic stage, and rate of PSA change are important factors for predicting recurrence. PSA recurrence usually precedes clinical recurrence by several years.
b. **Follow-up.** Patients should have their PSA levels monitored periodically following local therapy for prostate cancer. Various studies show that after radical prostatectomy, a rising PSA or a PSA that does not decline to zero predict an eventual failure. Tumor eradication following radiation is associated with a PSA of <0.5 ng/mL.
c. **Use of analogs of luteinizing hormone–releasing hormone (LHRH) after relapse following local therapy.** Treatment with agonists or antagonists (agonists overstimulate and cause shutdown of the system; antagonists block the system directly and thus cause shutdown; therefore, overstimulation = blockade.) of LHRH (also known as GnRH, for gonadotropin-releasing hormone) is now recommended in men with a rising PSA level after surgery or radiotherapy. However, long-term follow-up is needed to determine the benefits of adjuvant hormonal treatment in terms of local control, disease progression, and improvement in patient survival.

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2. **Locally advanced prostate cancer.** There are various opinions as to the best mode of therapy for men with locally advanced (T3) nonmetastatic disease. Subjects with stage T3 disease, especially those with poorly differentiated tumors, are usually treated with adjuvant hormonal therapy combined with radiotherapy. LHRH antagonists alone or agonists in combination with an antiandrogen may be useful prior to radical prostatectomy in those patients having surgery for T3 prostate cancer. In addition, neoadjuvant therapy with LHRH agonists started at the beginning of external-beam radiotherapy, and continued for 3 years, can

improve the 5-year overall survival of patients with locally advanced prostate cancer.

3. **Advanced prostate cancer.** The treatment of men with advanced prostate cancer is palliative and based on attaining total androgen deprivation. Endocrine therapy improves quality of life and prolongs survival. Standard therapies for advanced prostate cancer consist of bilateral orchiectomy or long-term administration of LHRH agonists, each with and without an antiandrogen, or, recently, administration of LHRH antagonist. Approximately 70% to 80% of patients with prostate cancer show symptomatic and objective responses to androgen ablation. Androgen deprivation leads to a decrease in libido, impotence, “hot flashes,” weight gain, muscle loss, cognitive change, and osteopenia. In addition, surgical castration has a psychological impact. Acceptance of LHRH analogs is excellent, and in surveys of patients who are offered a choice between orchiectomy and LHRH analog, the analogs are selected as primary treatment >70% of the time. Because the superactive agonists of LHRH initially stimulate the release of gonadotropins and sex steroids, an occasional temporary flare of the disease during the first weeks of administration has been observed. This can be of concern in patients with vertebral metastases and impending spinal cord compression, or those with impending ureteral or urethral obstruction. Administration of antiandrogens before and during early therapy with agonists, or the use of LHRH antagonist permanently or temporarily can prevent such disease flare.
4. **Use of LHRH antagonists in men with advanced prostate cancer.** Clinical trials in patients with advanced prostate cancer have been carried out with the LHRH antagonists cetrorelix (acetyl-D-2-naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-seryl-tyrosyl-D-citrullyl-leucyl-arginylprolyl-D-alanylamide) (available commercially as Cetrotide; Aeterna-Zentaris), Abarelix (Praecis Pharm), and Degarelix (Firmagon; Ferring). The third-generation LHRH antagonist, **Degarelix** [Ac-D-2Nal1-D-4Cpa2-D-3Pal3-Ser4-4Aph(X)5-D-4Aph(Y)6-Leu7-Ilys8-Pro9-D-Ala10-NH2], is the **only LHRH antagonist on the market** and available with low risk of histamine release for clinical use in advanced PCa. Additionally, no systemic anaphylactic reactions occurred during the clinical development of

Degarelix in patients with PCa.

LHRH antagonists could be beneficial as a monotherapy for patients with prostate cancer and metastases in the brain, spine, liver, and bone marrow in whom the LHRH agonists cannot be used as single drugs because of the possibility of flare. (Flare is a temporary effect produced by the overstimulation of LH just prior to that point at which the overstimulation causes system shutdown.) These antagonists act on the same receptor sites as those of LHRH and cause an immediate inhibition of the release of gonadotropins and sex steroids. Because the inhibition of LH and sex steroids can be induced with a single injection of a potent LHRH antagonist, the time of the onset of therapeutic effects is greatly reduced. It has been observed that attempts at androgen-deprivation therapy have led to increased cardiovascular risks. This was true in the days of stilbesterol therapy, which led to the current worldwide preference for LHRH therapy. Recently, however, **LHRH agonist therapy has been observed to increase cardiovascular risk**. A recent pooled analysis of randomized trials has suggested that the **LHRH antagonist, Degarelix, shows a reduced risk of cardiovascular events** and death as compared to therapy with the agonist.

5. **Hormone-refractory castration resistant prostate cancer.** Most patients with metastatic prostatic carcinoma eventually relapse because all hormonal therapies aimed at androgen deprivation, including bilateral orchiectomy, antiandrogens, p. 1032p. 1033LHRH analogs, and their combinations, can only provide a remission of limited duration. The relapse is manifested clinically, radiologically, and biochemically by an increase in pain or other symptoms, a change in x-ray or bone scan status, or a rise in serum PSA levels. Such patients eventually die of androgen-independent prostatic cancer. This androgen-independent growth of prostate cancer cells is apparently stimulated by various growth factors. The prognosis for patients with hormone-refractory prostate cancer is very poor, and no effective treatment exists at present. Chemotherapy produces poor response rates, although Docetaxel-based therapy confers an

improvement in survival. Palliative responses to mitoxantrone plus prednisone were recently demonstrated. Ketoconazole, Estramustin, Suramin, Abiraterone, and Enzalutamide have all been used to improve the clinical outcome in these patients.

6. **New approaches.** Efforts to slow the rate of progression of prostate cancer to a castrate-insensitive status have included alternate methods of attack on the androgen receptor (AR). These methods utilize some newer AR antagonists such as enzalutamide, and CYP17A inhibitors, such as ketoconazole and abiraterone, which indirectly inhibit the AR pathway. A recent publication indicates that kisspeptin and its analogs can also suppress testosterone and thereby prostate cancer. Chronic administration of **kisspeptin analog TAK448 suppresses testosterone levels** in normal men and prostate cancer patients.
   a. Questions regarding the optimal timing of hormone therapy, the proper sequence of utilization of extant therapeutics, the application of Radium-223 and other bone-targeted agents, and the use of adjuvant cytotoxic chemotherapy are still to be answered. The role of immune-based agents is also in its infancy. Other chemotherapeutic regimens and combinations have been suggested, as have bone-targeting agents (Radium-223, denosumab, zoledronic acid, and immunotherapeutically based agents (pembrolizumab [PD-1 inhibitor], sipuleucel-T [elicits immune response triggered by PAP], ipilimumab [supports T-cell activation], GVAX [cancer cell vaccine], and ProstVac [prostate cancer vaccine]).

      Epidermal growth factor, insulin-like growth factor I, and their receptors may be involved in neoplastic transformation. Interference with endogenous growth factors and their receptors by somatostatin analogs, bombesin/GRP (gastrin-releasing peptide) antagonists, and GHRH antagonists or the use of targeted cytotoxic peptide analogs could inhibit the growth of androgen-independent prostate cancers and improve the tumor treatment outcome. **GH or testosterone administration is contraindicated in both metastatic and nonmetastatic prostate cancer**.
   b. **Neuroendocrine prostate cancer**

      As more deaths from advancing prostatic castrate-resistant cancers are being delayed, we are observing an increase in small

cell/neuroendocrine variants. A recent survey showed that 13% of recurrence biopsies are pure classic small cell/neuroendocrine variants and 26% are mixed. These display visceral metastases, disease levels out of proportion to the PSA level, neuroendocrine markers, and extremely virulent disease. They may be responsive to chemotherapy but not to hormonal therapy. In addition to possible responses to cytotoxic chemotherapy, these tumors may respond to somatostatin and its analogs (octreotide [as a drug or as a radiopharmaceutical], lanreotide, and pasireotide), everolimus, or interferon-α-2.

7. **Preparations of LHRH agonists used clinically in tumor therapy**
   - **a.** Decapeptyl (Triptorelin, Trelstar): (pyro)Glu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2 (D-Trp-6-LHRH), Ipsen-Biotech, Ferring, Akzo-Organon, Ache.
   - **b.** Buserelin (Suprefact): (pyro)Glu-His-Trp-Ser-Tyr-D-Ser(Bu^t)-Leu-Arg-Pro-ethylamide, Hoechst-Marion-Roussel, Aventis (Canada).
   - **c.** Leuprolide (Lupron): (pyro)Glu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-ethylamide (D-Leu-6-Des-Gly-10-LHRH ethylamide), Abbott-Takeda, (TAP) Pharmaceuticals.
   - **d.** Zoladex (Goserelin): (pyro)Glu-His-Trp-Ser-Tyr-Ser-(Bu^t)-Leu-Arg-Pro-Azgly-NH_2 (ICI 118630), Astra-Zeneca Pharmaceuticals.

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   - **e.** Many therapeutic regimens are based on long-acting depot formulations consisting of analogs dispersed in microcapsules or implants of biodegradable polymers. Lupron depot and decapeptyl LP are available in the form of slow-release formulations containing 3.75-mg analog in microcapsules of poly(D,L-lactide-*co*-glycolide) and administered intramuscularly at monthly intervals through an 18- to 22-gauge needle. Depot formulations of leuprolide acetate 22.5 mg and 30 mg Triptorelin (Trelstar LA) containing 11.25 mg of the active drug have been developed. These formulations release the drugs for 3 to 4 months at the same daily dose as the monthly preparations. There are also implantable devices (Viadur, containing 65 mg

Leuprolide) for year-long release. Zoladex implant, containing 3.6 mg goserelin, is designed for subcutaneous injection with continuous release over a 28-day period. The analog is dispersed in a matrix of D,L-lactic and glycolic acids copolymer and supplied as a 1-mm-diameter cylinder preloaded in a single-use syringe with a 16-gauge needle. Zoladex 3-month goserelin implant contains 10.8 mg of goserelin and is designed for subcutaneous implantation with continuous release over a 12-week period. It is supplied as a 1.5-mm-diameter cylinder, preloaded in a single-use syringe with a 14-gauge needle. Suprefact depot (buserelin 2-month depot) is supplied in an applicator containing two implant rods, equivalent to a total of 6.3 mg buserelin, and is injected subcutaneously into the lateral abdominal wall every 8 weeks. About 7 days before the first injection of depot preparations of LHRH agonists, an antiandrogen such as bicalutamide (Casodex) should be administered in accordance with the manufacturer's directions. This comedication is to be continued at least for 2 to 4 weeks after the first agonist injection, until the testosterone levels have been lowered to the surgical castration range, or indefinitely.

f. LHRH antagonist, **Degarelix**, forms a physicochemical complex after subcutaneous injection. The drug is released in two phases into the bloodstream: a short, initial, prompt release phase followed by a slow-release phase in which serum levels display a half-life of several weeks. Data from a Phase III study demonstrated that with a single dose of 240 mg of Degarelix, the maximum plasma level (C_{max}) was 66 ng/mL, the area under the concentration–time curve (day 0 to 28) was 635 ng/day/mL, and the mean time to C_{max} was 40 hours. Median terminal half-lives for the starting and maintenance doses were about 43 days and 28 days, respectively. The extended half-life after subcutaneous injection of Degarelix is thought to be a consequence of a very slow release of the drug from the complex that is formed at the injection site. On the basis of the safety and efficacy demonstrated in the Phase II and Phase III studies, the Degarelix dosage of 240/80 mg (240 mg loading dose; 160 mg maintenance dose) was approved by the US Food and Drug Administration in 2008 and the European Medicines

Agency in 2009 for treatment of androgen-dependent advanced PCa.

II. BREAST CANCER

A. General principles

1. Breast cancer is the most common malignancy among American women. The American Cancer Society estimates that in 2017, 255000 new cases of breast cancer will be diagnosed in the United States annually and 41070 patients will die of the disease. Although <10% of patients with breast cancer are diagnosed as having advanced disease at the time of presentation, cancer statistics indicate that 40% to 70% of the remainder will eventually develop metastases in the course of their disease. From 1980 to 2000, the incidence of breast cancer rose about 30% in Western countries. This is thought to be due to changes in reproductive factors, the use of hormonal therapy for menopause, and an increase in screening, including tests for BRCA genes. From 2000 onward, incidence rates have declined, perhaps because of diminution in the use of menopausal hormone therapy and stabilization in the rates of mammographic/genetic screening.

   Endocrine treatment alone or in combination with chemotherapy has been utilized for the palliation of advanced breast cancer, as well as for adjuvant therapy for surgery and irradiation in patients with primary breast cancer.

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B. Primary breast cancer and risk factors for relapse

Special clinical problems exist concerning the initial evaluation of patients with early-stage breast cancer. As noted above, a significant number of these patients are at risk of relapse following local treatment. Thus, it is important to assess the risk factors for relapse at the time of diagnosis. For patients at risk of relapse, adjuvant treatment based on hormonal therapy, chemotherapy, or combinations should be given immediately after local treatment. The panel of the Sixth International Conference on Adjuvant Therapy of Primary Breast Cancer has identified the following factors as defining the **patients at increased risk at the time of diagnosis**:

1. Nodal status (node-positive breast cancer) and/or the number of regional lymph nodes involved are considered the most important

factors for the estimation of risk.

2. For patients without histologic evidence of lymph node involvement (node-negative disease), the following factors are relevant: tumor size, stage, histologic and nuclear grade, steroid hormone receptor status, presence of lymphatic and/or vascular invasion, and age of the patient at diagnosis.
3. **Hormone receptors.** The expression of estrogen receptors (ERs) and progesterone receptors (PRs) in tumor cells is the decisive factor predicting treatment response to endocrine therapy. Patients with ER-positive tumors appear to have longer survival rates compared with those with ER-negative tumors who are at high risk of relapse.

C. Endocrine therapy

Endocrine therapy is used as adjuvant therapy for surgery and irradiation in patients with primary breast cancer as well as in the palliation of advanced breast cancer. Approximately 30% to 40% of unselected premenopausal patients with breast cancer have estrogen-dependent tumors and can be treated with hormonal approaches, such as surgical oophorectomy, the antiestrogen tamoxifen, and agonists of LHRH.

1. **Early-stage breast cancer.** Adjuvant **Tamoxifen** has been used extensively in premenopausal and postmenopausal patients with early breast cancer who present with detectable **ER in their tumors**. Prolonged treatment with LHRH analogs or surgical oophorectomy is being investigated in randomized trials. The use of Tamoxifen following chemotherapy might be also considered for patients with minimal/trace levels of ER or PR.
2. **Advanced breast cancer. Tamoxifen** is the therapy of choice for the initial management of premenopausal and postmenopausal women with advanced breast cancer, particularly those with ER-positive tumors. However, for premenopausal women, some clinicians prefer the use of **LHRH agonists or oophorectomy**. Tumor remissions after therapy with LHRH agonists occur primarily in women with well-differentiated, slow-growing, and ER-positive tumors. In a large trial in premenopausal women with breast cancer, using **depot implants of Zoladex**, 53% of patients demonstrated objective tumor responses. In premenopausal women with ER-positive breast cancer, adjuvant treatment with LHRH agonists for 2 to 3 years is as effective as

chemotherapy and is burdened with fewer side effects. Combinations of agonists in long-acting depot preparations and Tamoxifen produced a superior response rate in premenopausal women with breast cancer than either modality alone. **Aromatase inhibitors** such as letrozole, which block the conversion of adrenal androgens to estrogens, are primarily effective in postmenopausal women with breast cancer, but can also be used in premenopausal women if they are combined with an agonist of LHRH, which produces ovarian estrogen deprivation. LHRH antagonists have been shown to be very effective in the management of experimental breast cancers (have not yet been used in humans) but have not been evaluated clinically. Because receptors for LHRH are found in >50% of human breast cancer specimens, **cytotoxic analogs of LHRH that contain doxorubicin** have been developed. These cytotoxic analogs, such as AN-152 (AEZS-108, zoptarelin), target breast cancers expressing LHRH receptors and are used in clinical trials.

Because some breast cancers are androgen-receptor positive, **enzalutamide**, **an androgen-receptor blocker**, has been tested for breast cancer, and the results have been fascinating. Among evaluable patients, the clinical benefit ratio at 16 weeks has been 35%.

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3. **Triple negative breast cancer**. These tumors, which are negative for ER, PR, and Her-2/neu (receptor for tyrosine protein kinase erbB-2), represent a more difficult category of treatment. Although, by definition, the tumors do not carry these receptors, they may carry others such as androgen-receptor and neuroendocrine receptors. They may thus be susceptible to treatment with blockers of neuroendocrine receptors such as LHRH antagonists and GHRH antagonists.

D. Chemoprevention

The incidence of breast cancer in the United States **declined after millions of women stopped taking hormone replacement therapy** (HRT) following the release of the Women's Health Initiative Study in July 2002, which indicated that HRT led to more risks than benefits. The U.S. Food and Drug Administration (FDA) approved the use of **tamoxifen** citrate (Nolvadex) **for prevention of breast**

cancer in women considered at high risk. However, tamoxifen does not completely antagonize the effect of ovarian estrogens and **may contribute to an increase in endometrial carcinomas**. A large clinical trial with tamoxifen and raloxifene, which included 22 000 postmenopausal women with a high risk of breast cancer, assessed breast cancer chemoprevention efficacy and endometrial safety of these agents. **Tamoxifen** alone lowered risk by 13% to 48% and raloxifene alone lowered risk by 18% to 58%. Taken together, the overall risk reduction was 38%. The risk of osteoporosis was also diminished.

Raloxifene (Evista) and tamoxifen are selective ER modulators (SERM). Fulvestrant (Faslodex) is also a novel antiestrogen without any agonistic activity and is approved for treatment of postmenopausal women with breast cancer.

1. **Use of radiolabeled somatostatin analogs for localization and treatment of tumors.** Radioiodinated analogs of somatostatin, such as [^{111}In-DTPA-D-Phe^{1}]-octreotide (**OctreoScan**), can be used clinically for the imaging of tumors that express receptors for somatostatin. Thus, the presence of somatostatin receptors, particularly subtypes 2 and 5, on tumors may permit their localization using such scanning techniques. Somatostatin receptor scintigraphy has now been carried out in thousands of patients and it is well established that various primary tumors, either neuroendocrine or nonneuroendocrine, containing high numbers of somatostatin receptors, can be localized in vivo. In addition, the sites of metastatic spread can also be visualized by scintigraphy with radiolabeled somatostatin analogs. **Neuroendocrine tumors that can be localized with OctreoScan** include growth hormone-secreting pituitary tumors, gastrinomas, insulinomas, glucagonomas, medullary thyroid carcinomas, neuroblastomas, pheochromocytomas, carcinoids, and small-cell lung cancers. Among nonneuroendocrine tumors that could be imaged by scintigraphy are non–small-cell lung cancers, meningiomas, breast cancers, and astrocytomas. Information from scintigraphy improves therapeutic planning.
2. **Use of radiolabeled somatostatin analogs for tumor therapy.** Attempts are being made to use somatostatin analogs labeled with radionuclides, such as ^{111}Indium, ^{90}Yttrium, or

^{68}Galium, for cancer therapy. Radiolabeled somatostatin analogs to deliver therapeutic doses of a radioactive isotope to the cancer cell may improve the treatment of somatostatin receptor–positive tumors.

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86 Endocrine-Disrupting Chemicals

Sheela Sathyanarayana

I. ENDOCRINE-DISRUPTING CHEMICALS

A. Background. Understanding of endocrine-disrupting chemicals (EDCs) has grown in the past 20 years with numerous research studies reporting widespread exposures in the general population and significant associations with adverse human health impacts. The definition of an EDC is "an exogenous chemical, or mixture of chemicals that interferes with any aspect of hormone action." Impacts on endocrine processes can be assessed in animal toxicity studies as well as human epidemiologic investigations. Hundreds of chemicals meet this definition, including naturally occurring compounds (soy or phytoestrogens), synthetic compounds (phthalates and bisphenol A), and pharmaceuticals (oral contraceptives). Some common classes of EDCs include pesticides (dichlorodiphenyltrichloroethane [DDT] or chlorpyrifos), plasticizers (phthalates and bisphenol A), and flame retardants (polybrominated diphenyl ethers [PBDEs]) (Table 86-1). For the purposes of this chapter, discussion will be limited to EDCs that are exogenous synthetic compounds or naturally occurring substances. The vast majority of these chemicals are not regulated and not tested for clinical toxicity, whereas pharmaceuticals undergo strict testing with animal studies and clinical trials.

B. Human exposure. Some EDCs are produced in large quantities for industrial use as well as in manufacturing of commonly used products. For example, bisphenol A (BPA) was produced in higher quantities (15 billion pounds) than any other chemical in 2013. BPA is used in food packaging, polycarbonate plastics, toys and numerous other consumer applications. Similarly, phthalates are used in flexible plastics, personal care productions, and food packaging. Phthalates are also used in medical settings in flexible plastics such as IVs and extra corporeal membranous oxygenation. Because these chemicals are used in so many different consumer products, they are ubiquitous and

pervasive in the general population. The National Health Nutrition and Examination Survey estimates that **over 90% of the population is exposed to several common EDCs**.

C. Health impacts. There is mounting peer-reviewed scientific evidence for adverse health effects associated with several EDCs. Effects can occur in the male and female reproductive organ systems, in the neuroendocrine system, and in metabolic pathways that are hormone dependent. Of note, the majority of these chemicals are not pharmaceuticals and therefore are not required to undergo toxicity testing or clinical trials. Therefore, health impacts remain largely unknown for hundreds of EDCs. A historical and well-known EDC in the medical field that has significant health impacts is diethylstilbestrol (DES), a high-dose synthetic estrogen. DES was widely used to prevent miscarriages in the 1950s. Exposure to the chemical led to significant reproductive toxicity in pregnant women, which, in turn, led to vaginal adenocarcinoma and subsequent impacts in their children including multiple reproductive tract defects. This chapter will summarize examples of currently used chemicals and associated peer-reviewed literature reporting their health impacts.

II. EDC MECHANISMS OF ACTION AND PHARMACOKINETICS

In the past, action through hormone receptors was thought to be the primary target for EDCs, but in recent years, our understanding has expanded to include multiple targets and mechanisms of action within the endocrine system. Specific targets for EDC p. 1039p. 1040p. 1040p. 1041action include, but are not limited to, nuclear receptors, nonnuclear steroid hormone receptors, nonsteroid receptors, and enzymatic pathways involved in steroid or hormone actions. Potential mechanisms of action at these targets include direct cytoxicity to endocrine active cells, receptor selectivity (differing at high vs. low concentrations), receptor downregulation, and desensitization changes as concentration of the exposure changes. Additional mechanisms include receptor competition differing at low versus high exposures and endocrine negative feedback loop action changing on the basis of duration of exposures. Some EDCs are known as persistent organic pollutants (POPs) and have very long half-lives such as dioxins (7 to 11 years), whereas others are metabolized and excreted within 2 to 3

days. POPs with longer half-lives present different and potentially greater risks to humans because they can bioaccumulate in human tissues over time for storage and release in the future. Chemicals with short biologic half-lives may superficially seem more safe, but most people are exposed to these chemicals in their everyday lives, making them ubiquitous. For example, if a woman uses a shampoo with phthalates, she is likely to use that same shampoo consistently and have chronic exposure over time. These chemicals are often metabolized through the liver and excreted through urine and stool. Therefore, urine is often used as the biologic matrix to measure metabolites of many parent chemical compounds.

TABLE 86-1 Classification, Sources of Exposure, Routes of Exposure, and Physiologic Effects of Common Endocrine-Disrupting Chemicals (EDCs)

EDC	Sources of exposure	Route of exposure	Half-life	Physiologic impacts
Bisphenol A (BPA)	Food packaging, dental sealants, thermal receipts	Ingestion, inhalation, dermal absorption	4–6 hr	Estrogenic, c neurologic reproducti effects
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	Contaminated water, food as byproduct of herbicide production	Ingestion, inhalation	7–11 yr	Reproductive carcinoger
Dichlorodiphenyltrichloroethane (DDT)	Contaminated water, soil, crops	Ingestion, inhalation, dermal absorption	6–10 yr	Carcinogen, system, ki
Polybrominated diphenyl ethers (PBDEs)	Furniture with foam cores, mattresses, and clothing	Ingestion, inhalation, dermal absorption	14–30 d	Reproductive developme thyroid eff neurodeve
Phthalates	Food contaminants, food packaging, flexible plastics, personal care products	Ingestion, inhalation, parenteral, dermal absorption	6 hr–2 d	Reproductive developme neurodeve obesogen
Genistein (component of soy)	Tofu, soybeans, bean sprouts, infant formula	Ingestion	3–5 hr	Can interact receptors i cancer, an

				but eviden health imp
Perfluorooctanoic acid (PFOA)	Contaminated food and water, Teflon, dust, firefighting foam, electrical wiring, stain-resistant carpet	Ingestion, inhalation	2–4 yr	Mammary gl developme toxicant, c

III. ROUTES OF EXPOSURE

Humans are exposed to these chemicals through various routes of exposure, including ingestion, dermal exposure, inhalation, and parenteral methods (through IVs in hospitals). EDCs can be contaminants that enter foods through industrial processing or are in food-packaging materials. For example, bisphenol A is used in the surfaces of can linings. Dermal exposures include lotions or other personal care products that contain these chemicals as part of the active or inactive ingredients. Parabens are an example of an EDC used in lotions. Because many of these chemicals are in commonly used products, they can shed and eventually settle in dust that can be inhaled. Indoor and outdoor dust can contain measureable EDCs. The parenteral route of exposure is especially important for those patients undergoing dialysis or in the ICU. A recent study showed that NICU infants had 10-fold higher concentrations of phthalates compared with children in the general population. Some adult occupations pose high risk of EDC exposures including pesticide applicators or laboratory workers. In central California, adult males working in a pesticide formulation plant were exposed to dibromochloropropane (DBCP) which caused infertility and birth defects. Worker protections have since been put into place to prevent exposures.

IV. ISSUES AFFECTING SUSCEPTIBILITY

A. Timing and age of exposure. Children are most vulnerable because of exposures during sensitive windows of development. In utero exposures can affect organ development as observed with DES and phthalates. Children are also more susceptible because of a small body size per unit mass, increased respiratory rate, decreased

metabolic capacity, and increased food/water consumption per unit mass. Other important life stages for exposure include puberty and reproductive life.

B. **Transgenerational effects.** EDCs can affect not only an exposed individual but also the subsequent generations. Children born to adult male workers exposed to DBCP had significant **birth defects**, suggesting significant **sperm toxicity** that impacted fetal development. Another example (mentioned earlier) is adult women exposed to **DES during pregnancy** which led to reproductive defects in their children.

C. **Developmental origins of disease.** EDC exposures can impact organ development during the fetal period, and the disease may not manifest until much later in life. For example, BPA exposure in utero in rodents leads to increased obesity in adult rats, suggesting that programming of metabolism can occur very early in fetal life.

D. **Nonmonotonic dose response.** Current animal toxicologic studies assess high-dose exposures and resulting health impacts. EDCs can cause health impacts at low exposure concentrations, and impacts may be different than those at high-dose exposures. This concept is called nonmonotonic dose response with inverted u-shape dose–response curves. These u-shaped curves have been observed for endogenous hormone actions.

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V. EXAMPLES OF EDC-ASSOCIATED HEALTH IMPACTS

EDCs can affect the **male and female reproductive systems** as well as **thyroid and neuroendocrine** pathways. Hundreds of animal studies and more recently, human epidemiologic investigations, highlight these relationships. A more comprehensive summary can be found in "EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals." Three key examples of chemicals and associated health impacts are listed below.

A. **Phthalates and male reproductive health.** Phthalates are a family of ubiquitous synthetic EDCs that are used as plasticizers and are known **antiandrogens** in mammalian systems. Phthalates have short half-lives, and over 95% of the population is exposed to these chemicals due to their ubiquity in the environment. In animal models, di-ethyl-hexyl phthalate (DEHP), di-butyl phthalate (DBP), and butyl

benzyl phthalate (BBzP) adversely affect male genital development via an antiandrogenic effect on testicular development. Some phthalates may also exert nonandrogenic dependent effects such as oxidative stress affecting sertoli cell function and other hormones such as INSL3, integral for testicular descent. The "phthalate syndrome" describes a constellation of male genital birth defects in rodents including reduced anogenital distance (AGD), hypospadias, cryptorchidism, and seminal vesicle deformation that develop in response to DEHP, DBP, and BBzP exposures early in gestation. The human corollary, called the "**testicular dysgenesis syndrome**," suggests that genetic defects and environmental factors such as phthalate exposure in utero can lead to a similar constellation of male birth defects. Many of these defects, including undescended testes and hypospadias, are known risk factors for impaired male reproductive function later in life. In human studies, phthalates have been associated with changes in testosterone concentrations, altered sperm parameters, and changes in AGD, a marker of androgen action in utero.

B. Dioxins and female reproductive health. Dioxins are highly toxic compounds that are formed during combustion processes. Dioxin was used as a defoliant in the Vietnam War and is a POP with a long half-life of 7 to 11 years. Dioxin is now banned from use, but is known as a "legacy chemical" because its legacy lives on on account of its persistence and bioaccumulation in the environment and "up the food chain." Current human exposure is through contaminated foods, and the largest contamination occurred in Seveso, Italy, where most human research has occurred.

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is the most toxic dioxin compound and can cause numerous reproductive abnormalities and increased development of cancer in animal studies. In humans, adult female TCDD exposure has been associated with reduced fertility, miscarriage, and increased time to pregnancy. In addition, TCDD was associated with an increased risk of breast cancer in this cohort. Although this was a high-dose exposure, studies of this compound teach us about how these chemicals can persist in our bodies and lead to long-term health impacts in the future.

C. Polybrominated diethyl ethers (PBDE) and neurodevelopment

PBDEs are a class of chemicals whose production began in the late 1970s. In 2001, approximately 33 000 tons were produced for use as

flame retardants in clothing and furniture. They are persistent, lipophilic compounds that can bioaccumulate in the body. Two specific PBDEs have now been banned because of toxic properties, but others remain in use. PBDE exposure in rodents reduces concentrations of thyroid hormone with associated defects in neurobehavior, and other mechanisms of action may be at play as well, including changes in calcium regulation. PBDE exposure in pregnancy has been associated with thyroid hormone changes, but these findings are not consistent across human studies. In human epidemiologic studies, PBDE exposure in pregnancy is associated with deficits in cognitive function, including full-scale IQ changes.

VI. HOW TO COUNSEL PATIENTS/FAMILIES

Endocrinologists can play a key role in scientific research, and also patient education regarding EDCs. Being aware of the chemical exposures and potential health impacts imparts trust among patients and strengthens the patient–provider relationship. p. 1042p. 1043Endocrine-disrupting chemicals do exist, and they can be active substances within the endocrine system.

Specific recommendations for clinicians are as follows:

A. Stay informed and know good resources. Be knowledgeable about common EDCs and resources for both clinicians and patients. The US Environmental Protection Agency and Centers for Disease Control funds the Pediatric Environmental Health Specialty Units to educate clinicians and the public about environmental toxicant exposures and health impacts. They can be a great resource for busy clinicians, and there is a unit in every federal region in the country (http://www.pehsu.net/). Another good resource for up-to-date research findings is The Endocrine Disruption Exchange (http://www.endocrinedisruption.org/).

B. Support continued research. Because endocrinologists are on the front lines of clinical work, they may see interesting cases or know of chemical exposures that could be of interest to researchers. It is important to capture these clinical pearls for future study.

C. Understand current regulations. EDCS are regulated only if they are pharmaceuticals, registered pesticides, or compounds that are active substances in foods. Only a few EDCs are regulated at the

federal level, and in such cases, only for specific uses. For example, some phthalates are banned in children's toys, but because they are prevalent in so many other products, they are still found in measureable concentrations in children's urine. Therefore, the general public is exposed to many EDCs, and reducing exposures can be difficult, given how ubiquitous some chemicals are in the environment. In some cases, federal regulation may be the only way to reduce general population exposures.

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87 Flushing and Sweating

Isabel Huguet and Ashley Grossman

I. INTRODUCTION

A. Flushing can be defined as a sensation of warmth accompanied by erythema that most commonly occurs on the face, but may also involve the neck, ears, chest, epigastrium, and arms or other areas. These attacks are typically transient, but when repeated over years may result in telangiectasias as the patient is left with a permanent flush.

B. Sweating is a physiologic mechanism for bringing the core body temperature back to baseline; however, sweating disorders can be observed in various systemic conditions related to autonomic dysfunction, autoimmunity, metabolic imbalance, or sometimes functionally in response to ongoing stress in one form or another.

This chapter will review the most common causes of flushing and sweating, and will suggest an algorithm for the diagnosis of these frequently challenging entities.

II. PATHOGENESIS

Flushing is the visual and subjective consequence of increased cutaneous blood flow secondary to vasodilatation, and the predilection for specific anatomical areas seems to be related to the volume of visible superficial vessels, and possibly a qualitative difference in facial cutaneous vascular response to systemic agents and neuronal control.

The neurologic control of vascular smooth muscle is predominantly exerted by autonomic nerve fibers. Because these fibers also supply eccrine sweat glands, neurally mediated flushing is frequently associated with sweating (“wet flushing”), as opposed to isolated (“dry”) flushing, mainly due to the action of circulating vasodilator substances. Endogenous vasodilators include kinins, prostaglandins, vasoactive intestinal peptide (VIP), calcitonin gene–related peptide, serotonin (5-HT), and histamine.

III. ETIOLOGY OF FLUSHING

The classification of the diverse causes of flushing will be divided into those associated with or without the presence or absence of sweating (Table 87-1).

A. "Wet flushing": a neural mechanism

Disturbances of the autonomic system frequently occur at both extremes of life: in early life, especially in young females, there appears to be instability of this system in response to stress, so-called **blushing**. Later in life, abrupt withdrawal of estrogens in women leads to menopausal flushing. Despite extensive study, the pathogenesis of menopausal **hot flushes** remains unclear, although the most widely accepted theory implicates a narrowing of the thermoneutral zone in symptomatic women, which would trigger an exaggerated reaction in response to minor elevations in core body temperature. Estrogens are known to be potent neuromodulators with complex interactions with both serotoninergic and noradrenergic systems, and such estrogen-associated modulations of norepinephrine and serotonin signaling have been proposed to be one of the mechanisms by which thermoregulatory dysfunction occurs because of hormonal changes. In essence, it is considered that withdrawal of estrogens leads to a disinhibition of gonadotrophin-releasing hormone, and it would appear that in some manner this disturbance leads to autonomic instability. Rarely, such flushing can also occur when the estrogen deficiency is in response to a pituitary defect.

Other thermoregulatory disorders of the autonomic nervous system (e.g., diencephalic autonomic epilepsy, cluster headaches, Parkinson disease, etc.) may cause a similar syndrome.

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TABLE 87-1 Causes of Flushing

Wet flushing	Dry flushing

• Menopause
• Emotional flushing
• Fever
• Neurologic disorders (autonomic)
  • Brain tumor
  • Diencephalic autonomic epilepsy
  • Cluster headache
  • Spinal cord injuries
	• Rosacea
	• Drugs
	• Food
	• Alcohol
	• Carcinoid syndrome
	• Mastocytosis
	• Pheochromocytoma
	• Medullary thyroid carcinoma

• Parkinson disease • Auriculotemporal syndrome • Harlequin syndrome • Riley–Day syndrome (familial dysautonomia)	• Anaphylaxis • VIPoma • Renal cell carcinoma
VIP, producing pancreatic tumor.	

B. “Dry flushing”

Isolated flushing is mainly related to the presence of vasodilators, which can be endogenous or exogenous.

1. **Carcinoid syndrome:** This syndrome occurs in around 20% to 30% of patients with midgut neuroendocrine tumors (NETs). The principal agent involved is 5-HT, and in general flushing occurs only in the presence of liver metastases because 5-HT needs to reach the systemic circulation and would otherwise be metabolized by hepatic enzymes. However, it may occasionally be present in patients with widespread peritoneal metastases, or with ovarian carcinoids even when localized because in these situations, the 5-HT may gain immediate access to the general circulation. Precipitating factors include alcohol and some foods such as cheese, chocolate, or vanilla.
2. **Mastocytosis:** This is a heterogeneous group of clonal disorders characterized by proliferation and accumulation of mast cells in various tissues, including the skin and the bone narrow. The inappropriate release of mediators can cause a wide variety of clinical manifestations (flushing, vomiting, abdominal pain, diarrhea, and/or anaphylaxis).
3. **Pheochromocytoma:** Flushing as a manifestation of pheochromocytoma is in our experience extremely **rare**. The major secretory product from most pheochromocytomas is norepinephrine, which causes predominant vasoconstriction through activation of α-adrenoceptors in skin and muscle. Thus, the most common occurrence during a paroxysmal release of catecholamines is pallor, often associated with tachycardia and occasionally with sweating. Pure flushing could occur if there was dominant epinephrine release, which is rare, or with the extremely rare dopamine-secreting tumors that are often large and malignant. However, there may be mild flushing after an attack as rebound vasodilatation of the facial cutaneous blood vessels.

IV. EVALUATION (Fig. 87-1)

A. It is important to take a careful **history** to look for precipitating factors and associated symptomatology such as headache and diarrhea. An exhaustive drug history is mandatory because many agents may cause flushing (Table 87-2). Physical examination of the skin can also guide the diagnosis: urticaria pigmentosa and excoriated lesions caused by scratching may suggest mastocytosis, whereas the presence of the dermatologic manifestations of pellagra, mainly photosensitive dermatitis, may appear in patients with NETs because of the loss of tryptophan which has been "diverted" by the tumor, thus leading to niacin deficiency.

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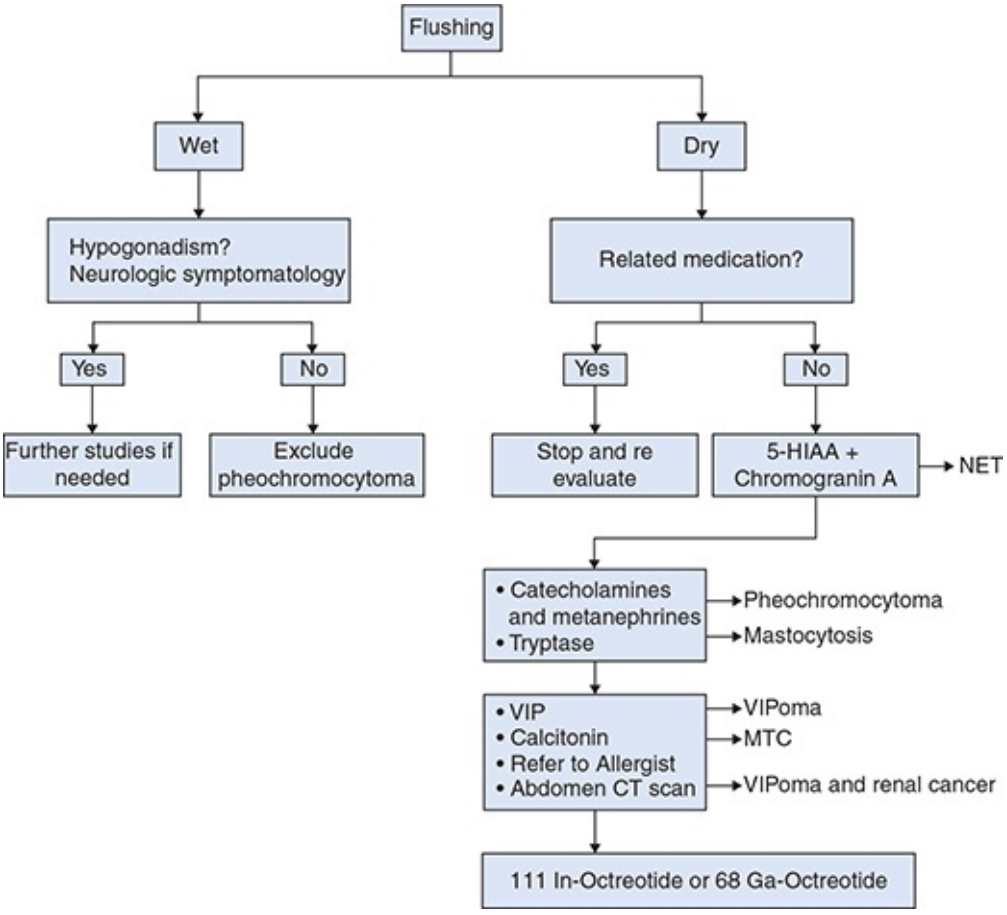

Figure 87-1. Proposed algorithm for the diagnosis of flushing. 5-HIAA, 5-hydroxyindoleacetic acid; CT, computed tomography; MTC, medullary thyroid carcinoma; NET, neuroendocrine tumor; VIP, vasoactive intestinal peptide.

B. The first diagnostic step will be to **differentiate dry flushing from wet flushing**. Patients with flushing secondary to hypogonadism tend to have wet flushes and these often occur at night, with sweating being the predominant aspect. As noted above, this can occur secondary to hypogonadism in both men and women, and with primary or secondary hypogonadism, especially when the onset is abrupt. A careful history and measurement of the gonadotropins FSH and LH, and the relevant gonadal steroid, should establish the diagnosis.

If the patient has dry flushes, the carcinoid syndrome has to be ruled out. The major investigation in suspected cases is the assessment of 24-hour urinary 5HIAA excretion, and plasma chromogranin A may be useful, but strict food and drugs precautions are necessary to prevent false positives (avoiding during 5 days prior to the test the following: avocados, bananas, plums, kiwifruit, melons, pineapple, and coffee and tomatoes, as well as nasal drops and sprays, tricyclic antidepressants and monoamine oxidase inhibitors, salicylates, L-dopa, and phenothiazines). Some laboratories offer a simpler plasma 5HIAA measurement, but this has been less explored as a diagnostic tool. It is also possible that a random urinary 5HIAA, corrected for creatinine, will be as diagnostic as the 24-hour collection but obviously more convenient.

When a carcinoid syndrome has been excluded, other investigations should include serum tryptase for systemic **mastocytosis** and plasma or urinary catecholamines and metanephrines for **pheochromocytoma**. However, as noted above, p. 1046p. 1047mastocytosis is extremely rare, and flushing as a manifestation of a pheochromocytoma is also very uncommon.

TABLE 87-2 Drugs Causing Flushing

Mechanism	Drugs
Vasodilatation	• Nitroglycerine, nitro derivatives • Phosphodiesterase 5 inhibitors • Calcium channel blockers (mainly dihydropyridine) • Calcitonin • Cholinergic drugs
Increased prostacyclins	• Prostaglandins D2, E • Nonsteroidal antiinflammatory drugs

Direct activation of TRPV-1	• Nicotinic acid
Release of vasoactive mediators	• Vancomycin, Rifampicin • Tamoxifen, Cyclosporine, Cisplatin, Dacarbazine • TRH • Bromocriptine • Morphine and opioids
Other/unknown mechanisms	• Triamcinolone • Catecholamines • Radiologic contrast agents • Cyproterone acetate • Metoclopramide • Isofluranes, Fentanyl

TRH, thyrotropin-releasing hormone; TRPV-1, transient receptor potential cation channel subfamily V member 1.

If this workup is unrevealing, other less frequent conditions such as **medullary thyroid carcinoma, VIPoma, and renal cell carcinoma** should also be considered. Medullary thyroid carcinoma can cause flushing and diarrhea when the levels of calcitonin are extremely high, whereas VIPomas characteristically have severe watery diarrhea as their principal clinical manifestation. We have found that measurement of serum calcitonin and a CT scan of the abdomen to exclude a pancreatic islet cell tumor or a renal cell carcinoma can be a reassuring set of investigations.

If attacks persist and no cause can be found, then a radiolabeled ^{111}In-octreotide or ^{68}Ga-octreotate PET scan may reveal an occult tumor, but this is rarely positive because flushing patients usually have obvious disease. It should be emphasized that in many patients no cause is ever found, and the investigations noted above are essential measures of exclusion of rare entities.

V. TREATMENT

The treatment will clearly depend on the underlying condition or trigger.

A. Classically, when treatment was needed for **menopausal hot flushes**, estrogen plus progestogen therapy was initiated, as long as no contraindications were present and targeting the shortest total duration of the treatment. This option has remained controversial over the years, and nowadays new nonhormonal options are available. Serotonin reuptake inhibitors, serotonin-norepinephrine reuptake

inhibitor, gabapentin, or pregabalin have been approved for the treatment of menopausal hot flushes, and when no response is found, a trial of clonidine is suggested. Other options such as botanicals, black cohosh, ω-3-fatty acids, red clover, and vitamin E lack consistent evidence for benefit, and therefore, we do not recommend them.

B. The management of **carcinoid-induced flushing** should be directed to the tumor, and a multidisciplinary team should preferably guide the treatment in order to p. 1047p. 1048combine the different therapies in the best way on behalf of the patient. The somatostatin analogs octreotide or lanreotide are effective in controlling the flushing in the great majority of patients, whereas in those with residual flushing, telotristat ethyl (a serotonin synthesis inhibitor) has shown some benefit in ongoing clinical trials. However, the fact that telotristat is only partially effective suggests that 5-HT is not the only agent involved in causing this syndrome.

C. In relation to systemic **mastocytosis**, treatment has to be adjusted to a number of disease-specific and patient-related variables, including *KIT* mutation status. In many patients, prophylactic and symptomatic treatment with antimediator-type drugs is sufficient to keep symptoms under control, but in other patients, additional therapy may be required for tumor control.

D. For most **benign etiologies** of flushing, there are no agents that readily eliminate the response even on a symptomatic basis.

Related to isolated sweating, thoracoscopic interruption of the sympathetic chain based on a patient's presenting distribution of pathologic sweating is a safe and effective treatment of focal primary hyperhidrosis, but surgical treatment of craniofacial sweating is much more likely to be followed by undesirable side effects.

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88 Intranasal Hormones

Norman Lavin

I. INTRODUCTION

The nasal cavity is covered by a thin mucosa, which is well vascularized. Therefore, a drug molecule can be transferred quickly across the single epithelial cell layer directly to the systemic blood circulation without first-pass hepatic and intestinal metabolism. The effect is often reached within 5 minutes for smaller drug molecules. Nasal administration can, therefore, be used as an alternative to oral administration or injection.

Nasal administration has been associated with a high variability in the amount of drug absorbed, and upper airway infections may increase this variability. There may also be long-term effects on the nasal epithelium. The major part of the approximately 150 cm^2 surface in the human nasal cavity is covered by respiratory epithelium, across which systemic drug absorption can be achieved. The olfactory epithelium is situated in the upper posterior part of the nose and covers approximately 10 cm^2 of the human nasal cavity. The nerve cells of the olfactory epithelium project into the olfactory bulb of the brain, which provide a direct connection between the brain and the external environment. Transferred drugs to the brain from the blood circulation are normally hindered by the blood–brain barrier, which is virtually impermeable to passive diffusion of all but small lipophilic substances. If drug substances, however, can be transferred along the olfactory nerve cells, they can bypass the blood–brain barrier and enter the brain directly.

The olfactory transfer of drugs into the brain is thought to occur by either slow transport inside the olfactory nerve cells to the olfactory bulb or by faster transfer along the perineural space surrounding the olfactory nerve cells into the cerebrospinal fluid (CSF) surrounding the olfactory bulbs in the brain.

II. INTRANASAL HUMAN GROWTH HORMONE

A. Introduction

A pharmaceutical group from the United Kingdom developed a human growth hormone (HGH) product (CPO24) administered by a

noninjectable route of delivery, specifically the nasal route, showing excellent nasal absorption in animal models initially and now in humans.

Previous nasal administration of HGH did not induce increased levels of insulin-like growth factor 1 (IGF-1) and, therefore, these former formulations were considered therapeutically inactive. This pharmaceutical group discovered a novel absorption enhancer called CriticalSorb (Solutol HS 15, BASF) that promotes the transepithelial transport of coformulated proteins and peptides across the nasal membrane. This resulted in the development of a dry powder nasal formulation of HGH known as CPO24. They showed that the proximity of the pituitary gland and its blood supply to the site of absorption in the nose and the potential for direct nose-to-brain delivery was easily obtained. This closeness reached HGH receptors in the brain and they also showed a more physiologic equivalent of the HGH plasma profile.

B. Pharmacokinetics

CPO24 is a spray-dried nasal powder formulation composed of HGH, Solutol HS 15, a gelling agent, and other excipients, and it was manufactured for Critical Pharmaceuticals by Quotient Clinical. The spray-dried powder was filled into nasal Aptar UDS powder devices (Aptar Pharma).

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The study group compared the CPO24 formulation (5 mg of HGH in each nostril) with two other formulations, a subcutaneous (SC) injection of 1 mg and 5 mg of HGH administered in each nostril as a simple solution.

During the study, no serious adverse events were reported. Some of the patients had a local nasal irritation, but this was transient. Overall, the most common side effects were rhinorrhea and a sensation of pressure in the nose. There were no clinically abnormal findings in the clinical laboratory measurements, vital sign assessments, electrocardiographic recordings, or the physical examination.

C. Conclusion

Three hours after the SC injection of HGH, there was a significant induction of IGF-1 that was sustained up to the 24-hour time point. The intranasal HGH control formulated without the CriticalSorb absorption enhancer had no effect on IGF-1 levels. However, a single

dose of CPO24 induced a significant increase in IGF-1 levels between 3 and 10 hours after dosing. There was no significant difference between the IGF-1 levels achieved after an SC injection and CPO24 at 10 hours after the dosing. Between 10 and 24 hours after a single dose of CPO24, the IGF-1 level slowly declined to baseline. When HGH was administered nasally without CriticalSorb, no IGF-1 inductions occurred and levels continually fell throughout the 24-hour period. The elevation in IGF-1 serum concentrations for each subject when treated with either the SC dose of HGH or CPO24 as a Biodose was highly significant compared with the intranasal administration of HGH alone without an absorption promoter.

The levels obtained after twice daily nasal dosing were the same as for SC injection of the HGH up to 19 hours after the first administration. It appears that for a given plasma level of HGH, intranasal dosing results in a greater induction of IGF-1 compared with an SC injection.

Achieving similar IGF-1 induction with lower serum GH levels has a potential to maintain efficacy, while reducing the risk of side effects because of the direct actions of HGH. By achieving similar IGF-1 levels with lower systemic exposure to HGH, CPO24 may mitigate this risk.

In conclusion, this group has developed a nasal spray formulation of HGH able to induce IGF-1 levels to a similar extent as that observed after SC injection.

III. INTRANASAL OXYTOCIN

A. Oxytocin, also known as Syntocinon Nasal Spray, is used to increase duration and strength of **contractions during labor**. It is also being actively investigated for many psychiatric conditions, including alcohol withdrawal, anorexia nervosa, posttraumatic stress disorder, autism, anxiety disorders, pain sensation, and schizophrenia.

B. The hormone oxytocin is also known for its widespread **effects on social processes**. Recent data from intranasal administration in humans have produced hope for its use as a therapeutic agent in autism, schizophrenia, and other disorders. This leap to human use, however, is occurring without previous animal studies of long-term oxytocin administration and with minimal knowledge of the neurobiologic mechanisms involved in the behavioral findings. Some research recently even suggests that long-term use of oxytocin may not

translate to positive effects. Research (by Dr. Karen Bales, Professor and Vice Chair of Psychology at the University of California) on prairie voles suggests that oxytocin treatment increased social behavior in male voles similar to some effects observed in humans. However, the long-term effects with male voles showed deficits in their typical behaviors. Her findings suggest caution in the long-term use of intranasal oxytocin in humans. “Special strategies will need to be studied more intensively if oxytocin is ever to become a long-term treatment for autism or schizophrenia,” said Dr. John Krystal, editor of *Biological Psychiatry.*

C. There are now hundreds of studies looking at the **effect of this hormone on the human brain**. One article suggested that one dose of oxytocin delivered in the form of nasal spray can make people nicer toward the ostracized, reduce marijuana cravings, p. 1050p. 1051and “enhance brain function” in autistic children, but this has not been confirmed or totally proven. Some doubt that nasal oxytocin even gets into the brain. Oxytocin is a peptide molecule, which means it cannot cross the blood–brain barrier and enter the central nervous system. Animal studies suggest that intranasal oxytocin might nonetheless get to the brain via some other route, perhaps along a nerve, but no one has directly tested this in humans. A paper from Bonn, Germany, states: “Elevated cerebrospinal fluid and blood concentrations of oxytocin were found following its intranasal administration in humans.” After 13 patients received intranasal oxytocin, a lumbar puncture was performed on them, the theory being that if the oxytocin enters the brain, it would certainly be in the CSF. The patients took either oxytocin or placebo nasal spray, and then oxytocin levels in the CSF were analyzed. In the group of three people who had an oxytocin intranasal spray 75 minutes before the spinal tap, oxytocin levels were higher than in the one person who had a placebo 75 minutes earlier. Therefore, with these tiny numbers, there is no scientific conclusion. Using medical lumbar puncture to validate nasal oxytocin in humans is not a bad idea, but obviously there needs to be higher numbers of patients to process this information. There is simply not enough data.

Intranasal Oxytocin (24 IU) reduced food intake in obese men

following an overnight fast. At the University of Tubingen, obese and normal weight men reduced food intake, but more so in normal subjects. These were small studies; therefore, long-term trials in larger numbers are needed to determine the clinical efficacy and safety of these observations.

IV. INTRANASAL GLUCAGON

A. Introduction

Hypoglycemia is obviously of great concern in patients with diabetes. Severe hypoglycemia can lead to a loss of consciousness or seizures, which makes treatment of hypoglycemia a high priority. It is estimated that 2% to 4% of deaths in type I diabetes in the world is secondary to hypoglycemia. It is even becoming more common in type II diabetics who are on insulin.

B. Clinical application

Severe hypoglycemia should be treated aggressively to prevent major complications. Currently, treatment for this problem outside of a hospital setting is limited to intramuscular (IM) glucagon, which requires reconstitution prior to administration. This, of course, can increase the chance for error. A randomized crossover noninferiority trial was conducted at eight clinical centers, enrolling 75 adults with type I diabetes with a mean age of 33 years and a median diabetes duration of 18 years. They matched two groups of volunteers—one received intranasal glucagon (3 mg) and the other received 1 mg of IM glucagon. The success of therapy was defined as increasing plasma glucose to greater than 90 mg/dL. Hypoglycemia was induced in the volunteer patients and was reversed by treatment with one of the two glucagon products within 5 minutes. The intranasal glucagon was administered by placing the device into the patient's nostril by simply pushing a plunger, by which the device releases the glucagon powder into the patient's nasal cavities. The glucagon is then absorbed in the nasal mucosa *without any need for inhalation by the patient*. It has been shown that the absorption of glucagon through the nasal cavity is not impacted by nasal congestion.

Intranasal glucagon successfully treated 74 of 75 patients, and IM glucagon was successful in 75 of 75. The one unsuccessful intranasal glucagon patient came close to meeting the success criteria, reaching a plasma glucose of 65 mg/dL after 30 minutes and had a further increase of 25 mg/dL in plasma after 40 minutes. The rise in blood

glucose in intranasal glucagon lagged 5 minutes behind IM glucagon, but this difference of 5 minutes is unlikely to be clinically significant because the patient's companion or family member has to reconstitute the IM glucagon before administration.

With the efficacy of intranasal glucagon being proved, this type of glucagon could replace IM glucagon as a standard of care. The ease of administration and p. 1051p. 1052accessibility makes it a much more practical solution for hypoglycemia. The ease of administration lacks the cumbersome and error-prone steps of IM injection, such as reconstitution and injection.

V. INTRANASAL THYROTROPIN-RELEASING HORMONE (TRH) FOR THE STIMULATION OF HYPOPHYSEAL AND THYROID RESERVES

Intranasal, IV, and oral TRH were compared in healthy volunteers. Intranasal administration of TRH leads to excellent stimulation of pituitary thyroid-stimulating hormone (TSH) secretion. TSH levels were significantly higher compared with IV TRH and lower than after oral TRH. As with IV TRH, peak TSH responses begin at 20 to 30 minutes, but the stimulatory effect is prolonged, and elevated TSH levels can be measured for up to 3 hours. Stimulation of T3 and free T4 at 3 hours is comparable in all the three administration forms of TRH. The practical advantages of the intranasal route are that no IV injections are necessary, overnight fasting is not required, and the duration of tests is short (30 minutes, in contrast to 3 hours in the oral tests).

VI. CALCITONIN

Intranasal calcitonin (calcitonin-salmon) is used to treat hypercalcemia arising out of malignancy, Paget disease of the bone, postmenopausal and steroid-induced osteoporosis, phantom limb pain, and other metabolic bone abnormalities. It is available as Rockbon, Fortical, and Miacalcin Nasal Spray.

VII. DESMOPRESSIN

Desmopressin is a medication for the treatment of diabetes insipidus, which is available for nasal and oral administration. The bioavailability of the commercial tablet is 0.1%, whereas that of the nasal spray is 3% to 5%, according to the Summary of Product Characteristics.

VIII. GONADOTROPIN-RELEASING HORMONE ANALOGS

Nasal gonadotropin-releasing hormone analogs, such as Nafarelin and Buserelin, are used for the treatment of anovulatory fertility, hypogonadotropic hypogonadism, delayed puberty, and cryptorchidism.

IX. INTRANASAL INSULIN

Intranasal insulin delivery has been widely investigated as an alternative to SC injection for the treatment of diabetes. The pharmacokinetic profile of intranasal insulin is similar to that obtained by IV injection and, in contrast to SC insulin delivery, bears close resemblance to the “pulsatile” pattern of endogenous insulin secretion during mealtimes. The literature suggests that intranasal insulin therapy has considerable potential for controlling postprandial hyperglycemia in the treatment of both insulin-dependent diabetes mellitus and noninsulin-dependent diabetes mellitus.

X. INTRANASAL STEROIDS

A. Introduction

Intranasal corticosteroids (INCs) are cortisone-like medicines. They belong to the family of medicine called steroids. These medicines are sprayed or inhaled into the nose to help relieve stuffiness, irritation, and discomfort of allergies, and other nasal problems. They are also used to prevent nasal polyps from growing back after they have been removed by surgery. Corticosteroids work on multiple cell types and mediators, such as mast cells, macrophages, and leukotrienes to control inflammation.

B. Effects on the endocrine system

Even though these products have been used for over three decades, concerns remain that they may reach the systemic circulation in sufficient concentration to produce adverse effects, but there is no absolute evidence that supports this claim. Some of these alleged side effects include growth inhibition induced by hypothalamus–pituitary–adrenal (HPA) axis suppression, decreased bone mineral density, myopathy, cataracts, glaucoma, hypertension, hyperglycemia, and thin or easily bruised skin. Many authors feel that these are misconceptions, perhaps found with some of the p. 1052p. 1053older intranasal corticosteroids and prolonged use of INCs in a broader patient population, raising concern regarding the long-term

effects of these agents.

C. Effects on the HPA axis

The primary action of corticosteroids on the HPA axis is a negative feedback effect caused by suppression of corticotropin-releasing hormone and adrenocorticotropic hormone levels, resulting in lower cortisol secretion. A large number of short- and long-term studies, however, in adults and children have found no significant impact on HPA axis function with the newer INC agents.

D. Effects on statural growth in children

Systemic corticosteroids are known to exert a suppressive effect on growth through several mechanisms, including decreased release of GH, inhibition of IGF-1 activity, downregulation of GH receptor expression, and suppression of collagen synthesis in adrenal androgen production. Overall, studies have shown that most INCs administered at recommended doses are not associated with impairment of growth or final adult height. Growth suppression, however, has been reported with long-term use of some INCs when recommended doses were exceeded.

E. Effects on bone density

Systemic corticosteroids exert their negative effect on bone metabolism by altering both calcium homeostasis (osteoblastic and osteoclastic activity) and sex hormone production. On the basis of the lack of significant changes in biochemical markers of bone turnover in several studies and the lack of a significant effect on bone density in a 1-year study, these INC agents do not appear to be associated with reduction in bone mineral density or osteoporosis.

F. Ocular effects

Some papers have reported a possible association between INCs and either increased intraocular pressure or cataract formation. However, several recent long-term studies have demonstrated no evidence of ocular changes with newer INCs.

G. Use in pregnancy

On the basis of their extremely limited systemic absorption, all second-generation INCs are generally considered relatively safe to use in pregnancy, and no data indicate an association between INCs and congenital malformations. The rating in pregnancy drugs for INCs is category C, as opposed to A or B, because sufficient data in pregnant women are lacking and animal studies have either not been performed or revealed adverse effects.

XI. INTRANASAL FEMALE HORMONES

The intranasal route has been evaluated for the administration of menopausal hormones and seems to be a viable alternative for drugs that are poorly absorbed after ingestion by avoiding hepatic first-pass elimination. Early studies demonstrate that it is safe, effective, and acceptable to postmenopausal women. In addition, the nasal administration of a combination of estradiol and progesterone would seem to be an attractive way to deliver hormones to nonhysterectomized postmenopausal women. Providing alternate routes of administration may also enhance compliance.

A pilot study was done to investigate the pharmacokinetics and acceptability of an intranasal 17 *β*-estradiol/progesterone formulation. It contained dimethyl-*β*-cyclodextrin as a solubilizer and absorption enhancer of the steroid hormones. It was performed in four oophorectomized and hysterectomized patients utilizing a nasal delivery of 0.34 mg estradiol and 0.85 mg progesterone. Concentration–time curves of progesterone, estradiol, and its metabolite estrone were established. Rapid absorption of progesterone and estradiol was demonstrated. Comparison with an earlier reported study in which only estradiol was administered shows that the addition of progesterone does not alter the pharmacokinetics of estradiol. This formulation was well accepted by the four patients studied and no adverse effects were noted.

XII. INTRANASAL TESTOSTERONE

A. Purpose

This product is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone, such as primary hypogonadism, p. 1053p. 1054cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals.

Hypogonadotropic hypogonadism can be idiopathic or secondary to gonadotropin or luteinizing hormone–releasing hormone deficiency. Causes include pituitary hypothalamic injury from tumors, trauma, or radiation. Men with such conditions have low testosterone serum concentrations, and gonadotropins are in the normal to low range.

B. Product

The Food and Drug Administration has approved the first-ever nasal testosterone replacement therapy (Natesto Nasal Gel, Trimel Pharmaceuticals). This product is approved for adult males with conditions associated with deficiency or the absence of endogenous testosterone as noted above. The product is self-administered into the nostrils via a metered dose pump applicator. One pump actuation delivers 5.5 mg of testosterone, and the recommended dose is 11 mg three times daily for a total of 33 mg/day. Because the gel is applied to the inner lining of the nostril, there should be little chance of transferring testosterone and causing higher than normal testosterone concentrations in women or children who come into close physical contact with a patient using the intranasal gel. It is not clear whether men will approve of a regimen that involves three times daily application.

Adverse reactions occurring in 3% or more of subjects in clinical trials were an increase in prostate-specific antigen, headache, rhinorrhea, epistaxis, nasal discomfort, nasopharyngitis, bronchitis, upper respiratory tract infection, sinusitis, and nasal scab.

It is important to note, but it is not clear what the significance is, that the brain testosterone levels will be much higher with intranasal testosterone gel than with other testosterone treatments. A study published in 2009 using mice showed brain levels of testosterone that were about twice as high in mice that received intranasal testosterone gel than in mice that received IV testosterone.

XIII. CONCLUSION

The safety profiles of INCs have been well established over 30 years of use. Safety has been particularly well demonstrated for newer agents.

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89 The Female Athlete

Stéphane Bermon

Female participation in sports rose dramatically in the 20th century, especially in the last quarter, reflecting changes in modern societies that emphasized gender parity, better lifestyle, and prevention of physical inactivity–related diseases. Although the level of participation and performance still varies greatly by country and by sport, women usually do train and compete on equal terms at the same level as men. However, regular and intense physical exercise may alter adolescent and young female athletes' endocrine functions and metabolisms.

I. POTENTIAL ENDOCRINE DISORDERS IN HIGH-LEVEL FEMALE ATHLETES

A. The gonadal axis

1. **Pubertal athletes.** In pubertal athletes, the **menarche is frequently delayed by 2 to 3 years**. This phenomenon does not seem to have genetic origin, because it is not observed in their mother or sisters. However, in some specific sports like ice skating, dancing, and gymnastics, where performance is favored by late maturation, a recruitment bias cannot be ruled out. Pubertal female gymnasts or ballet dancers do not show a significant rise in estradiol levels. This finding is associated with lower basal and stimulated secretion of gonadotropins after a gonadotropin-releasing hormone (GnRH) stimulation test. In contrast, 17-α-hydroxy-progesterone, dehydroepiandrosterone sulfate, and prolactin usually demonstrate plasma values within the normal range for the age.
2. **Adult athletes.** Intense physical training, especially when associated with low energy intakes and secondary low body fat mass can induce menstrual and neuroendocrine dysfunctions in young adult females (see section II). Moreover, the age of recalled menarche is positively correlated with training intensity, the number of years of training before menarche, and the age at which training was started. Secondary amenorrhea refers to an absence of three consecutive cycles post menarche. The prevalence is

estimated in collegiate women from 2% to 5% and as high as 69% in dancers and 65% in long-distance runners. Amenorrheic athletes are also thinner and present more frequent suppression or disorganization of luteinizing hormone (LH) pulsatility than eumenorrheic athletes do. LH secretion is also inversely associated with ghrelin and positively with leptin values. Most of these biologic and clinical features are **reversible** when physical training load is decreased, and eating habits and optimal weight are restored.

B. The adipokines

1. **Leptin.** Leptin is a polypeptide produced by the white adipose tissue. It has anorexigenic properties and regulates body weight by modulating feeding behavior. Energy deficit more than physical exercise alone controls leptin secretion. Leptin also has a permissive role in pubertal development and fertility. Serum leptin concentration is positively associated with the activity of the hypothalamic–pituitary–gonadal axis and LH pulsatility.

   In ballet dancers, gymnasts, soccer, and basketball players, leptin is positively correlated with fat mass and body mass index and peaks at pubertal stage V. Because of reduced fat mass, gymnasts and ballet dancers often show values below the normal range. Although a direct influence of leptin on the menstrual cycle has not been fully proven, it is likely that the reproductive system is sensitive to relative changes of leptin concentration rather than a critical concentration of this adipokine.

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2. **Adiponectin.** Adiponectin is produced by fat tissue and its circulation is negatively correlated with body fat. It shows anti-inflammatory and antiatherogenic effects and also enhances insulin action. Adiponectin is unchanged by puberty or by a single exercise bout. After the onset of puberty, adiponectin increases as a result of high training stress, and circulating adiponectin can be used as a marker of energy deprivation in elite female athletes.

C. Gastrointestinal peptides

1. **Ghrelin.** Ghrelin is an orexigenic peptide secreted from the stomach, which reflects energy status, and its concentration is negatively correlated with weight and fat mass. Ghrelin basal values are elevated in female adolescents and women with eating

disorders and amenorrhea, whether they are athletes or not. Ghrelin levels contribute to amenorrhea in athletes by altering the GnRH and LH pulsatility. Ghrelin concentration and also its pulsatile secretion parameters attest to a negative energy balance and are higher in amenorrheic athletes than in eumenorrheic or untrained pairs. Ghrelin and leptin independently contribute to the variability in LH pulsatility and secretion. An increase in energy intake in amenorrheic athletes induces a decrease in ghrelin concentration, associated with changes in body weight and resumption of menses.

2. **Peptide YY (PYY).** PYY is an appetite-suppressing hormone that is released from the L cells of the distal gut within 15 minutes of food ingestion and remains elevated for 90 minutes following a meal. PYY has been reported to regulate energy expenditure, and it has been found to be higher in amenorrheic female athletes when compared with eumenorrheic athletes and sedentary controls. PYY secretion, as well as appetite-suppression effect, seems to be positively linked with acute exercise intensity.

D. The somatotropic axis

Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) secretions are not modified by the menstrual cycle. Amenorrhea increases GH half-life and the number of secretory bursts, but amenorrheic athletes show a reduction of GH secretion following acute exercise. Oral contraceptive pill (OCP) changes GH secretion toward a pattern of smaller peaks at a higher frequency. Exercise intensity above 40% of $VO_{2\ max}$, more than exercise duration, stimulates GH secretion. Acute and chronic effects of exercise on the circulating IGF-I have yielded inconsistent results. However, caloric restriction and **negative energy balance reduce serum IGF-1** in gymnasts, ballet dancers, and runners.

E. The adrenal axis

At rest, **hypercortisolemia**, indicating an activation of the hypothalamic–pituitary–adrenal axis, is frequently reported in adolescent and young adult female athletes and ballet dancers with normal menstrual cycles and, to a greater degree, in amenorrheic athletes. However, when submitted to acute intense exercise, amenorrheic athletes show blunted cortisol response when compared with eumenorrheic athletes. Under the effect of intense training, diurnal variations of cortisol are almost abolished, and this

phenomenon is aggravated by chronic energy deficit. This mechanism is centrally driven by elevated corticotrophin-releasing factor concentration and contributes to hypercortisolemia and to the inhibition of GnRH pulsatile pattern observed in chronic energy-deficit female athletes.

F. The thyroid axis

A female athlete may show reduced activity of the hypothalamic–pituitary–thyroid axis as shown by a decrease in total T3 (TT3) concentration. **TT3 is a marker of energy status**. Amenorrheic athletes show frequent suppression of the thyroid axis when compared with eumenorrheic or sedentary peers. During such times, thyroid-stimulating hormone (TSH) and free T4 remain within the normal range and only TT3 is decreased. As a consequence, the resting metabolic rate and subsequently leptin concentrations can be decreased. When caloric restriction–induced amenorrhea disappears, resumption of menses is associated with an increase in fasting concentration of TT3. Although they do not affect the underlying causes of the amenorrhea in athletes (i.e., energy deficit), OCP increases TT3 values to within the normal range and may, therefore, be clinically helpful.

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II. THE RELATIVE ENERGY DEFICIENCY IN SPORT

A. Definition

The syndrome of relative energy deficiency in sport (RED-S) refers to impaired physiologic functions including, but not limited to, metabolic rate, menstrual function, bone health, immunity, protein synthesis, and cardiovascular health caused by a relative energy deficiency. It is a more comprehensive term for the condition previously known as “The Female Athlete Triad.”

B. Causes

The underlying problem of RED-S is an **energy imbalance (energy deficit)** leading to an inability to support the range of body functions involved in optimal health and athletic performance. In the case of athletes, energy availability (EA) is the amount of energy remaining to support all other body functions after the energy expended in exercise and sporting activities is removed from energy intake. In RED-S, the low EA causes adjustments to the body system

to reduce energy expenditure, leading to disruption of an array of hormonal, metabolic, and functional characteristics. Various forms of eating disorders are often responsible for this low EA.

1. **Disordered eating (DE)**

   DE covers a large spectrum of eating and exercise behaviors such as occasional or repetitive short-duration restrictive diets (<30 kcal/kg fat free mass [FFM]/day), anorexia nervosa, bulimia nervosa, binge eating disorder, eating disorder not otherwise specified (see *DSM-5* from the American Psychiatric Association), distorted body image, weight fluctuations, medical complications, and fluctuating athletic performance.

   The **prevalence of DE is about 20% and 13% among adult and adolescent female elite athletes, respectively**. It may differ significantly among sports. The most affected sports are those requiring a strict weight control for aesthetic, performance, or weight classification purposes such as **dancing, ice skating, rhythmic and artistic gymnastics, diving, endurance and long-distance running, long-distance triathlon, and combat sports**.

   The pathogenesis of eating disorders also includes cultural, familial, and genetic/biochemical factors, as well as personality factors, frequent weight cycling, and early start of sport-specific training, overtraining, recurrent and nonhealing injuries, and inappropriate coaching or family behaviors.

2. **Menstrual disorders and hormonal imbalance**

   RED-S is caused and associated with menstrual disorders. These disorders may vary from subtle menstrual dysfunction, such as very light bleeding, mildly extended menstrual interval, and premenstrual and postmenstrual spotting to oligomenorrhea and amenorrhea. Oligomenorrhea is defined as a cycle length >45 days. Primary amenorrhea is defined as no menarche by 15 years of age. In collegiate athletes, it was found to be 7% overall, and up to 22% in cheerleading, diving, and gymnastics. Marked reduction in EA disrupts the LH pulsatility by affecting the **GnRH secretion profile** which subsequently alters the menstrual cycle, ultimately completing a functional hypothalamic amenorrhea (FHA). FHA is often associated with inadequately low body fat stores and altered hormonal profiles:

   a. Increased serum CRH and cortisol

b. Low TT3
c. Elevated nighttime serum GH levels
d. Low-serum insulin and IGF-1
e. Increased insulin sensitivity
f. Lower 24-hour prolactin levels
g. Profound hypoestrogenism
h. Reduced kisspeptin level
i. Increased peptide YY level
j. Elevated ghrelin level
k. Lower leptin level
l. Elevated β-endorphin production under CRH control
m. Higher episodic release of allopregnanolone, a neurosteroid acting as an endogenous modulator of excitability of the central nervous system.

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C. Health consequences

The health consequences of RED-S are summarized in Table 89-1.

D. Diagnosis

Diagnosis of RED-S is sometimes challenging because its symptomatology can be subtle. Early diagnosis is of utmost importance in order to prevent long-term health consequences and maintains peek athletic performance in elite female athletes.

RED-S syndrome should be suspected when a female athlete presents with DE, abnormal weight loss, a lack of normal growth and development, menstrual dysfunction, recurrent injuries and illnesses, decreased performance, or mood changes.

1. Calculation of EA

Because low EA plays a pivotal role in RED-S onset, calculation of EA is helpful in diagnosing RED-S. EA is normalized by FFM and calculated as follows:

$$\text{EA (kcal/kg FFM/day)} = (\text{EI (kcal/day)} - \text{EEE (kcal/day)})/\text{kg FFM}$$

where EI is energy intake and EEE is exercise energy expenditure.

EI can be assessed by a dietician or a nutritionist or by the patient herself using either retrospective (recall) or prospective (written or electronic food diary) methods. EEE is usually assessed by an exercise log and tables of energy expenditure associated with

sports/exercise activities and/or by collecting data through p. 1058p. 1059modern sports technology (connected sports devices such as heart rate monitors, pedometers, tridimensional accelerometers, or power meters). FFM can be quantified by dual-energy x-ray absorptiometry (DXA), bioelectrical impedance analysis, or anthropometric (skin fold thickness and hydrodensitometry) measurements.

TABLE 89-1 Health Consequences and Main Mechanisms of RED-S

Organs or function	Health consequences	Mechanisms
Central nervous system	Stress Depression Anxiety Chronic fatigue	Hypoestrogenism HPA axis hyperactivation and hypercortisolemia
Nutrition—metabolism	Metabolic abnormalities Reduced basal and exercise metabolic rates	Micro–macro nutrients deficiency Iron-deficit anemia Reduced glucose utilization Reduced fat stores mobilization
Cardiovascular system	Increased risk associated with unfavorable lipid profile and endothelial dysfunction	Hypoestrogenism Impaired NO activity Impaired autonomic function Renin angiotensin activation
Reproductive system	Infertility Unexpected pregnancy Sexual dysfunction	Functional hypothalamic amenorrhea
Immune system	Increased risk of infection or illnesses	Stress-related immunosuppression
Skeletal system	Reduced bone mass (likely irreversible) Stress fracture	Hypoestrogenism Increased catecholamines and cortisol Low EA Low protein intakes Reduced GH and IGF-1 levels Low vitamin D status Low calcium intakes

		Compulsive physical activity
Digestive system	Esophagitis Esophageal perforation Dehydration	Vomiting Fasting Diuretics and laxative abuse

EA, energy availability; GH, growth hormone; HPA, hypothalamic–pituitary–adrenal; IGF, insulin-like growth factor; NO, nitric oxide; RED-S, relative energy deficiency in sport.

In healthy adults, EA should be measured around a value of 45 kcal/kg FFM/day. Athletes with an RED-S syndrome often display EA values lower than 30 kcal/kg FFM/day, which is a threshold to menstrual dysfunction and bone status impairment.

2. Eating disorders

Presenting signs and symptoms are presented in Table 89-2.

Questionnaires such as the Brief Eating Disorder in Athletes Questionnaire, the Eating Disorder Examination Questionnaire, or the Eating Disorder Examination interview can be used.

TABLE 89-2 Presenting Signs and Symptoms in Eating Disorders

System	Signs and symptoms	
General	Marked or sudden weight loss, gain, or fluctuation Failure to gain expected weight in child/adolescent who is still growing and developing	Hypothermia, cold intolerance Fatigue
Oral/dental and throat	Oral trauma/lacerations Dental erosion or caries	Perimolysis (decalcification of the teeth due to acid exposure) Parotid enlargement Recurrent sore throats
Gastrointestinal	Epigastric discomfort and/or abdominal pain Early satiety and delayed gastric emptying Gastroesophageal reflux	Hematemesis, hemorrhoids, rectal fissures, and rectal prolapse Constipation, diarrhea
Endocrine	Irregular or missed menses Loss of libido	Infertility
Neuropsychiatric	Memory loss/poor concentration Insomnia Depression, anxiety Obsessive compulsive behavior	Self-harm Suicidal ideation/attempt Seizures

Cardiorespiratory	Chest pain Palpitations Hypotension Bradycardia	Other cardiac arrhythmias Shortness of breath Edema
Musculoskeletal	Low bone mineral density	Stress fractures Fragility fractures
Dermatologic	Lanugo hair Hair loss Yellowish skin discoloration Calluses or scars on the dorsum of the hand (Russell sign)	Poor skin healing Evidence of self-harm (superficial lacerations in various stages of healing)
Genitourinary and renal	Electrolyte disturbances	Urinary abnormalities (both retention and frequency)

People at normal weight may also have an eating disorder. Do not rely on weight or body mass index alone to diagnose or rule out an eating disorder. Awareness of the broad array of signs and symptoms that may be present can facilitate early identification of patients struggling with an eating disorder. Reprinted with permission from Joy E, Kussman A, Nattiv A. 2016 update on eating disorders in athletes: a comprehensive narrative review with a focus on clinical assessment and management. *Br J Sports Med* 2016;50:154–162.

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Laboratory evaluation should include basic blood chemistry: electrolytes, renal function (blood urea nitrogen and creatinine); calcium, complete blood count serum; liver function tests; TSH; complete and differential blood counts, platelets, and urinalysis. When malnourishment is suspected, iron, vitamin D, vitamin B_{12}, magnesium, and phosphorus status should be added.

3. Menstrual dysfunction

Because FHA is a diagnosis of exclusion, amenorrhea should be, in each case, differentiated from other forms of primary or secondary amenorrhea. A key diagnostic tool is a **GnRH stimulation test**, which in the case of FHA shows a positive response of the gonadotropins to exogenous GnRH. This test distinguishes hypothalamic dysfunction from pituitary diseases, where hypogonadism is also characteristic. Although rare in athletes, amenorrhea of genetic origin (Kallman and Prader–Willi syndromes) and other rare syndromes with idiopathic hypogonadotropic hypogonadism must be ruled out. To rule out organic diseases of the hypothalamic area (neoplasms, sarcoidosis, tuberculosis, parasitoids, and other infiltrating lesions), imaging

evaluation might be helpful.

Medical history of menstrual dysfunction should include a menstrual history assessing age of menarche, regularity of menses, use of medications, the presence of other health issues, and a family menstrual history.

Physical examination includes assessment of anthropometry, pubertal stage, signs of eating disorders, and secondary causes of amenorrhea. Pelvic examination may reveal pregnancy or hypoestrogen-related vaginal atrophy.

Laboratory evaluation may not accurately predict and help in diagnosing RED-S. Numerous studies in female athletes have failed to find clear thresholds or associations between clinical features of low EA and objective measures of metabolic hormones. One should rather consider hormonal and endocrine profiles, as described in the Section II.B.2. of the present Chapter. However, measurement of hemoglobin, LH, FSH, prolactin, estradiol, T_4, TSH, pregnancy, and androgen profiles may be indicated. More extensive testing might include a pelvic ultrasound and endometrial sampling to rule out other gynecological pathologies.

4. **Bone status**

The minimal serum estradiol level, which has a positive impact on bone metabolism, is 40 to 50 pg/mL. Serum estradiol levels in patients with FHA are often below 20 pg/mL, putting them at higher risk of developing osteoporosis. According to the International Society for Clinical Densitometry, amenorrhea related to **hypoestrogenism lasting 6 months** is the indication to perform a DXA of the spinal column (whole body; head excluded in adolescent athlete with possible RED-S). DXA measures bone mineral density (BMD) and calculates *Z*-scores. High-impact physical activity increases BMD in adult women as well as in prepubertal children (4% to 5% gain in bone accrual). Unfortunately, menstrual dysfunction in RED-S female athletes may override the beneficial effects of physical activity on bone. One can expect amenorrheic athletes to have 10% to 20% less lumbar spine BMD than eumenorrheic athletes. Because athletes participating in weight-bearing activities typically have higher BMD than nonathletes, the American College of Sports Medicine defines “low BMD” in an athlete as a *Z*-score between −1 and −2

along with clinical risk factors for fracture (decreased EA, amenorrhea, and history of stress fractures). It considers **“osteoporosis” in an athlete to be a BMD Z-score ≤–2.0** with clinical risk factors for fracture. The recommended interval to reassess BMD via DXA scan for athletes at risk, or who are being treated for low BMD, is 12 months in adults and a minimum of 6 months in adolescents.

E. Treatment

The treatment of RED-S has the following four main components:

1. **Correction of low EA**

   Correction of a low EA should be achieved through an **increase in EI, a reduction in the amount of exercise and training, or a combination of both**. From a practical point of view, the daily EI should be increased by approximately 300 p. 1060p. 1061to 600 kcal (1.2 to 2.4 MJ/day). Female athletes who wish to lose weight and body fat should follow diet and exercise regimens that provide EA of 30 to 45 kcal/kg FFM/day until they reach their target.

2. **Restoration of menstrual function**

   Weight gain and adequate protein and carbohydrate intakes help recovery of normal menstrual function through restored liver glycogen stores which, in turn, increase LH pulsatility. Prescription of **OCP remains a controversial issue** because the delivered dose of estrogens is likely to be ineffective in restoring bone mass, while masking the symptoms of menstrual dysfunction. Although OCP helps female athletes “control” the occurrence of menstrual periods (mainly during competition), elite athletes are sometimes reluctant to use it because it **decreases the free serum testosterone (by increasing sex hormone–binding globulin (SHBG) concentration)**.

3. **Improving bone status**

   Weight gain and the restoration of energy is the most effective way to improve the mineralization of trabecular bone and growth of cortical bone. However, recovery of bone micro architecture is sometimes impossible to fully achieve. Because

mechanical loading and high-impact sports positively affect BMD and bone geometry, it is recommended, whenever possible to implement at least 2 to 3 days/week resistance training or impact loading programs for athletes in nonweight-bearing sports and/or those with decreased BMD. The diet should include 1 500 mg/day of calcium and 1 500 to 2 000 IU/day of vitamin D. Biphosphonates, raloxifen, teriperatide, and calcitonin are not approved for use in premenopausal women and should not be prescribed.

4. Improving mental health

An athlete with an RED-S syndrome should consult a **mental health specialist** for both assessment and therapeutic purposes. The frequency, type, and duration of the psychological treatment depend on the severity and duration of the eating disorders. Treatment may combine cognitive behavioral therapy, dialectical behavior therapy, or family-based therapy. Pharmacotherapy (mostly antidepressants) may be prescribed to treat associated anxiety, depression, or associated psychiatric conditions.

F. Participation in sports

A risk assessment model is presented in Table 89-3.

III. THE HYPERANDROGENIC FEMALE ATHLETE

A. Definition

Hyperandrogenism (HA) is a medical condition characterized by excessive levels of androgenic hormones in the body and the associated effects of these increased androgens levels. It can be of exogenous or endogenous origin.

B. HA from exogenous origin

1. General principles

In female athletes, abuse of anabolic–androgenic steroids (AASs) for the purpose of doping may result in HA. The magnitude of the **virilization** syndrome associated with this HA is positively linked to the **amount and duration** of AAS consumption.

The main reasons for a female athlete to use banned AAS are increased muscle mass and strength, red blood cell mass, shortened recovery time between workouts or competitions, and increased aggressiveness. AAS are drugs banned both by most of the sports governing bodies, including the International Olympic Committee, and by the World Anti-Doping Agency.

2. Prevalence of AAS abuse

Although the exact prevalence of anabolic steroid use is not known, several studies reported a lifetime prevalence of use around 2% in US female athletes. In late 2017, 94 among the 180 elite female athletes who committed an antidoping rule violation under athletics rules were AAS users.

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TABLE 89-3 RED-S Risk Assessment Model for Sport Participation

High risk: no start red light	Moderate risk: caution yellow light	Low risk: green light
Anorexia nervosa and other serious eating disorders	Prolonged abnormally low body fat measured by DXA or anthropometry Substantial weight loss (5%–10% body mass in 1 mo) Attenuation of expected growth and development in adolescent athlete	Healthy eating habits with appropriate EA
Other serious medical (psychological and physiologic) conditions related to low EA	Abnormal menstrual cycle: functional hypothalamic amenorrhea >6 mo. Menarche >16 yr Reduced BMD (either from last measurement or *Z*-score < −1 SD). History of one or more stress fractures associated with menstrual dysfunction and/or low EA	Normal hormonal and metabolic function Healthy BMD as expected for sport, age, and ethnicity Healthy musculoskeletal system
Extreme weight loss techniques leading to dehydration-induced hemodynamic instability and other life-threatening conditions	Athletes with physical/psychological complications related to low EA/disordered eating—ECG abnormalities—laboratory abnormalities Prolonged relative energy deficiency Disordered eating behavior negatively affecting other team members Lack of progress in treatment and/or noncompliance	

BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; EA, energy availability; ECG, electrocardiography; RED-S, relative energy deficiency in sport; SD, standard deviation.

Data from Mountjoy M, Sundgot-Borgen J, Burke L, et al. RED-S CAT. Relative Energy Deficiency in Sport (RED-S) Clinical Assessment Tool (CAT). *Br J Sports Med* 2015;49:421–423.

3. **Different types of AAS preparations**
   The main oral and intramuscular AAS preparations used by doped athletes are the following:
   Oral preparations. Androstenedione, dihydrotestosterone, fluoxymesterone, mesterolone, methandienone, methyltestosterone, mibolerone, oxandrolone, oxymetholone, stanozolol, and testosterone undecanoate. Many oral preparations of AAS show a common feature of **alkylation in the 17-a position** of the androgen molecule. This chemical characteristic makes these AAS potentially severely **liver toxic**.
   Intramuscular preparations. Boldenone undecylenate, methenolone enanthate, nandrolone decanoate or phenpropionate, testosterone (cypionate, enanthate, or propionate), and trenbolone acetate.
4. **Clinical features and side effects of AAS abuse (Table 89-4).**
   Till date, the hypothesis of an increased risk of breast cancer in women abusing AAS has not been supported by epidemiologic studies or case reports.

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TABLE 89-4 Clinical Features and Side Effects of AASs Abuse

Organs and functions	Clinical features or side effects
Reproductive system	Suppression of gonadotropins Anovulation and amenorrhea Dysmenorrhea Infertility Breast atrophy Clitoromegaly (likely irreversible) Virilization of a female fetus if AAS during pregnancy
Central nervous system	Aggressiveness and hostility Mood changes and depression Irritability, personality changes, and psychosis. AAS use addiction and dysmorphophobia
Dermatologic system	Acne and oily skin Seborrhea

	Striae Hirsutism and alopecia (male pattern balding)
Musculoskeletal system	Muscle hypertrophy Tendon and muscle injuries (excessive tensile load) Premature fusion of growth plates (adolescent)
Cardiovascular system	Increased hemoglobin concentration Venous thromboembolism Hypertrophic cardiomyopathy High blood pressure, stroke Myocardial infarction
Metabolism	Increased protein anabolism Reduced adiposity
Digestive system	Altered liver function (17-methylated steroids) Peliosis hepatis (blood-filled cavities throughout the liver) Hepatomegaly Cholestatic jaundice Increased risk of hepatic tumor
Miscellaneous	Raucous voice (likely irreversible) and hoarseness

AAS, anabolic–androgenic steroid.

5. **Laboratory findings**

   Although not found in a systematic way, laboratory findings may show:

   a. Evidence of a reduced GnRH pulsatility
   b. Low LH concentration in blood and urine
   c. Serum testosterone concentration above 5 nmol/L
   d. Reduced 17-β estradiol serum concentration
   e. Reduced SHBG serum concentration
   f. Decreased glucose tolerance
   g. Dyslipidemia
   h. Increased conjugated, unconjugated, and total bilirubin levels
   i. Increased transaminases levels

   It can take weeks or months to complete recovery of the axis. After cessation of AAS abuse in women, **it can take up to 20 months for serum testosterone concentration to return to normal level** (below 3 nmol/L).

6. **Differential diagnosis of AAS abuse**

   Because physical activities and athletic training often result in reproductive dysfunctions due to disruption of the GnRH pulse generator, it is difficult to disentangle the effects of exhaustive

sports activities and AAS abuse. In such p. 1063p. 1064situations, clinical features are sometimes insufficient, and one should refer to anamnestic data and results obtained from paraclinical and imaging investigations.

C. HA from endogenous origin

1. General principles

Moderate HA is not uncommon in women and is usually linked to hormonal dysfunction. Its consequences will have different expressions according to the age of the patient and the date of onset. Polycystic ovarian syndrome (PCOS) is the most common diagnosis, often associated with menstrual disturbances and infertility. However, serious underlying medical conditions should always be suspected if the onset of symptoms is fast and/or intense. Early diagnosis of more severe HA conditions, such as a disorder of sex development (DSD), can often help improve these conditions, avoid metabolic disorders, and possibly reduce the risk of later cardiovascular events and gynecological cancers. Although rare, the possibility of an androgen-secreting tumor should always be investigated. The exogenous administration of doping agents (anabolic steroids) should also be excluded by performing urinary antidoping tests.

2. Evaluation

Investigation requires careful history-taking (Table 89-5), clinical examination (Table 89-6), and paraclinical investigations (Table 89-7) to ensure accurate diagnosis and appropriate treatment. The development of HA depends on both an excessively **high level of circulating androgen** and **normal androgen sensitivity** of the receptor tissues. For instance, female athletes with p. 1064p. 1065complete androgen insensitivity syndrome show a very high level of circulating testosterone, but are not virilized because their androgen receptors are not functional. They are, however, at higher risk of developing gonadal tumor. As androgen receptor sensitivity is not quantifiable on a routine basis, clinicians should look for signs of virilization (Table 89-6) that

attest to the androgen receptor functionality.

TABLE 89-5 History-taking in the Context of an Athlete with Suspected Endogenous HA

Family History
Are the parents related to each other? (If yes, description)
Number of siblings (male/female)
Any family members with similar symptoms of HA? (If yes, description)
Any family members with fertility problems/childless marriages?
Was the mother virilized during pregnancy?
Ethnic background (Caucasian, African, Asian, etc.)

Birth History
Birth weight and length
Ambiguous genitalia at birth? (If so, description)

Pubertal History
Age at start of: pubic hair, breast buds, acne, deepening of voice, menstruation (menarche)
Menstruation characteristics
Date of last menstruation

Medical History
Previous illnesses and operations
Any pregnancies?
Ever hospitalized? Why?

Medication
Ever had long-term medication? If so, brand name? Why was this prescribed?
Ever had hormonal medication? If so, brand name? Why was this prescribed?
Ever used oral contraceptives? If so, brand name?
Ongoing oral contraception?
Any ongoing medication? If so, brand name? Why was this prescribed?

Cosmetic
Do you ever remove body or facial hair? If so, how often? How much? By what method(s)?

HA, hyperandrogenism.

TABLE 89-6 Physical Examination in the Context of an Athlete with Suspected Endogenous HA

General Physical Examination
Height, weight, BMI, sitting height
Body build, biacromial breadths (distance between the most lateral points of the two acromion processes) and biiliac breadth (distance between the outer edges of the upper iliac bones)
Adam's apple, **deep voice?**

Skin
Body hair (use Ferriman and Gallwey score: biologic investigations should be performed for a score over 16). Receding frontal hairline? Loss of scalp hair?
Facial hair (Shaving? How often?)

Oily skin on face? Abnormal pigmentation? Cutaneous striae? **Circulation** Blood pressure, pulse rate **Abdomen** Palpable masses? **Pubertal Signs** Breast (indicate Tanner–Whitehouse stage I–V) Pubic hair (indicate Tanner–Whitehouse stage I–V) Midline pubic hair extending toward umbilicus? **Genitalia** (to be performed by gynecologist–endocrinologist or pediatrician–endocrinologist for girls of <15 yr) Detailed measurements and vaginal palpation (may require general anesthesia, especially if the patient is young) **Clitoral enlargement? Length and width?** Abnormal size of labia minora or majora? Posterior fusion of labia? Anogenital distance. Are any lumps palpable in labia or in inguinal canals? Is uterus or prostate palpable per rectum?
HA, hyperandrogenism; BMI, body mass index.

3. Main diagnosis

PCOS is the most frequent medical condition reported in the female athlete with endogenous HA. For instance, PCOS has been shown to be overrepresented (up to 37%) in Swedish Olympic female athletes not using OCP. This recruitment bias is explained by the increased level of circulating androgens that confers a competitive advantage to these women. This recruitment bias also exists for 46 XY DSD because we reported 46 XY DSD prevalence at 7.1/1 000 in an elite female athletic population (140 times higher than the general population). The prevalence of hyperandrogenic 46 XY DSD athletes may also vary according to countries because diagnosis and treatment implementation at birth and during childhood largely rely on locally available medical expertise.

4. Treatment

For this topic, please refer to the chapters 26, 28, and 30 of this book focusing on PCOS and DSD.

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TABLE 89-7 Endogenous HA

Biologic Examinations
As a first-line screening, in the serum:
Total testosterone (reflection of ovarian, adrenal, or mixed production)
SHBG (allows the calculation of the Free Androgen Index)
17-OHP (plasma marker of the block in 21-hydroxylase)
DHEAS (reflection of the adrenal metabolism)

According to diagnostic orientation (in the serum):
Δ 4 Androstenedione,
LH, FSH
Prolactin
Anti-Müllerian hormone
17 *β*-estradiol
Inhibin B

Genetic tests
Karyotyping
SRY gene
Direct sequencing of a specific gene, and functional analyses of mutations.

Medical Imaging
Abdominal and pelvic ultrasound
Abdominal and pelvic MRI
DXA with measurement of global and appendicular fat free mass and fat mass

17-OHP, 17-hydroxyprogesterone; DHEAS, dehydroepiandrosterone sulfate; DXA, dual-energy x-ray absorptiometry; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MRI, magnetic resonance imaging; SHBG, sex hormone–binding globulin.

5. The controversy surrounding endogenous HA female athletes

Despite the rarity of such cases, their occurrence at regular intervals at the highest level of women's competition has proved to be controversial because the individuals concerned often display virilized phenotypes and have an uncommon athletic capacity in relation to their fellow female competitors.

For instance, we have reported several cases of virilized 46 XY DSD female athletes with serum testosterone concentrations between 15.6 and 29.3 nmol/L and hemoglobin levels within the male range. These features confer a significant p. 1066p. 1067competitive advantage through enhanced muscle

functions and recovery, increased mental drive, and increased oxygen-carrying capacity due to the high hemoglobin level. This raises the issue about the eligibility of these HA female athletes to compete in women's competition.

TABLE 89-8 Example of Medical Conditions Resulting in HA

Polycystic ovary syndrome: frequent, but poorly virilizing syndrome with serum testosterone usually below 5 nmol/L
5 α-reductase type 2 deficiency: 46 XY disorder of sex development (DSD) with sometimes very virilized female athletes
Complete androgen insensitivity syndrome: 46 XY DSD with no significant competitive advantage: unvirilized
Partial androgen insensitivity syndrome: 46 XY DSD with various virilized phenotypes
Ovotesticular DSD (previously called "true hermaphroiditism")
Congenital adrenal hyperplasia (CAH) 21-hydroxylase deficiency
CAH 11 β-hydroxylase deficiency
3 β-hydroxysteroid dehydrogenase (HSD) deficiency
17 β-HSD type 3 deficiency

IV. THE IRON STATUS IN FEMALE ATHLETE

A. General principles

Iron deficiency (ID) is the most prevalent nutrient deficiency in the world. In the United States, 3% to 5% of premenopausal women show ID with anemia (IDA), and 16% of premenopausal women show ID without anemia (IDWA). Physically active premenopausal women are twice as prone to IDWA as their sedentary counterparts are. This increased susceptibility of ID in female athletes is explained by one or a combination of the following factors: foot strike hemolysis (repeated strike impacts in endurance runners), increased gastrointestinal blood loss due to exercise-induced mesenteric ischemia-reperfusion, hematuria, increased iron loss in sweat, vegetarianism, chronic inflammation, and nonsteroidal anti-inflammatory drug abuse causing digestive tract bleeding.

IDWA can lead to impaired endurance performance through reduced activities of iron-containing cofactors (cytochrome and coenzymes from the Krebs cycle). In the IDA condition, these changes are even more marked and associated with a lower oxygen-carrying capacity ($VO_{2\ max}$ and maximal aerobic power) due to low hemoglobin levels.

B. Diagnosis and follow-up

In women, anemia is identified as a hemoglobin concentration lower than 12 g/dL. Serum ferritin is a good index of body iron stores and should be maintained above 12 to 20 μg/L. Because acute or chronic inflammation increases serum ferritin levels, one should always measure inflammatory markers such as the C reactive protein. Soluble transferrin receptor (s-TfR) is a marker of erythropoiesis and is a more sensitive index of ID. It is not affected by inflammation. s-TfR <8 mg/L attests to a normal tissue iron status.

Once or twice a year, female athletes most at risk (previous history of ID or IDA, high menstrual blood loss, vegetarians, RED-S, recent fatigue, or decreased physical performances) of ID should be tested using hemoglobin and serum ferritin cutoff levels at 12 g/dL and 20 μg/L, respectively.

C. Treatment

Recommended daily allowance for iron in premenopausal women is 18 mg/day. However, because regular physical training has been shown to increase daily requirements by up to 70%, daily intakes of 25 to 30 mg/day could be recommended in female athletes during cycles of high-intensity training (in particular endurance training). Because female athletes have been reported to show a higher incidence of amenorrhea, or high menstrual bleedings, each individual menstrual status should be taken into account prior to determining the iron daily allowance.

Supplementation should be prescribed in female athletes with hemoglobin <12 g/dL and serum ferritin <12 μg/L and with athletes with proven suboptimal dietary intakes (vegetarians, vegans, RED-S athletes, etc.). Whether female athletes with IDWA should be iron-supplemented is still a matter of controversy.

Iron intakes can be increased either by increased dietary (meat intake) or by oral supplementation using ferrous salts preparations. For instance, 20 mg of iron elemental can be provided by 100 mg of ferrous sulfate, or 60 mg of ferrous fumarate, or 165 mg of ferrous gluconate.

The iron supplementation should be continued 2 to 3 months following the return to a normal hemoglobin level. Adverse effects of iron supplementation (constipation, nausea, vomiting, and diarrhea) can be minimized by consuming a half dose twice daily.

Absorption of iron (dietary or supplemental) is reduced by a concomitant intake of polyphenolic compounds (tea and coffee) and

whole-grain products, and increased by a concomitant intake of vitamin C.

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A

Protocols for Stimulation and Suppression Tests Commonly Used in Clinical Endocrinology

Etty Osher and Naftali Stern

I. ANTERIOR PITUITARY

A. Diagnosis of growth hormone (GH) deficiency

In adults, the diagnosis of GH deficiency should be considered in subjects with known hypothalamic–pituitary disorders, particularly in the presence of significant or likely organic disease, such as the presence of a large pituitary tumor, pituitary trauma or significant head trauma, previous radiation treatment to the brain or the hypothalamic–pituitary region, and a childhood diagnosis of GH deficiency.

In subjects with significant organic pituitary disorders, the likelihood of GH deficiency in subjects with hypopituitarism increases in relation to the number of coexisting hormonal deficiencies in the anterior pituitary, rising from approximately 40% in the absence of coexisting deficiency to approximately 60% with a single impairment, approximately 80% with impaired secretion of two pituitary hormones, and approximately 100% when the secretion of three or more additional anterior pituitary hormones is deficient.

1. Measurement of serum insulin-like growth factor (IGF)-1.

Serum IGF-1 reflects GH activity, but unlike GH, it is fairly stable and does not fluctuate. IGF-1 levels should be adjusted to age and gender. In subjects with organic pituitary disease, serum IGF-1 concentration less than the age-defined lower limit of the normal range confirms the diagnosis of GH deficiency. Care must be taken, however, to exclude the presence of conditions known to lower serum IGF-I levels independent of pituitary disease, such as malnutrition, hepatic disease, poorly controlled diabetes mellitus, hypothyroidism, growth hormone insensitivity, renal failure, and

malignancy. Even normal IGF-1 levels, however, do not exclude GH deficiency, partly because of the inconsistent upward shifting of the results in some IGF-1 assays. In addition, the presence of three or more pituitary hormone deficiencies in association with low serum IGF-I level is highly suggestive of GH deficiency. Confirmation of the diagnosis by a provocative test of GH release is advisable. In patients with subnormal IGF-I, a single GH stimulation test is apparently sufficient to confirm the diagnosis. When GH deficiency is considered in the absence of organic pituitary disease or in a subject with known pituitary disease but normal IGF-1, performing two stimulatory tests appears preferable.

2. **Growth hormone stimulation tests**

   a. **General issues**

      Selection of tests. Insulin-induced hypoglycemia or arginine combined with growth hormone–releasing hormone (GHRH) is the potent stimulators of GH release. Other stimuli, such as arginine alone, clonidine, Levo DOPA (L-DOPA), glucagon, and the combination of arginine and L-DOPA, are much weaker and therefore more likely to give false-positive results. Wherever GHRH is available, the arginine combined with GHRH test is recommended because it is safer than the gold standard insulin-induced hypoglycemia. In countries where GHRH is not available, arginine and L-DOPA or glucagon alone comprises a reasonable alternative. **These tests are suitable to screen for GH deficiency in adults, where baseline GH levels are generally low even in the normal state.**

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      Preparation for tests. Patients should be adequately replaced with other deficient hormones before any testing of GH secretion performed. In adults, hypothyroidism should be excluded by performing thyroid function tests, and treated if needed. Priming with sex steroids before the GH stimulation test in the peripubertal period has been recommended but is still controversial.

      Interpretation. In general, GH secretion tests are more likely to give false-positive results in obesity because of the reduced GH secretory response in obese subjects.

   b. **Stimulation tests**

i. Combined arginine and GHRH test

a) Purpose

1) This test is now considered as reliable, but safer and more convenient than the traditional, gold standard insulin stimulation test, and is the test of choice to assess GH secretion.

b) Procedure

1) Perform the test in the morning, after an overnight fast.
2) Draw a baseline blood sample for GH (time −30 and 0).
3) Infuse (a) 1 μg/kg of GHRH via intravenous (IV) as a bolus dose; (b) a sterile solution of 10% arginine hydrochloride (0.5 g/kg IV, not to exceed 30 g) over 30 minutes.
4) Collect samples for the measurement of GH at 30, 60, 90, and 120 minutes following the initiation of the test.

c) Interpretation

1) As is the case for other methods, GH stimulation attaining peak levels are highly dependent on fat mass, and this has been particularly well studied with this test. Suggested minimal values for normalcy in lean (body mass index [BMI] <25), overweight (BMI ≥ 25 to <30), and obese (BMI ≥ 30) subjects are 11.5, 8.0, and 4.2 ng/mL. Others regard GH ≤ 4.1 ng/mL in a subject with organic pituitary disease as indicative of GH deficiency.

d) Pitfalls and precautions

1) GHRH directly stimulates the pituitary and can thus give a **falsely normal GH response in patients with GH deficiency of hypothalamic origin**, such as after irradiation within the past decade.

ii. Insulin-induced hypoglycemia test

a) **Purpose.** This is the most robustly validated test available to assess GH secretion and also the “gold standard” test to diagnose hypo function of the hypothalamic–pituitary–adrenal (HPA) axis.

b) Procedure

1) Perform the test in the morning, after an overnight fast.
2) An indwelling IV line should be placed and maintained patent, so that 50% glucose solution can be administered promptly if necessary.
3) Blood samples for glucose and **GH** should be obtained immediately before and at 15, 30, 45, 60, 90, and 120 minutes after insulin injection. (If evaluation of adrenocorticotropic hormone [ACTH] reserve is also desired, samples for cortisol should be obtained immediately before and at 30, 60, 90, and 120 minutes after insulin injection.)
4) Inject regular insulin, 0.1 U/kg IV. Higher doses (0.15 or 0.2 U/kg) may be needed in states of insulin resistance, such as obesity, pituitary Cushing syndrome (CS), or acromegaly. A lower dose is advisable (i.e., 0.05 U/kg) in patients suspected of having hypopituitarism.

c) Interpretation

1) **GH** levels generally peak at 40 to 90 minutes after insulin administration. Newer immunoradiometric assay (IRMA) or immunofluorometric p. 1070p. 1071assay is more sensitive and specific and yields results that are 30% to 50% lower than the traditional radioimmunoassay (RIA) tests, thus lower cutoff values should be defined with the newer, more sensitive assays. For appropriate stimulation of **GH** secretion, a fall in serum glucose levels of at least 50% from baseline levels (i.e., <40 mg/dL) is usually necessary. Thus mild hypoglycemic symptoms (e.g., nervousness, sweating, or tachycardia) are to be expected and do not require termination of the test. In children evaluated for short stature, most **pediatric endocrinologists use a cutoff serum concentration of 10 ng/mL** as evidence for

normal response. **In adults, peak GH levels of <5.1 ng/mL** are considered unequivocal evidence for GH deficiency. Obesity and insulin resistance complicate the interpretation of this test, in that lower insulin-stimulated GH levels are seen in normal obese individuals.

2) In assessing the **pituitary–adrenal axis,** a glucose level of <40 mg/dL provides an appropriate stimulus for sufficient ACTH/cortisol release. A peak cortisol exceeding 18 to 20 μg/dL implies an intact pituitary/adrenal response. Subnormal response suggests primary or secondary adrenal insufficiency. This test has been particularly reliable in patients with previous glucocorticoid therapy.
3) In patients with **severe depression** who have elevated plasma and urinary corticosteroid levels that are relatively resistant to suppression by dexamethasone, the plasma cortisol response to insulin-induced hypoglycemia is preserved. Lack of cortisol response is characteristic in patients with CS.

d) **Precautions.** Severe hypoglycemia may occur; therefore, close monitoring is indicated. This test is contraindicated in patients with epilepsy or coronary artery disease, and we usually resort to alternative tests in patients >50 years old, to avoid the risk of occult ischemic disease. Hypoglycemia may evolve late, especially in subjects with some renal impairment, so monitoring should be continued after the termination of the test.

iii. Glucagon stimulation test

a) **Procedure.** After an overnight fast, with the patient pre cannulated 30 minutes earlier and samples obtained at times −30 and 0, administer 1 mg (intramuscular [IM]) of glucagon (1.5 mg for patients who weigh >90 kg) and measure GH every 30 minutes for 4 hours.
b) **Interpretation.** Peak levels <3 ng/mL are suggestive of GH deficiency.
c) **Precautions.** Nausea, vomiting, abdominal cramps, diaphoresis, or headaches are common (up to 30%).

Rarely, rash, skin itchiness, and even breathing difficulty can be encountered. Late hypoglycemia caused by hyperstimulation of insulin is another risk, mandating monitoring for several hours.

iv. Arginine-L-DOPA infusion test

a) Purpose. Assessment of GH secretion

b) Procedure

1) Perform the test in the morning, after an overnight fast.

2) Draw a baseline blood sample for GH.

3) Give an oral dose of L-DOPA 500 mg, infuse a sterile solution of arginine hydrochloride 10% (0.5 g/kg IV, not to exceed 30 g) over 30 minutes.

4) Obtain blood samples for GH at 30, 60, 90, and 120 minutes.

c) Interpretation. A cutoff point for serum GH is 1.5 ng/mL.

d) Precautions. Nausea and vomiting are commonly encountered.

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B. Diagnosis of acromegaly

1. **IGF-1.** Serum IGF-I concentrations are **elevated in virtually all acromegaly patients**. Although IGF-1 can be viewed as an integrated measure of GH secretion, free of transient effects, such as stress, glucose levels, or circadian rhythm (which affect GH levels), it is strongly modified by age, peaking at puberty and declining steadily thereafter and increases in pregnancy, which leaves room for some misinterpretation. Considered collectively, normal IGF-1 level excludes almost entirely the diagnosis of acromegaly.

   False-positive results may occur in pregnancy and late-stage adolescence. Falsely low IGF-1 values occur in hypothyroidism, malnutrition, poorly controlled type 1 diabetes, liver failure, renal failure, and the use of oral estrogen (because of GH resistance). With the exception of diabetes, in these situations, the diagnosis of acromegaly in the proper clinical setting should not be dismissed before an oral glucose tolerance test (OGTT) with GH has been also performed.

2. **Diagnostic tests**
    a. **Glucose tolerance test for acromegaly**
        i. **Purpose.** To help establish the diagnosis of acromegaly
        ii. **Procedure**
            a) The patient should fast overnight. Ambulation should be minimal before and during the test.
            b) Draw baseline blood samples for glucose and GH.
            c) Give patients 75 to 100 g of glucose (or 1.75 g/kg to a maximum of 100 g) PO.
            d) Draw blood samples for glucose and GH at 30, 60, 90, and 120 minutes.
        iii. **Interpretation.** Interpretation highly depends on the type of assay used to measure GH. For example using IRMA, GH falls to <1 ng/mL levels within 30 minutes to 2 hours in normal subjects. Using various chemiluminescence assays, nadir posttest levels vary between 0.14 and 0.7 ng/mL. Although the Endocrine Society Consensus statement eventually selected 1 ng/mL as a "general" diagnostic threshold during OGTT, we recommend an assay-based approach. Typically, patients with acromegaly may demonstrate no suppression, incomplete suppression, or even a paradoxical rise in GH levels. In addition, blood glucose levels commonly show glucose intolerance. Exercise, ambulation, surgery, and hypoglycemia can elevate fasting GH levels. Stress can result in a false-positive test. Mild acromegaly, concomitant pituitary infarction, or prior therapy for acromegaly may lead to false-negative results. Incomplete or lack of GH suppression can be also seen in Laron dwarfism; pubertal or pregnant women; or subjects with malnutrition, diabetes mellitus, renal failure, or hepatic disease.

C. Thyroid-releasing hormone (TRH) tests and anterior pituitary disorders

1. **TRH test**
    a. **Purpose**
        i. Assessment of pituitary thyroid-stimulating hormone (TSH) secretion as a means to detect hypothalamo-pituitary pathology
        ii. **Ancillary test in the diagnosis of acromegaly**

iii. Differential diagnosis between the TSH-secreting pituitary adenoma and the syndrome of resistance to thyroid hormones

b. Procedure

i. Draw a blood sample for baseline TSH and GH.

ii. Give 200 μg (or 400 to 500 μg for GH) of synthetic TRH by IV injection.

iii. Draw blood samples for TSH at 30 and 60 minutes following TRH administration; for GH at 15, 30, 60, 90, and 120 minutes after TRH injection.

c. Interpretation

i. Assessing TSH response

a) **Central hypothyroidism.** Following TRH administration, TSH normally rises by 5 mU or more, the adult average peak response being 15 to 16 mU (20 to 40 minutes after TRH injection). In men older than 40 years, the response p. 1072p. 1073is smaller and increments of 2 mU or greater above baseline are considered normal. The only remaining indication for testing TRH-stimulated TSH secretion in the context of hypothyroidism is the consideration of subtle central hypothalamic hypothyroidism reflected by low-normal free thyroxine (FT_4) and/or free triiodothyronine (FT_3) and suspiciously "normal" to low-normal TSH. The test is not helpful in the "euthyroid sick syndrome" and should be used in inpatients with some serious underlying disease because blunted TSH response to TRH is typical in this setting. Pharmacologic doses of glucocorticoids, L-DOPA, bromocriptine, oral contraceptives, acetylsalicylic acid, and cyproheptadine can all decrease the TSH response to TRH. Decreased responses may also be seen in patients with renal failure, depression, and hypogonadotropic hypogonadism. TSH may typically remain low and unresponsive to TRH for several weeks following withdrawal of thyroid hormone replacement or after treatment of thyrotoxicosis.

b) **TSH-secreting adenoma versus the syndrome of resistance to thyroid hormones.** In the differential diagnosis between these conditions, particularly in the presence of a pituitary lesion of uncertain significance, TRH testing is often helpful, in that serum TSH concentration increases in response to TRH in patients with the syndrome of resistance to thyroid hormone, but not in most patients with TSH-secreting adenomas.

ii. **Assessing GH response.** This is now reserved for uncommon cases where IGF1 without or with OGTT do not provide unequivocal support for the diagnosis of acromegaly. **In normal individuals, GH levels are unaffected by TRH, whereas a rise can be seen in acromegaly.** False-positive increases have been reported in normal adolescent girls, and the paradoxical response of GH was also found in various pathologic conditions, such as severe hepatic failure, chronic renal failure, diabetes mellitus, and anorexia nervosa. In contrast, **GH levels will rise above baseline levels in most cases of acromegaly**. Positive results use the TRH ratio (the peak/basal ratio of GH during the test): those with a TRH ratio higher than 2 are defined as TRH responders.

d. **Precautions.** Transient nausea, warmth or flushing sensations, mild headache, or the urge to void may occur. Occasionally, subjects may display large increases in both systolic and diastolic blood pressures. In subjects with hypertension, we perform this test only after reasonable control of blood pressure has been achieved.

D. Gonadotropin-releasing hormone (GnRH)

GnRH test

1. **Purpose.** Assessment of pituitary gonadotropin secretion, when the combination of serum sex hormones and gonadotropins is difficult to interpret
2. **Procedure**
   a. Studies in women should preferably be done in the early follicular phase of the menstrual cycle (days 1 to 7).
   b. Because of the known pulsatile release of gonadotropins, at least two blood samples should be obtained 15 minutes before

and immediately before GnRH administration. The average of the two samples serves as the baseline luteinizing hormone (LH) and follicle-stimulating hormone (FSH) values.

c. GnRH, 100 μg, is given as a subcutaneous bolus or by rapid IV injection.

d. Draw blood samples for LH and FSH at 30, 60, 90, and 120 minutes after GnRH injection. Because the time of peak response is quite variable, additional samples at 15 and 45 minutes may enhance the reliability of this test.

3. Interpretation

a. This test can be used to clarify suspected hypogonadism, especially when circulating sex hormones are low and gonadotropin levels are within the low normal range or "inappropriately normal." The LH response to GnRH is usually more pronounced and is seen earlier than the FSH response. **In normal adults,** LH peaks are generally found at 15 to 45 minutes, whereas FSH peaks may occur later in some patients. In adults, LH levels will at least double following p. 1073p. 1074GnRH administration, and even greater increments are common. In women, the LH response to GnRH (but normally not the FSH response) is affected significantly by menstrual-cycle variability, with greater stimulation of LH observed during the luteal phase. In adults, the rise in FSH levels is usually of the magnitude of a 1.5- to 2-fold increase, but it is **not unusual to see little change in FSH levels even in normal subjects**.

b. The GnRH test is occasionally helpful for evaluating the functional capacity and response of the pituitary gonadotropins in adults but not in prepubertal children, in whom both basal and GnRH-stimulated gonadotropins levels are typically low. The test does not differentiate pituitary from hypothalamic disorders, because decreased response of plasma gonadotropins may indicate either pituitary disease or prolonged endogenous deficiency of GnRH. Furthermore, absent, impaired, or normal responses to the test can be seen in patients with known hypothalamic or pituitary disorders. When responses are

normal, however, the test does imply that the pituitary is capable of gonadotropin release when stimulated. Exaggerated LH response to GnRH is observed in **men with primary hypogonadism** and in women **with polycystic ovarian disease and precocious puberty** (see Chapter 29).

4. **Precautions.** Transient thirst during the test has been reported.

II. POSTERIOR PITUITARY-DIABETES INSIPIDUS

A. Water-deprivation test

1. **Purpose.** Diagnosis and differential diagnosis of **diabetes insipidus (DI)**. The test is particularly useful when the diagnosis is considered in the context of polyuria (≥40 mL/kg body weight per day), urine osmolality <300 mOsmol/kg, and in the absence of hypernatremia (suspected "compensated DI").
2. **Procedure**
   - **a.** This test requires close observation of the patient to ascertain complete withholding of fluids and carefully monitor the patient's status.
   - **b.** Withhold fluids from 6 A.M. (~2 hours before the initiation of testing).
   - **c.** Obtain baseline sodium, plasma, and urinary osmolality, and record body weight and, whenever feasible, plasma antidiuretic hormone (ADH).
   - **d.** As water deprivation continues, measure urine volume and osmolality, body weight every hour, and the plasma sodium concentration and osmolality every 2 hours until any of the following takes place: urine osmolarity has plateaued (increment in urine osmolality observed from two consecutive determinations is <30 mOsmol/kg); urine osmolality has reached 600 to 700 mOsmol/kg; plasma osmolality has reached 295 to 300 mOsmol/kg; serum sodium reached 145 mEq/L or higher; or body weight decreases by ≥2%. This normally occurs by early afternoon.
     - **i.** At that time, obtain blood and urine samples for osmolality and, whenever possible, plasma ADH. Record body weight and then administer 10 μg of 1-deamino, 8-D-arginine-vasopressin; desmopressin (dDAVP) by nasal insufflation or 2 μg of dDAVP IM or IV. Avoid the use of vasopressin in pregnancy because it subjects to increased degradation by

high circulating vasopressinase present in pregnancy.

ii. Obtain repeat urine and blood samples for osmolality 30 and 60 minutes later.

3. **Interpretation**

a. **A normal response** consists of maximal urinary osmolality ranging between 800 and 1 400 mOsmol/kg by the end of the dehydration test and only a small rise, if any (<9%), in urinary osmolality after vasopressin. Maximal urine osmolality is greater than plasma osmolality both before and following the administration of vasopressin.

b. Subjects with **primary polydipsia** have an essentially normal response, but a more prolonged dehydration period may be needed. Still, the maximal urine osmolality in primary polydipsia (500 to 600 mOsmol/kg) often falls short of the normal response (800 mOsmol/kg because of partial washout of the real medullary interstitial gradient).

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c. Subjects with partial central DI (**partial ADH deficiency)** display some endogenous capacity for urine concentration (i.e., maximal urine osmolality is more than plasma osmolality before the administration of vasopressin or desmopressin); in response to dDAVP, urine osmolality increases significantly (i.e., >15% to <50%). These patients occasionally fail to respond to exogenous ADH because, once high plasma osmolality has been reached during the test, endogenous ADH released has increased already, eliciting maximal stimulation during the dehydration period.

In **severe ADH deficiency**, maximal urine osmolality is lower than plasma osmolality. However, in response to dDAVP, urinary osmolality increases by >50%.

d. **Nephrogenic DI** is also associated with a submaximal rise in urine osmolality in response to water restriction. The elevation in plasma osmolality stimulates ADH release, and because most patients with acquired nephrogenic DI are partially (not completely) resistant to ADH, this may induce a modest increase in urine osmolality. The administration of vasopressin produces no elevation in urine osmolality in complete nephrogenic DI or just a small (<45%) elevation in urine

osmolality in partial nephrogenic DI. A more **striking difference between partial central DI and nephrogenic DI** in this setting is that urine remains very dilute in the latter condition, whereas patients with ADH deficiency usually attain urine osmolality of 300 mOsmol/kg or higher.

4. **Precautions**

Unless polyuria is mild or questionable, **overnight fluid restriction should be avoided** because potentially severe volume depletion and hypernatremia can be induced in patients with marked polyuria.

Severe weight loss and dehydration may occur in patients with true DI. Weight loss should not be allowed to exceed 3% of initial body weight.

B. Therapeutic trial with dDAVP

1. A therapeutic trial with a low standard dose of desmopressin for several days can be a useful approach in case of diagnostic uncertainty. Improvement can be expected with central DI, but water intoxication can be precipitated in primary polydipsia, such that close supervision is needed.

III. DIABETES MELLITUS

A. OGTT

1. **Purpose.** Diagnosis of prediabetes or diabetes mellitus
2. **Procedure**
   - **a.** This test should be reserved for ambulatory subjects without fever or infection. **Carbohydrate** content in the diet should be at least **150 g/day for the last 3 days** before the test.
   - **b.** The test should be done in the morning, following a fast of at least 8 hours but not exceeding 16 hours. Water is allowed during the fast. Coffee should be avoided.
   - **c.** Subjects should remain seated throughout the test and should refrain from smoking.
   - **d.** Glucose, 75 g (anhydrous glucose dissolved in water; 1.75 g/kg ideal body weight, not to exceed 75 g), is given PO to nonpregnant adults. Pregnant women receive 50, 75, or 100 g PO, as specified in the following paragraph.
   - **e.** For the standard OGTT in adults, blood samples for glucose determination are obtained before glucose ingestion as well as 120 minutes later (2 hour plasma glucose [PG]). For pregnant

women, obtain samples at the following time points, depending on the glucose dose: 50 g, 120 minutes; 75 g, 0, 60, 120 minutes; 100 g, 0, 60, 120, and 180 minutes.

3. **Interpretation** (glucose levels in venous plasma). Subjects are classified as normoglycemic, or having prediabetes impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or diabetes mellitus based on the following parameters (Table A-1).

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TABLE A-1 Diagnosis of prediabetes and diabetes mellitus

Normoglycemia	Prediabetes, Impaired Fasting Glucose (IFG), and Impaired Glucose Tolerance (IGT)	Diabetes Mellitus
Fasting plasma glucose <100 mg/dL	Fasting plasma glucose ≥100 mg/dL and <126 mg/dL (IFG)	Fasting plasma glucose ≥126 mg/dL
2 hr PG < 140 mg/dL	2 hr PG ≥ 140 mg/dL and <200 mg/dL (IGT)	2 hr PG ≥ 200 mg/dL
A1C < 5.7% (39 mmol/mol)	A1C 5.7%–6.4% (39–46 mmol/mol)	A1C ≥ 6.5%
		Symptoms of diabetes mellitus and casual plasma glucose concentration 200 mg/dL

a. Nonpregnant adults

Based on the OGTT, a **diagnosis of diabetes mellitus is established if the 120-minute serum glucose is ê200 mg%**. Subjects whose 120-minute glucose ranges between 140 and 199 mg% are considered as having IGT (see also Table A-1).

b. OGTT and pregnancy

Prenatal OGTT is recommended in women with risk factors for type 2 diabetes (positive family history, history of gestational diabetes mellitus [GDM], obesity [BMI > 30 kg/m^2]), high-risk ethnic group, previous delivery of a baby >4.1 kg, or unexplained perinatal loss or birth of a malformed infant, at their first *prenatal* visit, using standard diagnostic criteria. At this stage, the exclusion of diabetes in women with

A1Cs in the range associated with an increased risk for diabetes (A1C 5.7% to 6.4% [39 to 46 mmol/mol]) is best achieved with a **2-hour OGTT**, 75-g, early in pregnancy. Screening/testing can be performed as early as the first prenatal visit or later if there is a high degree of suspicion. The 75-g 2-hour OGTT is diagnostic of gestational diabetes when one glucose value is elevated.

Gestational diabetes. Women diagnosed with diabetes in the first trimester would be classified as having type 2 diabetes. For all other women not previously known to have diabetes, evidence supports an OGTT-based **screening for GDM at 24 to 28 weeks** of gestation, using a one-step or two-step approach.

The "**one-step approach**," oral OGTT (75 g), 2-hour diagnostic test, was recommended by International Association of Diabetes and Pregnancy Study Groups: blood glucose levels are determined at baseline as well as 1 hour, and 2 hours post challenge. The diagnosis of GDM is made if one or more of the plasma glucose values in Table A-2 are met or exceeded.

TABLE A-2 Diagnosis of Gestational Diabetes Mellitus with a 75-g Glucose Load

Time	Plasma Glucose
Fasting	≥92 mg/dL (5.1 mmol/L)
1 hr	≥180 mg/dL (10.0 mmol/L)
2 hr	≥153 mg/dL (8.5 mmol/L)

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TABLE A-3 Diagnosis of Gestational Diabetes Mellitus with a 100-g Glucose Load

Time	Plasma Glucose
Fasting	≥95 mg/dL (5.3 mmol/L)
1 hr	≥180 mg/dL (10.0 mmol/L)
2 hr	≥155 mg/dL (8.6 mmol/L)
3 hr	≥140 mg/dL (7.8 mmol/L)

The "**Two-step approach**" may be more cost-effective and most commonly used recommended by American College of Obstetricians and Gynecologists and American Diabetes Association. The **first step consists of a 50-g oral glucose** challenge, administered without regard to the time elapsed since the last meal. Plasma or serum glucose is measured 1 hour later; a value ≥130 to 140 mg/dL is considered abnormal. The full **100-g OGTT is administered as the second step** to women showing such abnormal results. In this test, plasma glucose levels are determined at baseline, 1, 2, and 3 hours post challenge. The diagnosis of GDM is made if two or more of the plasma glucose values in Table A-3 are met or exceeded. The test should be done in the morning, after an 8- to 14-hour fast. Screening women with GDM for persistent diabetes is recommended at 6 to 12 weeks postpartum.

B. Hypoglycemia in adults without diabetes mellitus

Hypoglycemia in non diabetic subjects can occur in the fasting or postprandial state and, at the time of spontaneous hypoglycemia, the diagnosis can be often established by ancillary blood tests (glucose, insulin, C-peptide). Whenever such information is not available, the diagnostic strategy is to imitate conditions in which hypoglycemia would be expected: (a) a 72-hour (prolonged) supervised fast for fasting hypoglycemia; (b) a mixed meal test for postprandial hypoglycemia.

1. Insulinoma

a. Prolonged fasting test

i. Purpose. Evaluation of hypoglycemia resulting from suspected insulinoma

ii. Procedure

a) The patient should be hospitalized for this test and placed on a **72-hour fast**. Only water and noncaloric, caffeine-free soft drinks are allowed.

b) Blood samples for glucose, insulin, C-peptide, proinsulin, and β-hydroxybutyrate (if available) should be obtained every 6 hours. Additional blood samples should be drawn when hypoglycemic symptoms occur. This requires close and continuous observation. Once glucose levels decline to <60 mg%, sampling frequency should be increased to every 1 to 2 hours.

c) If any serious neuroglycopenic or other hypoglycemic symptoms occur, blood samples for insulin and glucose should be drawn, and the test immediately terminated. Also, the test **should be ended when plasma glucose concentration falls to <45 mg/dL**.

d) At the end of the fast (72 hours or earlier as specified above), a sample for plasma β-hydroxybutyrate and oral hypoglycemic agents (sulfonylurea, meglitinides) screen is also collected (in addition to glucose, insulin, and C-peptide). Ancillary measurements may also include **chromogranin A**, a general marker for neuroendocrine tumors. Insulin antibodies, anti-insulin receptor antibodies, IGF-1, and plasma cortisol or GH can be measured if a non–islet-cell tumor, autoimmune etiology, or hormone deficiency is suspected.

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e) The fast is ended when plasma glucose concentration is ≤45 mg/dL or less, 72 hours have elapsed, or when the plasma glucose concentration is less than 55 mg/dL, if Whipple triad was documented before the fast.

f) At this time, 1 mg of glucagon is administered via IV, and samples for plasma glucose are collected 10, 20, and 30 minutes later. The patient must be fed before his or her discharge from the hospital.

iii. Interpretation. In the normal patient, insulin levels will be appropriate for the serum glucose level. Normal serum glucose levels during a 72-hour fast may fall to the range of 30 mg/dL in women and 50 mg/dL or lower in men. However, patients with serum glucose in these ranges will generally have low (<4 μU/mL) or undetectable serum insulin levels. In contrast, patients with an insulinoma will not only often develop symptoms (sometimes severe) of hypoglycemia, but they will also present with inappropriately high levels (>10 μU/mL) of serum insulin. A plasma insulin of ≥6 μU by RIA or ≥3 μU by radioimmunometric assay in connection with plasma glucose <45 mg/dL provides sufficient evidence for insulin excess. **C-peptide levels** (>0.2 nm/dL) will differentiate

between endogenous and exogenous hyperinsulinemia. In addition, if hypoglycemia (<45 mg%) is recorded during the 72-hour fast, **proinsulin levels** >5 pmol/L are indicative of insulinoma, with nearly 100% specificity and sensitivity. **Because of the antiketogenic effects of insulin, patients with insulinoma have low plasma *β*-hydroxybutyric acid levels** (<**2.7 mmol/L) despite the prolonged fast**. High levels of oral hypoglycemic drugs suggest factitious hyperinsulinemia. Finally, because hepatic glycogen stores are entirely depleted in normal individuals subjected to prolonged fasting, no significant increase in glucose (<25 mg/dL) is normally expected following the injection of glucagon at the end of the fast. In contrast, **patients with chronic hyperinsulinemia have larger hepatic glycogen stores owing to the antiglycogenolytic effect of insulin**. Thus, in patients harboring an insulinoma, glucose will rise by 25 mg/dL or more following glucagon administration. Care should be taken in interpolation of test results using insulin measured by immunoassay system methods, which measure lower insulin levels.

iv. **Precautions.** Glucose for rapid IV injection should be readily available. Severe hypoglycemic symptoms can occur and are an indication to terminate the test and institute immediate corrective measures.

2. **Postprandial hypoglycemia**
   a. **Mixed meal test**
      i. **Purpose.** If symptoms of hypoglycemia typically occur within 5 hours after eating, patients should be evaluated for a postprandial state.
      ii. **Procedure**
         a) After a 10-hour overnight fast, the patient is admitted to a closely supervised facility and allowed to consume either a meal that has previously resulted in postprandial symptoms on several occasions or approximately 900 kcal mixed meal composed of carbohydrates (~75 g), fat (~50 g), and protein (~36 g).
         b) Samples are collected for plasma glucose, insulin, C-peptide, and proinsulin before ingestion of the meal and

every 30 minutes thereafter for 5 hours.

c) If symptoms are noted at any time during the 5 hours, samples for the above lab tests should be collected, including blood levels of oral hypoglycemic agents and antibodies to insulin, before the administration of carbohydrates (to assess for correction of symptoms).

iii. Blood glucose is determined in all samples, but insulin, C-peptide, and proinsulin should be later analyzed in samples with plasma glucose <60 mg/dL or at any time point at which the Whipple triad is demonstrated.

iv. Interpretation. Standards for the interpretation of the mixed meal test are not established. Thus, the interpretation of the glucose, insulin, C-peptide, and proinsulin during hypoglycemia is based on the principles detailed for the 72-hour fast.

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IV. THE ADRENAL GLAND

A. Screening tests for CS

Unless exceptionally high cortisol values are seen, no single positive test should be taken as sufficient proof for the diagnosis of CS. The possibility of exogenous glucocorticoids should be carefully excluded before testing is undertaken. Despite best attempts to form rational algorithms for the work up of CS, significant pitfalls require reconsideration and often retesting with time.

1. **Screening tests for subjects with a <u>low</u> index of suspicion**

   Any **<u>one</u>** of the following procedures is considered adequate: late-night salivary cortisol (two measurements), 24-hour urinary free cortisol (UFC) excretion (two measurements), the overnight 1 mg dexamethasone test, or the 2 mg/day 48-hour dexamethasone test. A normal result is usually sufficient, unless suspicion persists or increases with time.

2. **Screening tests for subjects with a <u>high</u> index of suspicion**

   Any **<u>two</u>** of the following procedures are recommended: late-night salivary cortisol (two measurements), UFC (two measurements), the overnight 1 mg dexamethasone test, or the 2 mg/day 48-hour

dexamethasone test.

Two positive tests likely require further workup but so do even normal initial results with a strong clinical suspicion.

a. **Overnight dexamethasone suppression test.** This test is done in an outpatient setting and is a practical screening test for hypercortisolism.
    i. **Procedure**
        a) Dexamethasone, 1 mg PO, given at 11 to 12 P.M. A nonbarbiturate sedative may also be given to help the patient sleep.
        b) Obtain plasma cortisol at 8 A.M. the following morning.
    ii. **Interpretation.** Normal subjects should suppress plasma cortisol levels to <1.8 to 2 μg/dL, but in some subjects with CS, it can be suppressed to less than 2 μg%. Cortisol levels at this range may be around the lower detection limit for some assays and should be viewed with caution. Levels between 2 and 7 μg/dL may be difficult to interpret, because they are commonly seen in subjects with mental depression and alcohol and stress-induced adrenocortical activation, referred to, collectively, **as pseudo-Cushing disorders.** Additional forms of testing are, therefore, recommended under these circumstances. Constitutive variation in the metabolic clearance of dexamethasone and acceleration in dexamethasone metabolism by alcohol and drugs, such as nifedipine, rifampin, hydantoin, carbamazepine, phenobarbital, tamoxifen, and topiramate because of the induction of CYP3A4 enzymes, which also metabolize dexamethasone, can lead to false-negative results. Suppression of cortisol can be incomplete in chronic renal failure because of decreased cortisol clearance, or high-estrogen states, resulting from increased cortisol-binding globulin (CBG) level. Hence, the measurement of plasma dexamethasone, to verify that proper levels of dexamethasone have indeed been attained, can add much to the interpretation of any of the dexamethasone suppression tests.
b. **Standard 2-day, 2-mg test.** This test provides essentially the same type of information derived from the shorter overnight 1-mg dexamethasone suppression test.

i. **Procedure**
   a) **Baseline.** Obtain plasma cortisol at 8 A.M.
   b) **Day 1.** Administer dexamethasone, 0.5 mg PO q6h, beginning at 9 A.M. on day 1, at 6-hour intervals.
   c) **Day 2.** Administer dexamethasone, 0.5 mg PO q6h, with the last dose administered at 3 A.M.
   d) **Day 3.** Collect blood sample for serum cortisol at 9 A.M.

ii. **Interpretation.** Whether or not this test performs better than the 1-mg overnight dexamethasone test is debatable. The performance of this test is significantly enhanced if dexamethasone is also measured. In normal subjects, p. 1079p. 1080serum cortisol should decline to 1.8 to 3.6 μg/dL 6 hours following the last dexamethasone dose (last dose at 3 A.M.; sample collected at 9 A.M.). The cutoff level of 1.8 μg/dL enhances sensitivity, but few commercial assays have been tested for performance in this context.

c. **Urinary steroid excretion.** Absolute elevations of urinary steroid levels can be used to diagnose CS. The measurements are made on baseline 24-hour collections of urine, using creatinine and total volume as estimates of the adequacy of the collection.

   i. **UFC excretion** is the **measurement of choice** for the initial diagnosis of hypercortisolism. Proper measurement of UFC requires extraction of cortisol from the urinary sample, followed by RIA. High-performance liquid chromatography (HPLC)-based methods provide a more specific way to assess UFC, with an upper range of approximately 50 μg/24 hours. Liquid chromatography with mass spectrometry (LC-MS)–mass spectrometry (MS) normative data for UFC in Cushing disease are scarce, but some find that the receiver operating characteristic curve (ROC)-based use of the results with this assay alone is better than the combination of any other two screening tests. UFC is elevated in approximately 95% of CS patients. High water intake (e.g., >5 L/24 hours) with increased urine

volume might elevate the urine free cortisol (UFC). Diluted urine sample could “push” the detected values toward the lower end or “edge of assay,” where assay accuracy is variable. Small errors, when multiplied, owing to a large volume may lead to fortuitously high calculated total UFC, such as with the drug carbamazepine. Incomplete urine collection, low urine output, and renal failure (creatinine clearance ≤ 60 mL/min) may cause false-negative results. We recommend repeat testing over time and consideration of at least two additional screening tests.

d. Diurnal variation of circulating cortisol. Plasma cortisol values are highest from 6 to 8 A.M., declining during the day to less than 50% to 80% of morning values from 10 P.M. to midnight. This rhythm is typically lost very early in the course of CS.

i. Salivary cortisol concentration is correlated with free or biologically active cortisol levels in serum or plasma. A sampling device is available with which saliva can be collected by chewing on a cotton tube for 2 to 3 minutes. Cortisol in the saliva is quite stable and can be sent for determination over several days at room temperature. Testing is done at midnight or even later. Cutoff levels depend heavily on a regular awake/sleep pattern (e.g., not to be used in shift worker, during jet-lag, late sleeper) and the assay in use (e.g., RIA, electrochemiluminescence, or LC-MS), such that general guidelines are inappropriate. Still, late-night levels of salivary cortisol >1.6 ng/mL are suggestive of true hypercortisolism. False-positive cases have been noted in older obese hypertensive and/or type 2 diabetic men.

ii. Midnight serum cortisol seems intuitively to be a direct measure of circulating cortisol, but sample drawing requires hospitalization or some other special setting with obligatory disruption of normal late-night activities. This in itself may weaken the specificity of the measurement of serum cortisol.

a) Procedure. Sampling is best performed with an indwelling needle and basal conditions maintained for 30 minutes before sampling. Because cortisol is secreted

in pulsatile bursts, multiple samples are taken: Sampling for cortisol is done at 30-minute intervals between 10 P.M. and midnight. Patients should be in the supine position before and during the study.

b) **Interpretation. A midnight plasma cortisol of 7.5 μg/dL or greater** strongly suggests a diagnosis of CS. Values of 5.0 μg/dL or less are unlikely to be CS, and values of 2.0 μg/dL nearly exclude CS. This test has value in mild to moderate cases of hypercortisolism (in which **urine free cortisol is normal**, because of just small increase in cortisol production). A timed or spot UFC-to-creatinine ratio at midnight can also be used to establish the presence of hypercortisolism. Also, **a midnight "sleeping" plasma** **p. 1080p. 1081** **cortisol of 1.8 μg/dL or greater is shown to have a 100% diagnostic sensitivity for CS**, but specificity at this level is apparently low. In general, it has been difficult to obtain a nonstressed late-night cortisol value.

3. **Tests in special populations**
   - **a.** In **pregnant women**, the rise in cortisol secondary to the **increase in CBG** complicates the interpretation of serum cortisol. Because **UFC remains within normal limits in the first trimester** but can later increase up to threefold, it remains **useful in the first trimester**. Further more, after the first trimester, UFC values greater than three times the upper limit of normal range may be suggestive of CS.
   - **b.** In patients receiving drugs known to enhance dexamethasone clearance (e.g., antiepileptic drugs), the measurement of cortisol (UFC, late-night serum or salivary cortisol) perform better than dexamethasone-based tests.
   - **c.** In patients with severe renal failure, the 1-mg overnight dexamethasone suppression tests are superior to urine-based measurements.
   - **d.** For suspected cyclic CS, multiple measurements of UFC and late-night serum/salivary cortisol are preferable.

e. In cortisol-producing adrenal incidentalomas, lack of suppression by dexamethasone may precede overt hypercortisolism, thus rendering the 1-mg overnight dexamethasone suppression test the procedure of choice.

B. Ruling out pseudo-CS

1. **Corticotropin-releasing hormone (CRH) after low-dose dexamethasone suppression test (CRH-Dex).** This test was developed to **distinguish between patients with pseudo-Cushing and those with CS**. The test is based on the premise that suppression of ACTH by dexamethasone is more profound in normal subjects and depressed patients than in patients with Cushing disease, such that following proper suppression with dexamethasone, serum cortisol cannot be stimulated by CRH in these patients, but only in subjects with Cushing disease. The test is useful for patients with mild hypercortisolism and normal ACTH levels, whom the differential diagnosis is between Cushing disease or pseudo-Cushing states.
   a. **Choice of patients.** This test should be considered only for subjects who show normal suppression following dexamethasone administration, but in whom CS continues to be seriously suspected because of clinical considerations or other anomalous (positive) screening test(s) for Cushing states.
   b. **Procedure.** Give 0.5 mg dexamethasone at 6-hour intervals for 2 days, as of 12 A.M. on day 1. The CRH (bovine, which is more potent, or human) stimulation test is initiated at 8 A.M., 2 hours after completion of the last dexamethasone dose (at 6 A.M.). Both human and ovine CRH are available and can be administered as an IV bolus of 1 μg/kg body weight or as a fixed dose of 100 μg via IV.
   c. **Interpretation.** A measurable serum cortisol response to CRH (e.g., cortisol level >1.4 to 2.5 μg/dL measured 15 minutes after CRH administration) identifies patients with Cushing disease compared to those with pseudo-Cushing conditions, with a sensitivity of approximately 90% but with much lower specificity, ranging overall around 70% in reports published thus far. Although **abnormal results**, consistent with increased hypothalamic–pituitary arousal, have been **reported in anorexia nervosa**, patients with this condition are unlikely to be worked up for CS.

C. Differential diagnosis of CS: Is hypercortisolism ACTH-dependent?

1. **Plasma ACTH.** Plasma ACTH is now a powerful tool to address this question, but dynamic testing is still required for many patients. IRMA of ACTH offers good sensitivity and specificity in the differential diagnosis of CS. Samples should be taken at 8 A.M. under basal condition. As ACTH is rapidly degraded by circulating peptidases, the sample must be collected in an EDTA-containing, pre chilled tube, and plasma should be separated, aliquoted, and frozen immediately. The concomitant measurement of ACTH and cortisol provides a straightforward means to assess whether hypercortisolemia, once established and if present at the time of testing, is ACTH-dependent. Whenever basal levels of ACTH are

p. 1081p. 1082measurable (ACTH values >20 pg/mL) in a patient with high levels of plasma cortisol, ectopic or pituitary (ACTH-dependent) forms of CS should be suspected. Plasma ACTH is sometimes extremely high in **ectopic CS**, most often because of lung carcinoma, but it may be only mildly elevated or normal in patients with bronchial carcinoid tumor. Patients with **pituitary CS** have **elevated baseline plasma ACTH values in about half of cases**, often ranging between 50 and 250 pg/mL, with the remainder of patients having levels within the normal range. However, even very high levels of a slightly modified ACTH molecule formed by the ectopic tissue can be missed by the current highly specific assays for ACTH. Nevertheless, **undetectable levels of ACTH or ACTH values <5 pg/mL** in the presence of increased plasma cortisol levels suggest the diagnosis of **adrenal CS** (ACTH-independent forms of CS).

   Plasma ACTH values between 5 and 20 pg/mL are a "grey zone": Some excess in secretion of cortisol may not fully suppress ACTH levels, which also implies that cortisol secretion, either from the adrenal lesion or the normal surrounding cortex, is at least partially ACTH-dependent. This group may particularly benefit from the CRH-dexamethasone test with dynamic ACTH measurements.

2. **High-dose 8-mg dexamethasone suppression test.** Administration of large doses (8 mg/day for 2 days) of the potent

synthetic glucocorticoid dexamethasone will suppress urinary or plasma cortisol by >50% of baseline (or 8 A.M. serum cortisol to less than 5 μg/dL according to other reports) in pituitary but not in adrenal or ectopic CS. The test distinguishes pituitary CS from other causes in approximately 85% of cases. Some maintain that the high-dose dexamethasone suppression test has been made obsolete by the availability of reliable methods for the measurement of plasma ACTH, pituitary imaging, and inferior petrosal sinus sampling (IPSS). IPSS is a conventional abbreviation, whereas IPS is not. The inconvenience of the latter procedure, pitfalls in plasma ACTH, and the high rate of pituitary and adrenal incidentalomas (up to 10% of the general population) comprise sufficient grounds for continued performance of this test.

a. Procedure

- **i. Day 0—baseline.** Obtain a plasma cortisol at 8 A.M., and 24-hour urine samples for UFC.
- **ii. Day 1.** Administer dexamethasone, 2 mg PO q6h (usually at 8 A.M., 2 P.M., 8 P.M., and 2 A.M.). Collect 24-hour urine sample for UFC.
- **iii. Day 2.** Administer dexamethasone, 2 mg PO q6h. Collect 24-hour urine sample for UFC.
- **iv.** Obtain a plasma cortisol at 8 A.M.

b. Interpretation. Suppression to >50% of baseline plasma cortisol and/or UFC at day 2 indicates lack of complete autonomy of ACTH secretion and is, therefore, compatible with pituitary Cushing disease or, occasionally, bronchial carcinoid tumor; failure to suppress on 8 mg/day implies adrenal or ectopic CS. This test has a diagnostic sensitivity of 60% to 80% and specificity of 80% to 85%, due to "**anomalous responses**"**: (a)** as many as **15% of pituitary Cushing patients will not be detected by this test**. More recent criteria have been established that improve diagnostic accuracy. A decrease from baseline level UFC of >80% will detect 100% of patients with pituitary Cushing and exclude most ectopic cases. **(b)** Suppression in ectopic Cushing can occur particularly in bronchial tumors with low-grade malignancy. **(c)** Lack of suppression of cortisol and/or its metabolites can be seen in subjects harboring a large pituitary ACTH-secreting macroadenoma.

3. **The 8-mg overnight dexamethasone suppression test.** This test can be **used in place of the 2-day dexamethasone suppression test**, because it has roughly similar accuracy and specificity.
    a. **Procedure.** Obtain a plasma cortisol at 8 A.M. as baseline, then give 8 mg dexamethasone at 11 P.M. and draw another blood sample for plasma cortisol the next morning at 8 A.M.

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    b. **Interpretation.** More than 50% reduction in plasma cortisol from the baseline levels is consistent with Cushing disease.

D. Separating Cushing disease (pituitary) from other forms of CS, including ectopic ACTH-producing tumors

1. **CRH stimulation test.** CRH selectively stimulates the pituitary corticotrope cells to increase ACTH, which is followed by a rise in cortisol. CRH increases ACTH and cortisol levels in up to 90% of patients with Cushing disease because most pituitary ACTH-secreting tumors have CRH receptors. Patients with ectopic and adrenal CS do not usually have ACTH or cortisol response to CRH. This test differentiates ACTH-dependent from ACTH-independent CS but might not always distinguish pituitary (eutopic) from ectopic causes, mostly because some pituitary patients do not respond to CRH.
    a. **Procedure.** Human or ovine CRH is available and administered as an IV bolus of 1 μg/kg body weight or as a fixed dose of 100 μg via IV.
    b. **Interpretation.** Cutoff values of response depend on the type of CRH used (human vs. ovine). An increase above baseline of 35% to 50% in ACTH and 14% to 20% for cortisol at specific time points (ACTH, 15 to 30 minutes; cortisol, 15 to 45 minutes) is suggestive of Cushing disease. However, some ectopic ACTH- or ACTH/CRH-producing tumors can also respond to CRH.
2. **IPS sampling** with **CRH stimulation**
    a. **Purpose.** To distinguish between pituitary Cushing disease and CS secondary to ectopic ACTH secretion. The most common setting in which this test is helpful is suspected pituitary Cushing with a negative magnetic resonance imaging (MRI) of the pituitary (can be up to 50%) and equivocal levels

of plasma ACTH versus an ectopic ACTH-secreting tumor, usually a bronchial carcinoid that might be roentgenographically occult and have equivocal ACTH levels.

b. Procedure

i. Baseline samples for ACTH and prolactin (PRL) are obtained from a peripheral vein as well as from catheters reinserted into the veins draining both the left and right IPSs. Correction for PRL level in the obtained samples may assist in identifying problems related to localization of the draining catheter and dilution. PRL measurements may help to validate IPS results. High PRL from the IPS (IPS-PRL) with a high IPS/peripheral PRL ratio is an index of a "true" pituitary venous effluent (vs. a diluted sample originating from a nearby, but the desirable source). However, although this is a promising approach, the specific criteria for interpretation vary between centers.

ii. CRH (100 μg) is administered via IV. Samples for ACTH are obtained simultaneously from each IPS before as well as 2 to 3 and 5 to 6 minutes (and in some centers, 10 minutes) after CRH administration.

c. Interpretation. Basal IPS-to-peripheral (P) ACTH ratio ≥2.0 or to post-CRH ratio ≥3.0 confirms the presence of a pituitary ACTH-secreting tumor. Other values are assumed to have an ectopic source. CRH testing is needed because up to 15% of pituitary tumors will not show an abnormal basal gradient. Correct preoperative lateralization of an ACTH-secreting microadenoma to the right or left hemisphere of the pituitary gland can be accomplished much less frequently than was initially believed, probably because of asymmetric venous drainage in many pituitary glands. The **procedure carries some risk**, including false-positive and false-negative results. Direct procedure-related risks are not common but include, besides inguinal and jugular hematomas or transient arrhythmias, rare serious consequences, such as perforation of the right atrium, cavernous sinus thrombosis, and cerebrovascular events (0.2%), sometimes with permanent brainstem damage. Hence, IPS should be reserved for clearly equivocal cases, such as normal pituitary MRI or the presence of very small pituitary lesions and/or atypical response to

dexamethasone and/or CRH. Sources of error include some cases of Cushing disease that show no response to CRH, incorrect identification of the petrosal sinus or anomalous draining of the petrosal sinus, and rare cases of ectopic CRH-producing tumors.

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E. Workup of primary bilateral macronodular adrenal hyperplasia (ACTH-independent macronodular adrenal hyperplasia, AIMAH)

1. Dynamic tests to detect excessive cortisol secretion induced through anomalous routes.

Ectopically expressed G-protein–coupled hormone receptors can be abnormally activated by hormones that do not normally affect adrenal cortical function, resulting in **anomalous stimulation of cortisol secretion**. This mechanism not infrequently underlies excess cortisol secretion in AIMAH as well as in some unilateral adrenal adenomas. Aberrant receptors thus far reported to be functionally coupled to steroidogenesis include receptors for gastric inhibitory peptide (GIP), vasopressin, *β*-adrenergic, LH/human chorionic gonadotropin, serotonin angiotensin II, leptin, glucagon, interleukin-1, and TSH. Some of these conditions can be treated medically. Lacroix's group has developed clinical protocols to screen for such dysfunctional activation of the adrenal cortex, which have been subsequently widely adopted, particularly for the workup of AIMAH. A 3-day protocol offers opportunity to capture the most common forms of anomalous cortisol secretion under these conditions.

a. Day 1

i. Ambulation test

a) Purpose. To detect potential modulation of cortisol by posture-induced signals, such as increase in angiotensin II, vasopressin, or catecholamines, or a decline in atrial natriuretic peptide.

b) Procedure

Fasting baseline samples for cortisol are collected after 2 hours in the supine position.

Subjects are then ambulated for 2 hours, and samples for cortisol are collected at 30- to 60-minute intervals.

ii. Standard mixed meal test

a) **Purpose.** A standard mixed meal follows to identify activation of cortisol release through GIP or other gastrointestinal hormones, whose receptors might be abnormally and functionally expressed in cortisol-producing cells.

b) **Procedure**

Blood samples for cortisol are collected at 0, 30, 60, 120, and 240 minutes with respect to the initiation of the meal.

iii. ACTH test

At the end of the preceding tests, within the same day, the short 250-μg ACTH test is carried out, to serve as a reference test, with samples for cortisol collected at times 0 (before ACTH administration), 30, and 60 minutes.

b. Day 2

i. GnRH and TRH tests

a) **Purpose.** To detect anomalous activation of cortisol through GnRH, LH, FSH, TRH, TSH, or prolactin receptor (PR)

b) **Procedure**

1) Collect fasting baseline samples for cortisol.
2) Administer 100 μg GnRH via IV, as described earlier, and obtain blood samples for cortisol at 30, 60, and 120 minutes to detect potential increases related to GnRH, LH, and FSH.
3) After a 2-hour interval, administer 200 μg TRH via IV and obtain blood samples for cortisol at 0, 30, 60, and 120 minutes to detect potential increases in cortisol induced by TSH, PR, or TRH.

c. Day 3

i. Glucagon, vasopressin, and metoclopramide tests

a) **Purpose.** To assess the possibility that cortisol secretion is modulated by glucagon, arginine vasopressin, or serotoninergic receptors.

b) **Procedure**

1) Inject 1 mg glucagon IV and collect samples for cortisol at times 0, 30, 60, and 120 minutes.

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2) Inject 10 μg of desmopressin as a very slow bolus (10 IU of vasopressin IM was recommended initially, but native vasopressin is unavailable in most countries, and this dose is "borrowed" from the workup of Cushing disease) at times 0, 30, 60, and 120 minutes.
3) Inject metoclopramide (10 mg) IV and collect samples at times 0, 30, 60, and 120 minutes.

c) **Interpretation.** Cortisol usually declines with time in the morning to noon hours, reflecting a normal diurnal variation. With this limitation in mind and to avoid false-positive diagnoses, an arbitrarily defined, increase in cortisol <25% is considered as lack of response. Increments ≥25% are viewed as significant responses (25% to 49%, "partial response"; ≥50%, "positive response"). Any positive change warrants further investigation to identify the precise pathway involved. Detailed description of these further lines of testing is available elsewhere.

F. Assessing adrenal cortical secretory function

1. Rapid ACTH stimulation test (cosyntropin [Cortrosyn] test)

a. Purpose

i. Evaluation of adrenocortical function cases of suspected primary or secondary adrenal insufficiency
ii. Diagnosis of late-onset or mild congenital adrenal hyperplasia (CAH) secondary to 21-hydroxylase deficiency.

Cosyntropin is a potent and rapid stimulator of cortisol and aldosterone secretion. The cosyntropin test can be used on an inpatient or outpatient basis and is apparently unaffected by time of day and food intake. In a previously undiagnosed patient, it can, and indeed should, be performed even in the emergency room, while glucocorticoid replacement with dexamethasone is concomitantly initiated.

b. Procedure

i. Draw baseline samples to determine serum cortisol, renin

(plasma renin activity [PRA]) and aldosterone, and ACTH, which will help differentiate primary from secondary adrenal hypofunction.

ii. Inject 250 μg of cosyntropin by IV or IM route. For IV use, dilute cosyntropin in 2 to 5 mL sodium chloride 0.9% and inject over 2 minutes.

iii. Obtain repeat samples for serum cortisol (and aldosterone) 30 and 60 minutes following ACTH administration.

c. Interpretation

i. **Hypoadrenalism.** A normal adrenal response to ACTH consists of a rise in serum cortisol to 18 μg/dL or greater. With the change in assays over time, a **higher cutoff value of 20 μg/dL is now also used** to increase the sensitivity of the test. A normal response effectively rules out primary adrenal insufficiency. Patients with secondary adrenal insufficiency usually show a blunted response to cosyntropin but occasionally have a normal response. Baseline ACTH levels in primary adrenal insufficiency are high, generally >50 to 100 pg/mL, whereas levels in secondary adrenal insufficiency are low or normal (10 pg/mL or less). The recommended diagnostic cutoff for ACTH in primary adrenal insufficiency is two times the upper limit of the reference interval.

Evaluation of **renin and aldosterone** helps in distinguish primary from secondary adrenal insufficiency. An elevated PRA or concentration in combination with a (inappropriately) normal or low serum aldosterone suggests primary adrenal insufficiency.

ii. **CAH.** 21-Hydroxylase deficiency is the most common form of late-onset/mild CAH detected by the ACTH test. Exaggerated response of 17α-hydroxyprogesterone (17-OH progesterone), the compound proximal to the enzymatic block, to levels >15 ng/mL (at 60 minutes) is the hallmark of this condition. In normal subjects, levels are <10 ng/mL. Heterozygotes for the various forms of 21-hydroxylase deficiency may have 60-minute post-ACTH levels as low as 5 ng/mL, which overlap with values in the p.

1085p. 1086general population. Patients with more severe forms may present with high basal levels of 17-OH progesterone that are not further stimulated by exogenous ACTH. Less commonly, the diagnosis of relatively rare forms of CAH can be established using the ACTH test. In patients with 11β-hydroxylase deficiency, ACTH-stimulated values of 11-deoxycortisol, the steroid most proximal to the 11β-hydroxylation step, are very high (>1 μg/dL) compared with the normal population. In the rare condition of 3β-hydroxysteroid dehydrogenase deficiency, 17-OH pregnenolone rises more steeply than in normal subjects following the injection of ACTH, resulting in a ratio of 17-OH pregnenolone to 17-OH progesterone >10 (and usually >20). Recently, modified age-related criteria have been proposed for genetically proven 3β-hydroxysteroid dehydrogenase deficiency based on ACTH-stimulated 17-OH pregnenolone values: infants, ≥12 600 ng/dL; Tanner stage I children, ≥5 490 ng/dL; children with premature pubarche, ≥9 790 ng/dL; adults, ≥9 620 ng/dL. In all, the number of adults studied for ACTH responses in this condition is limited.

2. **Low-dose (1-μg) ACTH test**
   a. **Purpose.** A screening test for impaired HPA axis
   b. **Procedure**
      i. The test can be performed at any time during the day.
      ii. Draw a blood sample for cortisol. A sample for ACTH is optional.
      iii. Inject 1 μg of ACTH via IV. As no standard packaging for this dose is currently available, the 250-μg Cortrosyn vial must be serially diluted in saline to a final volume of 2 mL containing 1 μg of ACTH.
      iv. Draw blood for serum cortisol at 20, 30, and 40 minutes after the injection of ACTH.
   c. **Interpretation.** This test is more sensitive and accurate than the 250-μg dose of ACTH in detecting partial adrenal gland insufficiency, especially in patients with secondary adrenal deficiency. The 250-μg dose of ACTH produces massive pharmacologic concentrations of ACTH, exceeding blood

concentrations of 10 000 pg/mL, which is way above the ACTH level seen even under extreme conditions in real life. Therefore, the 250-μg dose tends to test only for maximum adrenocortical capacity and overrides any more partial loss of cortisol function. The 1-μg cosyntropin test can replace the 250-μg dose because it is more likely to detect partial or more subtle forms of adrenal insufficiency, in particular secondary adrenal insufficiency resulting from pituitary tumors or chronic glucocorticoid treatment. Indeed, even this dose of ACTH may be much higher than the required dose to stimulate cortisol effectively because **it has been recently shown that 0.03 μg dose of ACTH increases cortisol to >20 μg/dL**. However, at this very low dose of ACTH, the test has not been validated for use in adrenal insufficiency. **Two important limitations, however, should be considered** with the 1-μg test: (a) care must be taken to produce the 1-μg dose accurately by serial dilutions; (b) **the test may be unreliable in the first few weeks after acutely induced secondary hypoadrenalism (e.g., after pituitary surgery)** because the evolution of impaired adrenal reserve (cortisol response to ACTH) under these conditions requires some time, yet the HPA axis may already be severely damaged as a result of ACTH deficiency.

3. **Metyrapone tests**
   a. **Single-dose metyrapone test**
      i. **Purpose. Metyrapone** activates the HPA axis by blocking cortisol production at the 11-hydroylase step, which leads to lowering of cortisol levels. This test is used to **establish or confirm the diagnosis of adrenal insufficiency** and is particularly **useful when secondary or partial adrenal insufficiency is suspected**. Metyrapone is an inhibitor of 11β-hydroxylase, the adrenal enzyme responsible for catalyzing the conversion of 11-deoxycortisol (compound S) to cortisol—the last step in cortisol synthesis. Following metyrapone administration, cortisol synthesis is blocked, and the low levels of cortisol lead to increased ACTH p.

1086p. 1087release, which accelerates the production of adrenal steroids proximal to the enzymatic block, particularly the immediate preblock precursor 11-deoxycortisol. **11-Deoxycortisol can be measured in serum or urine** (as tetrahydro-11-deoxycortisol).

ii. Procedure

a) Metyrapone. Two to three grams as a single dose, depending on body weight (<70 kg, 2 g; 70 to 90 kg, 2.5 g; >90 kg, 3 g), is given at midnight with a snack, to minimize the nausea accompanying metyrapone.

b) Serum cortisol and 11-deoxycortisol are collected at 8 A.M. the following morning.

iii. Interpretation. A normal response is an increase in serum 11-deoxycortisol >7 μg/dL; patients with primary or secondary adrenal insufficiency exhibit <5 μg/dL. Cortisol levels should fall below 5 μg/dL to confirm adequate metyrapone-induced blockade of cortisol synthesis. An abnormal metyrapone test in a subject with a near-normal response to the rapid ACTH stimulation test suggests **secondary adrenal insufficiency**. The dose of metyrapone needs to be increased in patients receiving phenytoin (Dilantin), rifampin, mitotane, or phenobarbital, which enhance the clearance of both metyrapone and steroids. Alternatively, short-term discontinuation of these agents or reliance on tests other than metyrapone should be considered. **Adverse effects of metyrapone** include gastric irritation, nausea, and vomiting. The overnight (single-dose) metyrapone test is generally safer than the standard multiple-dose metyrapone test; however, caution must be applied, especially in patients in whom primary adrenal disease is likely, because adrenal crisis can be precipitated. Hospitalization with proper monitoring of the patient's condition is, therefore, suggested for this test. It is advisable to demonstrate some responsiveness of the adrenal cortex to ACTH before initiating a metyrapone test. If the ACTH stimulation test is already markedly blunted, then the metyrapone test may not be required.

b. Standard (multiple-dose) metyrapone tests

i. **Purpose.** Assessment of the functional capacity of the pituitary–adrenal axis. This test can be used to establish or confirm the diagnosis of primary or secondary adrenal insufficiency and, for this purpose, should be carried out as an inpatient procedure only. It may also be helpful in the differential diagnosis of established CS.

ii. **Procedure: serum**

a) Administer metyrapone, 750 mg PO q4h, for six doses from 8 A.M. on the first morning to 4 A.M. on the following morning.

b) Four hours following the last metyrapone dose (at 8 A.M.), draw blood for serum cortisol and 11-deoxycortisol levels.

iii. **Procedure: urine**

a) **Day 1.** Beginning at 8 A.M., collect a 24-hour urine sample for baseline creatinine and 17-hydroxycorticosteroids (17-OHCS) levels.

b) **Day 2.** Repeat day 1. (Some investigators skip day 2 and use only one 24-hour urine collection, on day 1, for baseline determinations.)

c) **Day 3.** Repeat day 1. In addition, starting at 8 A.M., 750 mg metyrapone is given PO q4h for six doses.

d) **Day 4.** Repeat day 1.

iv. **Interpretation**

a) The normal response is a serum 11-deoxycortisol level of 10 μg/dL or greater at 8 A.M., 4 hours following the last dose of metyrapone. The plasma cortisol levels should be <5 μg/dL, indicating effective blockade by metyrapone. If a normal 11-deoxycortisol response is not seen and the cortisol levels are >5 μg/dL, the test should be repeated.

b) The normal response using the urine test is a two- to fourfold rise in 17-OHCS on the day of metyrapone treatment or on the day after. Generally, 17-OHCS will increase by at least 6 mg over baseline levels. In patients with primary or secondary adrenal insufficiency, little or no increase in 17-OHCS excretion is seen.

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c) Because of enhanced metabolism of metyrapone, patients on phenytoin (Dilantin) generally have subnormal increase in serum 11-deoxycortisol levels after standard metyrapone administration. This can be corrected by administering a double dose of metyrapone, 750 mg q2h (12 doses), instead of 750 mg q4h (6 doses). Patients receiving estrogens (or who are pregnant) as well as those with hypothyroidism, renal failure, cirrhosis of the liver, or malnutrition may have subnormal urine 17-OHCS responses to metyrapone. Exaggerated peak plasma 11-deoxycortisol has been encountered in women taking oral contraceptives and patients with hypothyroidism, diabetes mellitus, chronic renal failure, or congestive heart failure.

d) **In the differential diagnosis of CS,** stimulation of 17-OHCS excretion by >70% or of a plasma 11-deoxycortisol level by >400-fold is indicative of pituitary (ACTH-dependent, cortisol feedback–sensitive) disease. The latter criterion, however, is difficult to implement, because most assays do not measure low basal (unstimulated) levels of plasma 11-deoxycortisol reliably.

v. **Precautions.** Metyrapone-induced gastric irritation leading to nausea and vomiting can be reduced by administering the drug with food or milk. Headaches and dizziness may be seen with the multiple-dose test and can be alleviated by bed rest. Caution should be observed when administering metyrapone to patients suspected of having primary adrenal insufficiency, because there is a risk of adrenal crisis. They should be closely observed during the test so that supportive measures can be given if needed.

4. **Insulin-induced hypoglycemia test.** Although this test remains the “gold standard” to diagnose hypofunction of the HPA axis, it is now performed less often than it was previously.
5. If a corticotropin stimulation test is not feasible, a low morning cortisol <140 nmol/L (5 μg/dL) in combination with plasma ACTH as a preliminary test may be suggestive of adrenal insufficiency (until confirmatory testing is available). Very **low morning cortisol (<3 μg%) is nearly always indicative of**

hypoadrenalism, except for rare subjects with CBG deficiency or at least some reversal of the normal day/night circadian rhythm.

6. **Assay issues with cortisol.** Commercial assays vary considerably. In contrast, structurally based assays, such as HPLC and tandem mass spectrometry (LC-MS/MS), are being more widely used.

V. DYNAMIC ASSESSMENT OF HYPER- AND HYPOALDOSTERONISM

A. Dynamic testing for the diagnosis of primary hyperaldosteronism

1. Salt-volume loading tests

a. Purpose. Confirmation of the diagnosis of primary hyperaldosteronism (primary aldosteronism; PA), following initial screening based on the aldosterone/PRA or aldosterone/renin ratio (ARR). These tests should be **deferred until hypokalemia is corrected and are not recommended in individuals with severe hypertension, renal or congestive heart failure, or cardiac arrhythmia**. Given the variability of basal aldosterone levels in this disorder, the effect of blood pressure–lowering drugs on both PRA and aldosterone levels, and the age-related decline in PRA, nonsuppressibility of aldosterone in response to volume-expansion maneuvers has proved to be an excellent indicator of primary hyperaldosteronism. Volume expansion via saline infusion, high salt intake, or mineralocorticoid administration in any condition other than primary hyperaldosteronism suppresses aldosterone levels by >50%. In primary hyperaldosteronism, an additional volume load has only a minimal effect on aldosterone concentration. Spuriously increased ARR may be corrected by the use of one or more of the following tests.

b. Saline infusion test

i. Procedure

a) Patients should be on a regular diet. Obtain serum K^+ and proceed only if concentration is ≥4 mmol/L.

b) Obtain baseline aldosterone levels.

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c) Infuse 0.9% sodium chloride solution for 4 hours (500 mL/hour, a total of 2 L).

d) Obtain repeat samples for aldosterone and potassium.

ii. Interpretation

Following the infusion, plasma aldosterone will normally suppress by at least **50%** or to <5 ng/dL, whereas patients with primary hyperaldosteronism will display postinfusion levels >10 ng/dL. Values between 5 and 10 ng/dL are indeterminate. Unfortunately, these values were not established based on currently used assays, such that judicious interpretation is required. A recent Chinese study suggested a cutoff level of 11.5 ng/dL.

iii. Precautions

This test should not be performed in patients with severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, or severe hypokalemia.

c. Oral salt loading test

i. Procedure

a) Increase sodium intake to >200 mmol/L (6 g/day) for 3 days and add slow-release potassium chloride tablets to keep serum potassium in the normal range.

b) Obtain 24-hour urine collection to verify that the intended intake has been attained.

c) Obtain 24-hour urine collection starting on the morning of day 3 for the measurement of urinary sodium and aldosterone.

ii. Interpretation

Urinary sodium excretion >200 mmol/24 hour is an indicator of proper compliance with the prescribed increased salt intake. Urinary aldosterone excretion **>12 to 14 *μ*g/24 hours is highly suggestive of PA, whereas excretion <10 *μ*g/24 hours practically excludes this diagnosis**. HPLC/tandem MS is the preferred method of measurement because RIAs for urinary aldosterone perform poorly in this setting.

iii. Precaution

Increasing dietary sodium may be risky and should be

considered on an individual basis in patients with severe hypertension, renal failure, or congestive heart failure. As sodium loading increases, kaliuresis and hypokalemia may occur; therefore, serum potassium should be measured daily and replacement of potassium chloride should be prescribed.

B. Aldosterone posture test: An ancillary test for equivocal cases of primary hyperaldosteronism

1. **Background.** Aldosterone-producing adenoma (APA) appears to be quite responsive to ACTH, but not to angiotensin II. The opposite pertains to bilateral adrenal hyperplasia (BAH), in which angiotensin II is the major regulator.
2. **Procedure for posture test**
   - **a.** Samples for PRA and plasma aldosterone are obtained between 8 and 9 A.M., after the patient has been in the supine position for 30 minutes.
   - **b.** The patient assumes upright posture and ambulates moderately for 4 hours, at which time samples are collected again.
3. **Interpretation.** Normal subjects assuming upright posture always increase PRA and, therefore, plasma aldosterone levels, and this is further enhanced with ambulation. Because PRA is suppressed with an APA, plasma aldosterone does not respond to posture and declines in association with the diurnal reduction in ACTH (8 A.M. to noon). Patients with BAH show a normal increase (>25% of the baseline value) in aldosterone levels with upright posture, accounted for by a partially intact renin response and enhanced adrenal gland sensitivity to angiotensin II. The accuracy of the posture stimulation test has been estimated at 85%. The Endocrine Society guidelines therefore recommended that this test, particularly if it does not show a rise in aldosterone (consistent with angiotensin II-unresponsive APA or familial hyperaldosteronism type I), may serve an ancillary role, for example, when adrenal venous sampling was unsuccessful (or, more commonly, is simply not available) in a patient harboring a unilateral adrenal mass on a computed tomographic scan.

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C. Renin stimulation test: Confirming a “low-renin status”

1. **Purpose.** This test is suitable to confirm the presence of a low-

renin status. The test is useful to detect low-renin forms of hypertension, including mineralocorticoid excess syndromes, and to confirm the diagnosis of hyporeninemic hypoaldosteronism.

2. **Procedure**
   - **a.** This test should be performed between 8 A.M. and noon. Patients may be on a regular diet. If possible, all antihypertensive medications should be discontinued for 2 weeks before testing.
   - **b.** The patient should rest supine for at least 30 minutes, and a blood sample for plasma renin should then be drawn.
   - **c.** Furosemide, 60 to 80 mg PO, is given. The patient should then ambulate for 3 to 4 hours, after which a sample for plasma renin analysis is taken with the patient in the sitting or upright position.
3. **Interpretation.** Basal levels <1 ng/mL/hour and stimulated levels <2 ng/mL/hour are considered suppressed. Suppressed levels are typically seen in patients with PA, low-renin essential hypertension, CS, mineralocorticoid ingestion, 11-hydroxylase– and 17-hydroxylase–deficient forms of CAH, and Liddle syndrome. Lack of an increase in renin can also be seen in hyporeninemic hypoaldosteronism.

VI. THE ADRENAL MEDULLA

A. Dynamic testing for pheochromocytoma and paraganglioma (PPGL)

To establish the diagnosis of PPGL, the most reliable forms of biochemical testing are the measurements of plasma free metanephrines or urinary fractionated metanephrines, using LC-MS or electrochemical detection methods. To distinguish true-positive from false-positive borderline elevations of metanephrines, the **clonidine suppression test** with measurements of plasma normetanephrine using the above mentioned methods is recommended. The test is claimed to provide a diagnostic specificity of 100% and sensitivity 97%. Depending on the type of assay, avoid the use of the following medications/agents during the measurements of blood or urine metanephrine/normetanephrines, which may lead to false-positive results: acetaminophen, labetalol (urine), sotalol (urine), *α*-methyldopa, buspirone, tricyclic antidepressants, phenoxybenzamine, monoamine oxidase inhibitors, sympathomimetics, cocaine, sulfasalazine, and L-DOPA.

1. **Clonidine suppression test**
   a. **Purpose.** Evaluation of suspected PPGL
   b. **Procedure**
      i. If possible, all medications should be discontinued 1 week before the test. Sympatholytic drugs should be withdrawn 48 hours before testing.
      ii. The patient should be fasted overnight before the test and prohibited from drinking coffee or smoking on the day of the test.
      iii. An indwelling IV line kept open with normal saline should be inserted for blood drawing at least 30 minutes before the test.
      iv. The patient should be kept supine in quiet surroundings for at least 30 minutes before and during the entire test.
      v. Draw baseline blood samples for normetanephrines. A baseline blood pressure and heart rate should also be obtained. The test should be cancelled if baseline blood pressure is <110/60 mm Hg or the patient is volume depleted.
      vi. Give 0.3 mg clonidine PO with water.
      vii. Draw blood samples for free normetanephrines 3 hours after clonidine administration. Blood pressure and heart rate measurements should be obtained every 30 minutes.
   c. **Interpretation.** An abnormal test result indicating a PPGL includes an elevated concentration of plasma free normetanephrine 3 hours after clonidine administration and a less than 40% decrease in levels compared with baseline.

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   d. **Precautions.** Hypotension, sometimes marked, has been described during this test and may be a particular problem in patients who have received antihypertensive medications within a few days before the test. Patients should be observed during the entire test and frequent blood pressure readings obtained. **Clonidine is not recommended for use during pregnancy.**

VII. THE THYROID GLAND

A. Human recombinant (hr) TSH (“thyrogen”) test

1. **Purpose.** Detection, through TSH-stimulated thyroglobulin (Tg) secretion level for the estimation of residual/recurrent local or metastatic thyroid cancer in subjects who have already undergone total thyroidectomy for differentiated thyroid cancer. This applies to subject who underwent total thyroidectomy followed by radioiodine treatment. It is not suitable for subjects undergoing hemithyroidectomy only.
2. **Procedure.** Although this test can be performed either in conjunction with or independent of total-body radioiodine scan, it is presently most often performed without total-body scan (TBS). The test is intended to assess Tg secretion in subjects receiving TSH-suppressive doses of T_4 on a regular basis. **Patients with increased circulating anti-Tg antibodies are not candidates for this test because of interference of the antibodies with the Tg assay, but they can still undergo thyrogen-stimulated TBS.**
   a. If the test is combined with TBS, patients are placed on a low-iodine diet for 2 to 4 weeks and urine iodine is determined to verify that a low-iodine state has been attained.
   b. Although the patient continues to receive the usual dose of L-thyroxine required to attain TSH suppression, administer thyrogen (0.9 mg) IM on day 1 and again on day 2.
   c. If TBS is to be performed, administer the diagnostic dose of radioiodine on day 3 and proceed with scanning on day 5 (72 hours after the last thyrogen injection).
   d. On day 5, 72 hours after the last thyrogen injection, collect blood for the measurement of Tg, anti-Tg antibodies, and TSH.
3. **Interpretation**

   Post stimulation Tg <1 ng/mL: Consistent with excellent response to treatment and low risk

   Post stimulation Tg 1 to 10 ng/mL: “Grey zone”

   Post stimulation ≥10 ng/mL: Biochemical evidence of incomplete response to treatment

B. TRH test

See Anterior Pituitary, Section III.A.

C. Dynamic testing in medullary thyroid carcinoma (MTC)

The widely available genetic testing for *RET* mutations has made dynamic calcitonin stimulation tests largely obsolete. Calcitonin

stimulation tests are optional under the following circumstances: **(a)** thyroid nodule of uncertain nature by fine-needle aspiration, with borderline or mildly elevated circulating calcitonin levels; **(b)** follow-up of patients with established MTC; **(c)** diagnosis of MTC in a patient with multiple endocrine neoplasia type 2 (MEN2), who did not undergo prophylactic thyroidectomy and who has no other evidence of MTC; **(d)** diagnosis of MTC in seemingly unaffected members of the rare families with MEN2 without identifiable *RET* mutations; **(e)** young children with MEN2 in whom the parents wish to delay thyroidectomy; **(f)** occasional patients with MEN2, who have already had thyroidectomy but who are being evaluated for the appearance of a new lesion in the neck or elsewhere; and **(g)** differentiating MTC from begin C-cell hyperplasia (CCH), to avoid unnecessary thyroidectomy, because CCH is a benign condition associated with non-MTC thyroid diseases (autoimmune thyroiditis or benign nodules) or other diseases/conditions (severe renal insufficiency, hyperparathyroidism, or hypergastrinemia).

Calcitonin should be measured by a highly specific assay (e.g., immunometric chemiluminescent assays) to avoid heterophilic antibody interference causing a false hypercalcitoninemia.

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1. **Calcium infusion tests**
   a. **Purpose.** Screening and diagnostic test for MTC
   b. **Procedure. Short calcium infusion**
      i. The patient is fasted overnight.
      ii. The dose of infused calcium is weight-adjusted: calcium gluconate, 25 mg (2.3 mg or 0.12 mEq of elemental calcium)/kg.
      iii. Obtain a baseline blood sample for calcitonin.
      iv. Calcium gluconate is administered IV, as a very slow bolus, administered during no less than 3 minutes. By the end of the infusion, additional blood samples are drawn at 2, 5, and 10 minutes. Continuous cardiac monitoring should be carried out during the test to detect cardiac arrhythmia and allow prompt treatment, when indicated.
   c. **Interpretation.** To separate non-MTC (including normal and CCH cases) from MTC patients, basal calcitonin cutoff were >26 pg/mL in females and >68 pg/mL in males, whereas the

best stimulated calcitonin thresholds for the identification of MTC were >79 and >544 pg/mL for women and men, respectively.

d. **Precautions.** Particular caution must be observed in patients with cardiac disease or arrhythmia and in subjects treated with digitalis glycosides. Electrocardiographic evaluation of heart rate QTc and PR intervals should be taken (heart rate of <40 or >110 beats/minute and/or the presence of second - or third-degree atrioventricular block contraindicates the execution of the test). It is mandatory to secure that blood levels of calcium, potassium, phosphate, and magnesium are within the normal range before testing. The short calcium infusion test is relatively free of side effects except for a brief feeling of warmth serum. It has been reported to be free of heart rate variations, except for transient bradycardia with a spontaneous resolution, likely related to a vasovagal reaction. Calcium levels generally are not increased by more than 1 mg/dL.

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