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increased risk for germ cell cancer, requiring monitoring and potential gonadectomy. Long-term urogynecologic follow-up may be needed. Psychosocial and psychosexual evaluation and management are also important, particularly to address the reported increased rates of mental health symptoms and poorer quality of life sometimes related to social relationships.

■ ■GLOBAL CONSIDERATIONS The approach to an individual with atypical genitalia or another DSD requires cultural sensitivity, as the concepts of sex and gender vary widely around the world. Rare genetic DSDs can occur more frequently in specific populations (e.g., 5 α -reductase type 2 in the Dominican Republic). Different forms of CAH also show ancestral and geographic variability. In many countries, appropriate biochemical or genetic tests may not be readily available, and access to appropriate forms of treatment and support may be limited. PART 12 Endocrinology and Metabolism ■ ■FURTHER READING Ahmed SF et al: Turner HE. Society for Endocrinology UK Guidance on the initial evaluation of a suspected difference or disorder of sex development (Revised 2021). Clin Endocrinol (Oxf) 95:818, 2021. Claahsen-van der Grinten HL et al: Congenital adrenal hyperplasiacurrent insights in pathophysiology, diagnostics and management. Endocr Rev 43:91, 2022. Cools M et al: Caring for individuals with a difference of sex development (DSD): A consensus statement. Nat Rev Endocrinol 14:415, 2018. Gravholt CH et al: The changing face of Turner syndrome. Endocr Rev 12:44, 2023. Gravholt CH et al: Clinical practice guidelines for the care of girls and women with Turner syndrome. Eur J Endocrinol 190:G53, 2024. Mongan NP et al: Androgen insensitivity syndrome. Best Pract Res Clin Endocrinol Metab 29:569, 2015. Morin J et al: Gonadal malignancy in patients with differences of sex development. Transl Androl Urol 9:2408, 2020. Zitzmann M et al: European Academy of Andrology guidelines on Klinefelter syndrome: Endorsing organization: European Society of Endocrinology. Andrology 9:145, 2021. Shalender Bhasin, J. Larry Jameson

Male Reproductive System The male reproductive system regulates sex differentiation, androgenization, and the hormonal changes that accompany puberty, ultimately leading to spermatogenesis and fertility. Under the control of the pituitary hormones—luteinizing hormone (LH) and follicle-stimulating hormone (FSH)—the Leydig cells of the testes produce testosterone and germ cells are nurtured by Sertoli cells to divide, differentiate, and mature into sperm. During embryonic development, testosterone and dihydrotestosterone (DHT) induce the Wolffian duct and virilization of the external genitalia. During puberty, testosterone promotes somatic growth and the development of secondary sex characteristics. In the adult, testosterone is necessary for spermatogenesis, libido and normal sexual function, and maintenance of muscle and bone mass. This chapter focuses on the physiology of the testes and disorders associated with decreased androgen production, which may be caused by gonadotropin deficiency or by primary testis dysfunction. Infertility occurs in ~5% of men and is increasingly amenable to treatment by hormone replacement or by using sperm transfer techniques. For further discussion of

sexual dysfunction, disorders of the prostate, and testicular cancer, see Chaps. 409, 92, and 93, respectively.

DEVELOPMENT AND STRUCTURE

OF THE TESTIS The fetal testis develops from a single bipotential progenitor cell population in the undifferentiated gonad after expression of a genetic cascade that is initiated by the gene encoding SRY (sex-related gene on the Y chromosome) (Chap. 402). SRY, whose expression is regulated by histone modification and DNA methylation, induces differentiation of Sertoli cells, which surround germ cells and, together with peritubular myoid cells, form testis cords that will later develop into seminiferous tubules. Sertoli cells direct the differentiation of fetal germ cells into spermatogenic precursors. Fetal Leydig cells and endothelial cells migrate into the gonad from the adjacent mesonephros but may also arise from interstitial cells that reside between testis cords. Fetal Leydig cells atrophy after birth and do not contribute to the origin of adult Leydig cells, which originate from undifferentiated progenitor cells that appear in the testis after birth and acquire full steroidogenic function during puberty. Testosterone produced by the fetal Leydig cells supports the growth and differentiation of Wolffian duct structures that develop into the epididymis, vas deferens, and seminal vesicles. Testosterone is also converted to DHT (see below), which induces formation of the prostate and the external male genitalia, including the penis, urethra, and scrotum. The development of the germ cells is dependent on normally functioning Sertoli and Leydig cells and cannot occur without them; in contrast, the somatic cells can develop and function without the germ cells. Testicular descent through the inguinal canal is controlled in part by Leydig cell production of insulin-like factor 3 (INSL3), which along with testosterone, acts through their cognate receptors—relaxin/insulin-like family peptide receptor 2 (RXFP2) and androgen receptor (AR)—to guide the inguinoscrotal descent of the testes. Sertoli cells produce Müllerian inhibiting substance (MIS), which causes regression of the Müllerian structures, including the fallopian tube, uterus, and upper segment of the vagina.

NORMAL MALE PUBERTAL DEVELOPMENT Puberty commonly refers to the maturation of the reproductive axis, initiation of gametogenesis, rhythmic sex hormone secretion, and the development of secondary sex characteristics. In addition to reproductive hormones, it requires a coordinated response of multiple hormonal systems including metabolic signals (e.g., leptin), as well as the adrenal and growth hormone (GH, IGF-1) axes (Fig. 403-1). The development of secondary sex characteristics is initiated by adrenarche, which usually occurs between 6 and 8 years of age when the adrenal gland begins to produce greater amounts of androgens from the zona reticularis, the principal site of dehydroepiandrosterone (DHEA)

production. The sex maturation process is accelerated by the activation of the hypothalamic-pituitary axis and the production of gonadotropin-releasing hormone (GnRH). The GnRH pulse generator in the infundibular stalk. Height velocity Testicular volume (mL) 4–6 10–12 15–25 Genitalia

Pubic hair

Tanner stages

Age (years)

FIGURE 403-1 Pubertal events in males. Sexual maturity ratings for genitalia and pubic hair and divided into five stages.

nucleus is active during fetal life and early infancy but is restrained until the early stages of puberty by a neuroendocrine brake imposed by the inhibitory actions of glutamate and γ -aminobutyric acid (GABA) in the mediobasal hypothalamus and neuropeptide Y. Kisspeptin 1 (kiss1), neurokinin B, dynorphin (KNDy) neurons in the arcuate nucleus and possibly other kiss1 neurons in the anteroventral periventricular nucleus (AVPV), and neurons producing neuropeptide Y (NPY), agouti-related protein (AgRP), pro-opiomelanocortin (POMC), and cocaine and amphetamine-regulated transcript (CART) play an important role in the control of puberty. The Kisspeptin pathway plays a critical role in puberty. Individuals with mutations of G protein-coupled kisspeptin receptor fail to enter puberty. Infusion of the Kiss1 is sufficient to induce premature puberty in nonhuman primates. Kisspeptin signaling plays an important role in mediating the feedback action of sex steroids on gonadotropin secretion and in regulating the tempo of sexual maturation at puberty. The metabolic control of puberty is mediated via the action of leptin secreted by adipocytes, and by neurons expressing NPY and AgRP, and by POMC and CART expressing neurons that transmit the energy sensing signals communicated by leptin to the Kiss1 neurons. MKRN3, an imprinted gene encoding makorin ring finger protein 3, serves as an upstream inhibitor of GnRH secretion and plays an important role in directing the onset of puberty. Leptin plays a permissive role in the resurgence of GnRH secretion at the onset of puberty, as leptin-deficient individuals also fail to enter puberty (Chap. 413). The adipocyte hormone leptin, the gut hormone ghrelin, neuropeptide Y, AgRP, CART, and kiss 1 integrate the signals originating in energy stores and metabolic tissues and control the onset of puberty through regulation of GnRH secretion. Energy deficit and excess and metabolic stress are associated with disturbed reproductive maturation and timing of puberty. The early stages of puberty are characterized by nocturnal surges of LH and FSH. Growth of the testes is usually the first clinical sign of puberty, reflecting an increase in seminiferous tubule volume. Increasing levels of testosterone deepen the voice and stimulate muscle growth. Conversion of testosterone to DHT leads to growth of the external genitalia and pubic hair. DHT also stimulates prostate and facial hair growth and initiates recession of the temporal hairline. The growth spurt occurs at a testicular volume of ~10–12 mL. GH increases early in puberty and is stimulated in part by the rise in gonadal steroids. GH increases the level of insulin-like growth factor 1 (IGF-1), which enhances linear bone growth. The prolonged pubertal exposure to gonadal steroids (mainly estradiol) ultimately induces epiphyseal closure and limits further bone growth. REGULATION OF TESTICULAR FUNCTION ■ ■ REGULATION OF THE HYPOTHALAMIC-PITUITARY-TESTIS AXIS IN ADULT MAN Pulsatile secretion of GnRH in the hypothalamus is regulated by kisspeptin, neurokinin B (NKB), and dynorphin (DYN) (Fig. 403-2)

that are co-expressed within the KNDy neurons in the arcuate nucleus and are important regulators of mammalian reproduction. Kisspeptin binds to the kisspeptin (GPR54) receptors in the cell bodies of the GnRH neurons as well as in the GnRH nerve terminals in the median eminence to induce pulsatile GnRH secretion into the portal blood. As a component of this autocrine/paracrine loop, NKB released by the KNDy neurons activates NK3R to stimulate kisspeptin release. KNDy neurons also produce dynorphin A, which inhibits basal as well as NKB-stimulated kisspeptin release through the mediation of K-type opioid receptor. Exogenous opioids suppress LH and FSH and inhibit LH pulsatility likely by mimicking the effects of DYN, an endogenous opioid peptide that acts primarily through the κ -opioid receptor (KOR). The negative feedback effects of testosterone, estradiol, and progesterone are mediated through KNDy neurons in the preoptic area by inhibition of kisspeptin release. Mutations in the genes encoding NKB, tachykinin 3 (TAC3), or its receptor (TACR3) are associated with hypogonadotropic hypogonadism. Hypothalamic GnRH regulates the production of the pituitary gonadotropins LH and FSH (Fig. 403-2). GnRH is released in discrete

Arcuate nucleus NK3R KOR Dyn NKB Preoptic area KNDY neurons Kiss Negative feedback by sex steroids Dyn – Disorders of the Testes and Male Reproductive System CHAPTER 403 GnRH neuron GPR54 GnRH Kiss Pulsatile GnRH secretion Median eminence Anterior pituitary E2 Pulsatile LH, FSH secretion Testosterone Inhibin B + – DHT Seminiferous tubules Tunica albuginea Vas deferens LH FSH Epididymis + + Interstitial Leydig cells (testosterone) Sertoli cell (Inhibin B) Spermatid Spermatogonium

FIGURE 403-2 Hypothalamic-pituitary-gonadotropin axis, structure of testis, seminiferous tubule. DHT, dihydrotestosterone; Dyn, dynorphin A; E2, 17 β -estradiol; FSH, follicle-stimulation hormone; GnRH, gonadotropin-releasing hormone; KISSR, G protein-coupled receptor 54 for kisspeptin; Kiss, kisspeptin; KNDY, kisspeptin, neurokinin B, dynorphin neurons; KOR, K-type opioid receptor; LH, luteinizing hormone; NKB, neurokinin B; NK3R, neurokinin 3 receptor. pulses approximately every 2 h, resulting in corresponding pulses of LH and FSH. These dynamic hormone pulses account in part for the wide variations in LH and testosterone, even within the same individual. LH acts primarily on the Leydig cell to stimulate testosterone synthesis. The regulatory control of androgen synthesis is modulated by dynamic integration of the feedforward elements exerted on the testis by LH

and FSH and the feedback exerted by testosterone and estrogen on both the hypothalamus and the pituitary. FSH acts on the Sertoli cell to regulate spermatogenesis and the production of inhibin B, which acts to selectively suppress pituitary FSH. Despite these somewhat distinct Leydig and Sertoli cell-regulated pathways, testis function is integrated at several levels: GnRH regulates both gonadotropins; spermatogenesis requires high levels of testosterone; and numerous paracrine interactions between Leydig, Sertoli, and germ cells are necessary for normal testis function.

■ ■ THE LEYDIG CELL: ANDROGEN SYNTHESIS LH binds to its transmembrane G protein-coupled receptor to activate the adenylyl cyclase/cyclic AMP/protein kinase A pathway. Stimulation of the LH receptor induces steroid acute regulatory (StAR) protein, along with several steroidogenic enzymes involved in androgen

PART 12 Endocrinology and Metabolism

C D

A 10 B

Cholesterol Cholesterol side chain cleavage enzyme CYP11A1 StAR 3 β HSD 1 Pregnenolone
 Progesterone allopregnenolone 3 β -hydroxy steroid dehydrogenase 2 17 α -hydroxylase CYP17A1
 17 α -hydroxylase CYP17 17-hydroxyprogesterone 17 hydroxypregnenolone CYP17A1 CYB5 δ 4
 Androstenedione DHEA 17 β -hydroxysteroid dehydrogenase 3 17 β -HSD 3 Androstenediol
 Testosterone OH O Steroid 5 α -reductase type 2 SRD5A2 CYP19 Aromatase OH O H OH 5 α -
 dihydrotestosterone Estradiol Alternate Backdoor Pathway Classical Pathway FIGURE 403-3 The
 biochemical pathway in the conversion of 27-carbon sterol cholesterol to androgens and estrogens.

synthesis. LH receptor mutations cause Leydig cell hypoplasia or agenesis, underscoring the importance of this pathway for Leydig cell development and function. The rate-limiting process in testosterone synthesis is the transport of intracellular cholesterol to the inner mitochondrial membrane by a protein complex that contains the steroidogenic acute regulatory (StAR) protein and a translocator protein (TSPO), previously called peripheral benzodiazepine receptor protein. Mutations of the StAR protein are associated with congenital lipid adrenal hyperplasia, a rare form of congenital adrenal hyperplasia (CAH) characterized by very low adrenal and gonadal steroids. The major enzymatic steps involved in testosterone synthesis are summarized in Fig. 403-3. After cholesterol transport into the mitochondrion, the formation of pregnenolone, catalyzed by CYP11A1 (side chain cleavage enzyme) and auxiliary electron transferring proteins, is a limiting enzymatic step. The 17 α -hydroxylase and the 17,20-lyase AKR1C2/4 CYP17A1 CYP17A1 Steroid 5 α -reductase type 1 17 hydroxydihydroprogesterone 17 hydroxy allopregnanolone SRD5A1 HSD17B6 17 β -hydroxysteroid dehydrogenase 6 Androsterone Androstenedione 17 β hydroxy steroid dehydrogenase

17 β -hydroxy steroid dehydrogenase 3 HSD17B3 AKR1C1-4 HSD17B3 OH 17 β hydroxy steroid dehydrogenase 6 HSD17B6 AKR1C2 Androstenediol

reactions are catalyzed by a single enzyme, CYP17A1; posttranslational modification (phosphorylation) of this enzyme and the presence of specific enzyme cofactors, such as cytochrome B, confer 17,20-lyase activity selectively in the testis and zona reticularis of the adrenal gland. Although CYP17A1 is able to catalyze the conversion of progesterone to 17 α -hydroxyprogesterone, most of δ 4-androstenedione in humans is derived from the conversion of 17 α -hydroxypregnenolone to DHEA in the δ 5 pathway and further conversion of DHEA to δ 4-androstenedione. Abiraterone is a dual inhibitor of 17 α -hydroxylase and 17,20-lyase activities, which play an important role in androgen synthesis in castration-resistant prostate cancers. Testosterone can be converted to the more potent DHT by a family of steroid 5 α -reductase enzymes, and it is aromatized to estradiol by CYP19 (aromatase). At least two isoforms of steroid 5 α -reductase, SRD5A1 and SRD5A2, have been described; most known patients with 5 α -reductase deficiency have had mutations in SRD5A2, the predominant form in the prostate and the skin. Finasteride predominantly inhibits SRD5A2, whereas dutasteride is a dual inhibitor of both SRD5A1 and SRD5A2. DHT can also be derived through the backdoor pathway in which 17 α -hydroxyprogesterone is converted to androsterone and eventually to DHT. Recent reports of mutations in the AKR1C2/4 genes in under virilized 46,XY individuals suggest that the backdoor pathway for DHT formation, which was originally described in the tammar wallaby, is active in the human fetal testis. The placental progesterone serves as a substrate for the synthesis of

androstosterone via the backdoor pathway, which is then converted to DHT in the genital tubercle.

Testosterone Transport and Metabolism In males, 95% of circulating testosterone is derived from testicular production (3–10 mg/d). Direct secretion of testosterone by the adrenal and the peripheral conversion of androstenedione to testosterone collectively account for another 0.5 mg/d of testosterone. Only a small amount of DHT (70 µg/d) is secreted directly by the testis; most circulating DHT is derived from peripheral conversion of testosterone. Most of the daily production of estradiol (~45 µg/d) in men is derived from aromatase-mediated peripheral conversion of testosterone and androstenedione. Circulating testosterone is bound predominantly to sex hormone-binding globulin (SHBG) and albumin (Fig. 403-4) and, to a lesser extent, to cortisol-binding globulin (CBG) and orosomucoid (also known as α_1 acid glycoprotein). SHBG binds testosterone with much higher affinity than albumin, CBG, and orosomucoid. SHBG binds testosterone with much higher affinity than albumin, CBG, and orosomucoid. SHBG binds testosterone with much higher affinity than albumin, CBG, and orosomucoid.

Testosterone Bioavailability Testosterone (3–10 mg/d) Aromatase (0.3%) Steroid 5 α -reductase (6–8%) Testosterone 5 α -Dihydrotestosterone (DHT) Estradiol • Masculinization of external genitalia • Prostate growth • Hair growth • Bone resorption • Epiphyseal closure • Hypothalamic/ pituitary feedback • Fat mass • Some vascular and behavioral effects • Libido • Wolffian duct • Muscle mass • Bone formation • Spermatogenesis • Erythropoiesis

FIGURE 403-4 Androgen metabolism and actions. SHBG, sex hormone-binding globulin.

greater affinity than albumin, CBG, and orosomucoid. The binding proteins regulate the transport and bioavailability of testosterone. SHBG circulates as a dimer, and testosterone's binding to SHBG involves intermonomeric allosterity such that neither the conformation nor the binding affinity of the two monomers is equivalent. Similarly, estradiol binding to SHBG involves bidirectional, intermonomeric allosterity that changes the distribution of both monomers among various energy and conformational states. Intermonomeric allosterity offers a mechanism to extend the binding range of SHBG and regulate hormone bioavailability as sex hormone concentrations vary widely during life. Albumin contains multiple, allosterically coupled binding sites for testosterone. Testosterone shares these binding sites on albumin with free fatty acids. Commonly used drugs such as ibuprofen and some antibiotics can displace testosterone from albumin under various physiologic states or disease conditions, affecting its bioavailability. SHBG concentrations are decreased by androgens, obesity, diabetes mellitus, hypothyroidism, nephrotic syndrome, and genetic factors. Conversely, polymorphisms in the SHBG gene, estrogen administration, hyperthyroidism, chronic inflammatory illnesses, infections such as HIV or hepatitis B and C, aging, and the use of some anticonvulsants are associated with high SHBG concentrations.

Disorders of the Testes and Male Reproductive System CHAPTER 403 Testosterone is metabolized predominantly in the liver, although some degradation occurs in peripheral tissues, particularly the prostate and the skin. In the liver, testosterone is converted by a series of enzymatic steps that involve 5 α and 5 β -reductases, 3 α - and 3 β -hydroxysteroid dehydrogenases, and 17 β -hydroxysteroid dehydrogenase into androstosterone, etiocholanolone, DHT, and 3 α -androstenediol. These compounds undergo glucuronidation or sulfation before being excreted by the kidneys. Polymorphisms of these enzymes are associated with altered testosterone metabolism and circulating testosterone levels.

Mechanism of Androgen Action Testosterone exerts its biologic effects by either binding to androgen receptor (AR) directly or after its conversion to its metabolites, DHT, and 11-ketotestosterone. 11-Ketotestosterone and 11-ketoandrostenedione are 11-oxygenated steroids and potent androgens that are produced in the testes, adrenals, and some peripheral tissues by the action of CYP11B1 and CYP11B2. DHT is converted in some tissues by 3 β -hydroxysteroid

dehydrogenase to 5 α -androstane-3 β ,17 β -diol, which is a high-affinity ligand and agonist of estrogen receptor β . 5 α -DHT can also be converted by 3 α -hydroxysteroid dehydrogenase in some cell types to 5 α -androstane-3 α ,17 β -diol, a modulator of GABA_A receptors. Testosterone also is aromatized by CYP19 to 17 β estradiol, a ligand for estrogen receptor, that can be further converted in tissues to catechol estrogens by addition of hydroxyl groups at C2 and C4 that are inhibitors of the catecholamine methyltransferase and affect angiogenesis and cell proliferation (Fig. 403-5). 16-Hydroestradiol levels have been associated with breast cancer risk in women. The actions of testosterone on the Wolffian structures, skeletal muscle, erythropoiesis, and bone in men do not require its obligatory conversion to DHT. However, the conversion of testosterone to DHT is necessary for the masculinization of the urogenital sinus and genital tubercle but is not obligatory for mediating its effects on the muscle, bone, or hematopoiesis. Aromatization of testosterone to estradiol mediates additional effects of testosterone on bone resorption, epiphyseal closure, sexual desire, vascular endothelium, and fat. The AR is structurally related to the nuclear receptors for estrogen, glucocorticoids, and progesterone (Chap. 389). The AR, a 919-amino acid protein with a molecular mass of ~110 kDa, is encoded by a gene on the long arm of the X chromosome. A polymorphic region in the amino terminus of the receptor, which contains a variable number of glutamine and glycine repeats, modifies the transcriptional activity of the receptor. The ligand binding to the AR induces conformational changes that dissociates it from heat shock protein and allows the recruitment and assembly of tissue-specific cofactors and causes it to translocate into the nucleus, where it binds to specific androgen response elements in the DNA or other transcription factors already bound to DNA. Thus, the AR is a ligand-activated transcription factor that regulates the expression of androgen-dependent genes in a tissue-specific manner. Some

OH O Testosterone Androgen receptor OH OH PART 12 Endocrinology and Metabolism O H H O O
 11-ketotestosterone 5 α DHT OH H OH H OH 5 α -androstenediol,3 β ,17 β -diol 5 α -androstane,3 α ,17 β -
 diol ER β receptor GABA_A receptor FIGURE 403-5 Testosterone as an androgen and precursor of
 other steroids with diverse actions. DHT, dihydrotestosterone; ER α , estrogen receptor α ; ER β ,
 estrogen receptor β . androgen effects, such as those on the smooth muscle, may be mediated by
 nongenomic AR signal transduction pathways. The nongenomic actions of testosterone involve
 direct activation of kinase signaling cascades such as the Src tyrosine kinase that activates the
 epidermal growth factor receptor and induces the downstream mitogen-activated protein kinase
 cascade (RAF, MEK, and ERK), resulting in increased transcription of the cyclic AMP response
 element binding protein transcription factor-regulated genes. Some effects of testosterone on cell
 proliferation and autophagy require the mediation of GPRC6A. Testosterone and DHT improve
 penile blood flow and erections by rapid nongenomic endothelial-dependent (increased nitric oxide
 production) and endothelium-independent inhibition of L-type calcium channels and/or activation of
 potassium channels in the vascular smooth muscle. ■ ■THE SEMINIFEROUS TUBULES:
 SPERMATOGENESIS The seminiferous tubules are convoluted, closed loops that empty into the rete
 testis, a network of progressively larger efferent ducts that ultimately form the epididymis (Fig.
 403-2). The seminiferous tubules total ~600 m in length and compose about two-thirds of testis
 volume. The walls of the tubules are formed by polarized Sertoli cells that are apposed to
 peritubular myoid cells. Tight junctions between Sertoli cells create the blood-testis barrier. Germ
 cells compose the majority of the seminiferous epithelium (~60%) and are intimately embedded
 within the cytoplasmic extensions of the Sertoli cells, which function as “nurse cells.” Germ cells
 progress through characteristic stages of mitotic and meiotic divisions. A pool of type A
 spermatogonia serve as stem cells capable of self-renewal. Primary spermatocytes are derived

from type B spermatogonia and undergo meiosis before progressing to spermatids that undergo spermiogenesis (a differentiation process involving chromatin condensation, acquisition of an acrosome, elongation of cytoplasm, and formation of a tail) and are released from Sertoli

OH OH OH OH OH ER α 17 β -estradiol 16 hydroxyestradiol ER β OH OH OH OH OH OH OH 2-hydroxyestradiol 4 hydroxyestradiol Catechol estrogens cells as mature spermatozoa. The complete differentiation process into mature sperm requires 74 days. Peristaltic-type action by peritubular myoid cells transports sperm into the efferent ducts. The spermatozoa spend an additional 21 days in the epididymis, where they undergo further maturation and capacitation. The normal adult testes produce

“ 100 million sperm per day. Naturally occurring mutations in FSH β or in the FSH receptor confirm an important, but not essential, role for this pathway in spermatogenesis. Females with mutations in FSH β or the FSH receptor are hypogonadal and infertile because ovarian follicles do not mature; males with these mutations exhibit variable degrees of reduced spermatogenesis, presumably because of impaired Sertoli cell function. Because Sertoli cells produce inhibin B, an inhibitor of FSH, seminiferous tubule damage (e.g., by radiation) causes a selective increase of FSH. Testosterone reaches very high concentrations locally in the testis and is essential for spermatogenesis. The cooperative actions of FSH and testosterone are important in the progression of meiosis and spermiation. In the prepubertal testis, testosterone alone is insufficient for completion of spermatogenesis; however, in men with postpubertal onset of gonadotropin deficiency, human chorionic gonadotropin (hCG) or recombinant LH can reinitiate spermatogenesis without FSH. FSH and testosterone regulate germ cell survival via the intrinsic and extrinsic apoptotic mechanisms. FSH may also play an important role in supporting spermatogonia. Gonadotropin-regulated testicular RNA helicase (GRTH/DDX25), a testis-specific gonadotropin/androgen-regulated RNA helicase, is present in germ cells and Leydig cells and may be an important factor in the paracrine regulation of germ cell development. Several cytokines and growth factors are also involved in the regulation of spermatogenesis by paracrine and autocrine mechanisms. The human Y chromosome contains two pseudoautosomal regions that are located at the two tips of Y chromosome and can recombine with homologous regions of the X chromosome (Fig. 403-6). The genes

Pseudoautosomal region 1 Short arm Yp Euchromatic region of short arm Male Specific Region of y (MSY) Centromere AZFc AZFb AZFa Euchromatic region of long arm b1/b3 G1/G3 Long arm Yq Heterochromatic region of long arm Pseudoautosomal region 2 FIGURE 403-6 Structure of the Y chromosome relevant for spermatogenesis. In the pseudoautosomal regions are involved in cell signaling, transcriptional regulation, and mitochondrial function. Mutations of genes in pseudoautosomal region 1 are associated with mental disorders and short stature. The euchromatic part of the Y chromosome that does not recombine with the X chromosome is referred to as the male-specific region of the Y chromosome (MSY) and contains X-transposed sequences

that have 99% homology with the X chromosome, singlecopy genes or pseudogene homologues of X-linked genes, and ampliconic sequences that are organized in large palindromes. The MSY contains nine families of Y-specific multicopy genes; many of these Y-specific genes are testis-specific and necessary for spermatogenesis. Nonallelic homologous recombination between highly homologous repeated sequences in the MSY region renders the Y chromosome susceptible to microdeletions. Microdeletions in four major nonoverlapping subregions of the Y chromosome—AZFa, AZFb, AZFbc, and AZFc—which contain many spermatogenic genes, are associated with oligospermia or azospermia. Microdeletions involving the AZFc region are the most common Y microdeletions in infertile men. Several partial deletions of the AZFc region have been described including the gr/gr deletion, which is associated with infertility among Caucasian men in Europe and the Western Pacific region, whereas the b2/b3 deletion is associated with male infertility in African and Dravidian men. Approximately 6 to 15% of infertile men with nonobstructive azospermia or severe oligozoospermia harbor a Y microdeletion. Complete deletions of the AZFa and AZFb subregions are typically associated with Sertoli cells only and azospermia and a poor prognosis for sperm retrieval. In contrast, AZFc subregion microdeletions are typically associated with oligozoospermia and higher success rates for sperm retrieval.

TREATMENT Male Factor Infertility Treatment options for male factor infertility have expanded greatly in recent years. Secondary hypogonadism is highly amenable to treatment with pulsatile GnRH or gonadotropins (see below). Assisted reproductive technologies, such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), have provided new opportunities for patients with primary testicular failure and disorders of sperm transport. Choice of initial treatment options depends on sperm concentration and motility. Expectant management should be attempted initially in men with mild male factor infertility (sperm count of $15\text{--}20 \times 10^6/\text{mL}$ and normal motility). Treatment of moderate male factor infertility ($10\text{--}15 \times 10^6/\text{mL}$ and $20\text{--}40\%$ motility) should begin with intrauterine insemination alone or in combination with treatment of the female partner with clomiphene or gonadotropins, but it may require IVF with or without ICSI. For men with a severe defect (sperm count of $<10 \times 10^6/\text{mL}$, 10% motility), IVF with ICSI or donor sperm has

become the treatment of choice. Yq microdeletions will be transmitted through ICSI from the affected father to his male offspring if sperm carrying the Yq microdeletion is used.

CLINICAL AND LABORATORY EVALUATION OF MALE REPRODUCTIVE FUNCTION ■ ■ HISTORY AND PHYSICAL EXAMINATION The history should focus on developmental stages such as puberty and linear growth, as well as androgen-dependent events such as early morning erections, frequency and intensity of sexual thoughts, and frequency of masturbation or intercourse. Although libido and the overall frequency of sexual acts are decreased in androgen-deficient men, young hypogonadal men can achieve erections in response to visual erotic stimuli. Men with acquired androgen deficiency often report decreased energy, low mood, and less commonly hot flashes. Disorders of the Testes and Male Reproductive System

CHAPTER 403 The physical examination should focus on secondary sex characteristics such as hair growth, gynecomastia, testicular volume, prostate, and height and body proportions. Eunuchoid proportions are defined as an arm span >2 cm greater than height and suggest that androgen deficiency occurred before epiphyseal fusion. Hair growth in the face, axilla, chest, and pubic regions is androgen-dependent; however, changes may not be noticeable unless androgen deficiency is severe and prolonged. Ethnicity also influences the intensity of hair growth (Chap. 406). Testicular volume is measured by using a Prader

orchidometer. Testes range from 3.5 to 5.5 cm in length, which corresponds to a volume of 12–25 mL. Advanced age does not influence testicular size, although the consistency becomes less firm. Because of its possible role in infertility, the presence of varicocele should be sought by palpation while the patient is standing; it is more common on the left side. Patients with Klinefelter syndrome have markedly reduced testicular volumes (1–2 mL). In congenital hypogonadotropic hypogonadism, testicular volumes provide a good index of the degree of gonadotropin deficiency and the likelihood of response to gonadotropin therapy. ■ ■GONADOTROPIN AND INHIBIN MEASUREMENTS LH and FSH are measured using two-site immunoradiometric, immunofluorometric, or chemiluminescent assays, which have very low crossreactivity with other pituitary glycoprotein hormones and hCG and have sufficient sensitivity to measure the low levels present in patients with hypogonadotropic hypogonadism. In men with a low testosterone level, an LH level can distinguish primary (high LH) versus secondary (low or inappropriately normal LH) hypogonadism. An elevated LH level indicates a primary defect at the testicular level, whereas a low or inappropriately normal LH level suggests a defect at the hypothalamic-pituitary level. LH pulses occur about every 1–3 h in normal men. Thus, gonadotropin levels fluctuate, and samples should be pooled or repeated when results are equivocal. FSH is less pulsatile than LH because it has a longer half-life. Selective increase in FSH suggests damage to the seminiferous tubules. Inhibin B, a Sertoli cell product that suppresses FSH, is reduced with seminiferous tubule damage. Inhibin B is a dimer with α - β B subunits and is measured by two-site immunoassays. GnRH Stimulation Testing The GnRH test is performed by measuring LH and FSH concentrations at baseline and at 30 and 60 min after intravenous administration of 100 μ g of GnRH. A minimally acceptable response is a twofold LH increase and a 50% FSH increase. In the prepubertal period or with severe GnRH deficiency, the gonadotrope may not respond to a single bolus of GnRH; in these patients, GnRH responsiveness may be restored by chronic, pulsatile GnRH administration. With the availability of sensitive and specific LH assays, GnRH stimulation testing is used rarely. ■ ■TESTOSTERONE ASSAYS Total Testosterone Total testosterone includes both unbound and protein-bound testosterone and is measured by radioimmunoassays, immunometric assays, or liquid chromatography tandem mass

spectrometry (LC-MS/MS). LC-MS/MS involves extraction of serum by organic solvents, separation of testosterone from other steroids by high-performance liquid chromatography and mass spectrometry, and quantitation of unique testosterone fragments by mass spectrometry. LC-MS/MS provides accurate and precise measurements of testosterone levels even in the low range and has emerged as the method of choice for testosterone measurement. The use of LC-MS/MS for the measurement of testosterone in laboratories that have been certified by the Centers for Disease Control and Prevention's (CDC) Hormone Standardization Program for Testosterone (HoST) can ensure that testosterone measurements are accurate and calibrated to an international standard. Serum testosterone levels fluctuate because of its pulsatile, diurnal, and circannual secretory rhythms. Testosterone is generally lower in the late afternoon, or after eating a meal, and is reduced by acute illness. The harmonized normal range for total testosterone, measured using LC-MS/MS in nonobese populations of European and American men aged 19–39 years, is 264–916 ng/dL. This harmonized reference range can be applied to values from laboratories that are certified by the CDC's HoST program.

PART 12 Endocrinology and Metabolism Alterations in SHBG levels due to aging, obesity, diabetes mellitus, hyperthyroidism, some types of medications, chronic illness, or genetic factors can affect

total testosterone levels. Heritable factors contribute substantially to the population-level variation in testosterone levels. Genome-wide association studies have revealed polymorphisms in the SHBG gene as well as other loci that are uniquely associated with total and bioavailable testosterone levels, but not with SHBG levels, as important contributors to variation in testosterone levels.

Measurement of Unbound Testosterone Levels Most circulating testosterone is bound to SHBG and to albumin; only 2.0–4.0% of circulating testosterone is unbound, or “free.” Free testosterone should ideally be measured by equilibrium dialysis under standardized conditions using an accurate and reliable assay for total testosterone. The unbound testosterone concentration also can be calculated from total testosterone, SHBG, and albumin concentrations. Recent research has shown that testosterone binding to SHBG is a multistep process that involves complex allosteric interactions between the two binding sites within the SHBG dimer; a novel ensemble allosteric model of testosterone’s binding to SHBG dimers provides good estimates of free testosterone concentrations. The previous law-of-mass-action equations based on linear models of testosterone binding to SHBG used assumptions that have been shown to be erroneous. Tracer analogue methods are relatively inexpensive and convenient, but they are inaccurate. The term bioavailable testosterone refers to unbound testosterone plus testosterone bound loosely to albumin and reflects the concept that albumin-bound testosterone can dissociate at the capillary level, especially in tissues with long transit time, such as the liver and the brain. Bioavailable testosterone can be determined by the ammonium sulfate precipitation method. However, the measurements of bioavailable testosterone using the ammonium sulfate precipitation are technically challenging, susceptible to imprecision, and not recommended.

hCG Stimulation Test The hCG stimulation test is performed by administering a single injection of 1500–4000 IU of hCG intramuscularly and measuring testosterone levels at baseline and 24, 48, 72, and 120 h after hCG injection. An alternative regimen involves three injections of 1500 units of hCG on 3 successive days and measuring testosterone levels 24 h after the last dose. An acceptable response to hCG is a doubling of the testosterone concentration in adult men. In prepubertal boys, an increase in testosterone to >150 ng/dL indicates the presence of testicular tissue. No response may indicate an absence of testicular tissue or marked impairment of Leydig cell function. Measurement of Anti-Müllerian hormone, a Sertoli cell product, is also used to detect the presence of testes in prepubertal boys with cryptorchidism. ■ ■

SEMEN ANALYSIS Semen analysis is the most important step in the evaluation of male infertility. Samples are collected by masturbation following abstinence for 2–3 days. Semen volumes and sperm concentrations vary considerably among fertile men, and several samples may be needed

before concluding that the results are abnormal. Analysis should be performed within an hour of collection. Using semen samples from

“ 4500 men in 14 countries, whose partners had a time to pregnancy of <12 months, the World Health Organization (WHO) has generated the following one-sided reference limits for semen parameters: semen volume, 1.5 mL; total sperm number, 39 million per ejaculate; sperm concentration, 15 million per mL; vitality, 58% live; progressive motility, 32%; total (progressive + nonprogressive) motility, 40%; and morphologically normal forms, 4.0%. Some men with low sperm counts are fertile. Some studies suggest that sperm counts

have declined in recent decades. A variety of tests for sperm function can be performed in specialized laboratories, but these add relatively little to the treatment options. ■ ■

TESTICULAR BIOPSY

Testicular biopsy is useful in some patients with oligospermia or azospermia as an aid in diagnosis and in assessing the feasibility of treatment. Fine-needle aspiration biopsy is performed under local anesthesia to aspirate tissue for histology. Alternatively, open biopsies can be performed under local or general anesthesia when more tissue is required. A normal biopsy in an azospermic man with a normal FSH level suggests obstruction of the vas deferens, which may be correctable surgically. Biopsies are also used to harvest sperm for ICSI and to classify disorders such as hypospermatogenesis (all stages present but in reduced numbers), germ cell arrest (usually at primary spermatocyte stage), and Sertoli cell-only syndrome (absent germ cells) or hyalinization (sclerosis with absent cellular elements).

Testing for Y Chromosome Microdeletions

Testing for Y chromosome microdeletions is indicated in infertile men with nonobstructive azospermia or severe oligozoospermia (sperm density < 5 million/mL). Y chromosome microdeletions are detected by extracting DNA from peripheral blood leukocytes and using polymerase chain reaction (PCR) analysis of a small number of sequence-tagged sites on the Y chromosome (typically sY84 and sY86 in AZFa region, sY127 and sY134 in AZFb region, and sY254 and sY255 in AZFc region). Because these Y chromosome markers account for only a small fraction of the 23 million base pairs on the Y chromosome, a negative test does not exclude microdeletions in other subregions of the Y chromosome.

DISORDERS OF SEXUAL DIFFERENTIATION

See Chap. 402.

DISORDERS OF PUBERTY

The onset and tempo of puberty vary greatly in the general population and are affected by genetic, nutritional, and environmental factors. Although the mean age for reaching Tanner stage 2 in boys is 11.5 years, the range is much wider (9–14 years). A substantial fraction of the variance in the timing of puberty is explained by heritable factors. The timing of pubertal onset is highly correlated within families and between twins. Genome-wide association studies for age of menarche in girls and age of voice deepening in boys have identified nearly 400 independent loci in girls and boys. Over the past century, the age of onset of puberty has fallen by 3 years and this secular trend towards earlier onset of puberty has continued during the past decade, in part due to improved nutrition as well as increasing obesity rates in children. ■ ■

PRECOCIOUS PUBERTY

Precocious puberty in boys is defined by progressive testicular enlargement (>4 mL) before 9 years of age associated with acceleration of linear growth and bone age. Earlier onset of puberty is associated with increased risk of breast and endometrial cancer, cardiovascular disease, hypertension, type 2 diabetes, hair pigmentation, and shorter life span. Isosexual precocity refers to premature sexual development consistent with phenotypic sex and includes features such as the development of facial hair and phallic growth. Isosexual precocity is divided into gonadotropin-dependent and gonadotropin-independent causes of androgen excess (Table 403-1). Heterosexual precocity refers to the premature

development of estrogenic features in boys, such as breast development.

TABLE 403-1 Causes of Precocious or Delayed Puberty in Boys I. Precocious puberty A. Gonadotropin-dependent

1. Idiopathic
 2. CNS tumors such as hypothalamic hamartoma, optic glioma, arachnoid cysts, astrocytoma, ependymoma, or tuberous sclerosis
 3. Inflammatory and infectious lesions
 4. Mutations in genes that regulate GnRH secretion, such as kisspeptin (KISS1), kisspeptin receptor (KISS1R), and makorin ring finger protein 3 (MKRN3) B. Gonadotropin-independent
 5. Congenital adrenal hyperplasia
 6. hCG-secreting tumor
 7. McCune-Albright syndrome
 8. Activating LH receptor mutations (familial male-limited precocious puberty)
 9. Exogenous androgens
 10. Androgen producing tumors of the adrenal or the testis II. Delayed puberty A. Constitutional delay of growth and puberty B. Systemic disorders
 11. Chronic disease
 12. Malnutrition
 13. Eating disorders C. CNS tumors and their treatment (radiotherapy and surgery) D. Hypothalamic-pituitary causes of pubertal failure (low gonadotropins)
 14. Congenital disorders associated with GnRH or gonadotropin deficiency (Table 403-2)
 15. Acquired disorders a. Pituitary tumors b. Hyperprolactinemia c. Infiltrative disorders, such as hemochromatosis E. Gonadal causes of pubertal failure (elevated gonadotropins)
 16. Klinefelter syndrome
 17. Bilateral undescended testes
 18. Orchitis
 19. Chemotherapy or radiotherapy
 20. Anorchia F. Androgen insensitivity
- Abbreviations: CNS, central nervous system; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone. Gonadotropin-Dependent Precocious Puberty This disorder, also called central precocious puberty (CPP), is less common in boys than in girls. It is caused by premature activation of the GnRH pulse generator, sometimes because of central nervous system (CNS) lesions such as hypothalamic hamartomas, but it is often idiopathic. CPP is characterized by gonadotropin levels that are inappropriately elevated for age and LH and FSH responses to GnRH typical of those seen in postpubertal boys or adults. Magnetic resonance imaging (MRI) should be performed to exclude a mass, structural defect, infection, or inflammatory process. Mutations in MKRN3, an imprinted gene encoding makorin ring finger protein 3, that serves as an upstream inhibitor of GnRH secretion and is expressed only from the paternally inherited allele, have been associated with CPP. Loss-of-function mutations in MKRN3 remove the brake that restrains pulsatile GnRH secretion, resulting in precocious puberty. Additional activating mutations in kisspeptin

and kisspeptin receptor and loss-of-function mutations in delta-like homolog (DLK1) have been identified in patients with CPP. Gonadotropin-Independent Precocious Puberty In boys with gonadotropin-independent precocious puberty, circulating androgens are increased but gonadotropins are low. This group of disorders includes hCG-secreting tumors; CAH; sex steroid-producing tumors of the testis, adrenal, and ovary; accidental or deliberate exogenous sex

steroid administration; hypothyroidism; and activating mutations of the LH receptor or Gs α subunit.

Familial Male-Limited Precocious Puberty Also called testotoxicosis, familial male-limited precocious puberty is an autosomal dominant disorder caused by activating mutations in the LH receptor, leading to constitutive stimulation of the cyclic AMP pathway and testosterone production. Clinical features include premature androgenization in boys, linear growth acceleration in early childhood, and advanced bone age followed by premature epiphyseal fusion. Testosterone is elevated, and LH is suppressed. Treatment options include inhibitors of testosterone synthesis (e.g., ketoconazole, abiraterone, medroxyprogesterone acetate), AR antagonists (e.g., flutamide and bicalutamide), and aromatase inhibitors (e.g., anastrozole).

Disorders of the Testes and Male Reproductive System

CHAPTER 403 MCCUNE-ALBRIGHT SYNDROME This is a sporadic disorder caused by somatic (postzygotic) activating mutations in the Gs α subunit that links G protein-coupled receptors to intracellular signaling pathways (Chap. 424). The mutations impair the guanosine triphosphatase activity of the Gs α protein, leading to ligand-independent signaling of the Gs-coupled receptor, constitutive activation of adenylyl cyclase, and stimulation of testosterone production. In addition to sexual precocity, affected individuals may have autonomy in the adrenals, pituitary, and thyroid glands. Café au lait spots are characteristic skin lesions that reflect the onset of the somatic mutations in melanocytes during embryonic development. Constitutive Gs α activation in the postnatal multipotent skeletal stem cells leads to the formation of immature woven bone and replacement of the bone marrow with fibrotic stroma (polyostotic fibrous dysplasia). Treatment is similar to that in patients with activating LH receptor mutations. Bisphosphonates have been used to treat bone lesions.

CONGENITAL ADRENAL HYPERPLASIA Boys with CAH who are not well controlled with glucocorticoid suppression of adrenocorticotrophic hormone (ACTH) can develop premature virilization because of excessive androgen production by the adrenal gland (Chaps. 398 and 402). LH is low, and the testes are small. Some children with CAH, who are poorly controlled with glucocorticoid treatment, may develop gonadotropin-dependent precocious puberty with early maturation of the hypothalamic-pituitary-gonadal axis, elevated gonadotropins, and testicular growth. Similar development of gonadotropin-dependent precocious puberty has been reported in children with androgen-secreting tumors or other conditions associated with androgen excess, likely due to androgen-induced skeletal maturation. Adrenal rests may develop within the testis of poorly controlled patients with CAH because of chronic ACTH stimulation; adrenal rests do not require surgical removal and regress with effective glucocorticoid therapy.

Heterosexual Sexual Precocity Breast enlargement in prepubertal boys can result from familial aromatase excess, estrogen-producing tumors in the adrenal gland, Sertoli cell tumors in the testis, marijuana smoking, or exogenous estrogens or androgens. Occasionally, germ cell tumors that secrete hCG can be associated with breast enlargement due to excessive stimulation of estrogen production (see "Gynecomastia," below).

APPROACH TO THE PATIENT

Precocious Puberty After verification of precocious development, serum testosterone, LH, and FSH levels should be measured to determine whether gonadotropins are increased in relation to

chronologic age (gonadotropin-dependent) or whether sex steroid secretion is occurring independent of LH and FSH (gonadotropin-independent). In children with gonadotropin-dependent precocious puberty, CNS lesions should be excluded by history, neurologic examination, and MRI scan of the head. If an organic cause is not found, one is left with the diagnosis of idiopathic central precocious puberty. Patients with high testosterone but suppressed LH concentrations have gonadotropin-independent precocious puberty; in these patients,

DHEA sulfate (DHEAS) and 17α -hydroxyprogesterone should be measured. High levels of testosterone and 17α -hydroxyprogesterone suggest the possibility of CAH due to 21α -hydroxylase or 11β -hydroxylase deficiency. If testosterone and DHEAS are elevated, adrenal tumors should be excluded by obtaining a computed tomography (CT) scan of the adrenal glands. Patients with elevated testosterone but without increased 17α -hydroxyprogesterone or DHEAS should undergo evaluation of the testis by palpation and ultrasound to exclude a Leydig cell neoplasm. Activating mutations of the LH receptor or Gs α subunit should be considered in children with gonadotropin-independent precocious puberty in whom CAH, androgen abuse, and adrenal and testicular neoplasms have been excluded.

PART 12 Endocrinology and Metabolism TREATMENT Precocious Puberty In patients with a known cause (e.g., a CNS lesion or a testicular tumor), therapy should be directed toward the underlying disorder. In patients with idiopathic CPP, treatment with long-acting GnRH analogues is indicated in boys showing rapid pubertal progression, who are more advanced in pubertal development (e.g., Tanner stage 3 or greater genital development) and experiencing rapid linear growth or psychological distress. GnRH analogues suppress gonadotropins and testosterone, halt early pubertal development, delay accelerated bone maturation, prevent early epiphyseal closure, promote final height gain, and mitigate the psychosocial consequences of early pubertal development without causing osteoporosis. The treatment is most effective for increasing final adult height if it is initiated before age 6. Puberty resumes after discontinuation of the GnRH analogue. Counseling is an important aspect of the overall treatment strategy. In children with gonadotropin-independent precocious puberty, inhibitors of steroidogenesis, such as ketoconazole or abiraterone, AR antagonists, and aromatase inhibitors have been used empirically. Long-term treatment with spironolactone (a weak androgen antagonist) and ketoconazole also has been reported to normalize growth rate and bone maturation and to improve predicted height in small, nonrandomized trials in boys with familial male-limited precocious puberty.

Aromatase inhibitors, such as testolactone and letrozole, have been used as adjuncts to antiandrogen therapy for children with familial male-limited precocious puberty, CAH, and McCune-Albright syndrome. More potent novel inhibitors of testosterone synthesis, such as abiraterone, have not been systematically evaluated in boys with gonadotropin-independent precocious puberty. ■ ■ **DELAYED PUBERTY** Puberty is considered delayed in boys if it has not ensued by age 14, an age that is 2–2.5 standard deviations above the mean for healthy children. Pubertal delay is not necessarily pathologic and may be a variant of normal pubertal development in some children. Delayed puberty has been associated with lower peak bone mass, higher risk for metabolic and cardiovascular disorders, and lower risk for breast and endometrial cancer in women. Delayed puberty is more common in boys than in girls. There are four main categories of delayed puberty: (1) self-limited delayed puberty (previously called constitutional delay of puberty) (~60% of cases); (2) functional hypogonadotropic hypogonadism caused by systemic illness, malnutrition, or eating disorders (~20% of cases); (3) hypogonadotropic hypogonadism caused by congenital or acquired defects in the hypothalamic-pituitary region (~10% of cases); and (4) hypogonadism secondary to primary gonadal failure (~15% of cases) (Table 403-1). The self-limited delayed puberty is the

most common cause that accounts for nearly two-thirds of boys and one-third of girls with delayed puberty. The self-limited puberty clusters in families and

displays a complex inheritance pattern, having an autosomal dominant pattern of inheritance in some families, but autosomal recessive, X-linked, or bilineal pattern in other families. Self-limited delayed puberty and congenital hypogonadotropic hypogonadism share similarities in their clinical presentation but differ in their clinical course and treatment. In boys with self-limited delayed puberty, pubertal progression will occur eventually, while in those with congenital hypogonadotropic hypogonadism, hormone treatment will be needed to induce secondary sex characteristics. Genetic studies of patients with congenital hypogonadotropic hypogonadism have identified >65 genes that are involved in regulating one or more of the following: (1) development and migration of GnRH neurons (e.g., ANOS1, PROK2, PROK2R, FGFR1, FGF8, FGF17, WDR11, and CHD7); (2) regulation of GnRH secretion (KISS1, KISS1R, TAC3, and TACR3); and (3) GnRH function (e.g., GNRH1, RNRHR). The mutations in some of these genes are associated with dysmorphic features or occur as a part of a syndromic constellation that can facilitate their identification. Some of the genes associated with self-limited delayed puberty are found uniquely in kindreds of children with this disorder, while others are similar to those found in families with congenital hypogonadotropic hypogonadism. Furthermore, 10 to 20% of children with congenital hypogonadotropic hypogonadism may experience spontaneous restoration of GnRH and gonadotropin secretion in adulthood. Functional hypogonadotropic hypogonadism is more common in girls than in boys. Permanent causes of congenital hypogonadotropic hypogonadism or primary testicular failure are identified in <25% of boys with delayed puberty.

APPROACH TO THE PATIENT

Delayed Puberty History of systemic illness, eating disorders, excessive exercise, social and psychological problems, and abnormal patterns of linear growth during childhood should be verified. Boys with pubertal delay may have accompanying emotional and physical immaturity relative to their peers, which can be a source of anxiety. Physical examination should focus on height; arm span; weight; visual fields; and secondary sex characteristics, including hair growth, testicular volume, phallic size, and scrotal reddening and thinning. Testicular size >2.5 cm generally indicates that the child has entered puberty. The main diagnostic challenge is to distinguish those with self-limited delayed puberty, who will progress through puberty at a later age, from those with congenital hypogonadotropic hypogonadism as both conditions present with low testosterone and low gonadotropin levels, delayed bone age and short stature. Pituitary priming by pulsatile GnRH is required before LH and FSH are synthesized and secreted normally. Thus, blunted responses to exogenous GnRH can be seen in patients with self-limited delayed puberty, congenital hypogonadotropic hypogonadism, or pituitary disorders. On the other hand, low-normal basal gonadotropin levels or a normal response to exogenous GnRH is consistent with an early stage of puberty, which is often heralded by nocturnal GnRH secretion. The presence of micropenis or history of cryptorchidism are more suggestive of congenital hypogonadotropic hypogonadism. However, self-limited delayed puberty remains a diagnosis of exclusion that requires ongoing evaluation until the onset of puberty and the growth spurt.

TREATMENT

Delayed Puberty A major challenge in the treatment of children with delayed puberty is to determine whether and when to initiate hormonal treatment. Reassurance without hormonal treatment is appropriate for many individuals with presumed self-limited delayed puberty. However, the impact of delayed growth and pubertal progression on a child's social relationships and school performance should be weighed.

Boys with self-limited delayed puberty are less likely to achieve their full genetic height potential and have reduced total body bone mass as adults, mainly due to narrow limb bones and vertebrae as a result of impaired periosteal expansion during puberty. Furthermore, the time of onset of puberty is negatively associated with bone mineral content and density in boys at skeletal maturity. Judicious use of testosterone therapy in carefully selected boys with self-limited delayed puberty can induce pubertal induction and progression and promote short-term growth without compromising final height, and when administered with an aromatase inhibitor, it may improve final height. If therapy is considered appropriate, it can begin with 25–50 mg of testosterone enanthate or testosterone cypionate every 2–4 weeks or by using a 2.5-mg testosterone patch or 25-mg testosterone gel. Because aromatization of testosterone to estrogen is obligatory for mediating androgen effects on epiphyseal fusion, concomitant treatment with aromatase inhibitors may allow attainment of greater final adult height. Testosterone treatment should be interrupted after 6 months to determine if endogenous LH and FSH secretion have ensued. Other causes of delayed puberty should be considered when there are associated clinical features or when boys do not enter puberty spontaneously after a year of observation or treatment. Boys with confirmed congenital hypogonadotropic hypogonadism require an earlier institution of hormonal treatment than those with self-limited delayed puberty. Optimization of future fertility potential may require initial treatment with hCG to induce development of secondary sex characteristics as well as spermatogenesis to enable harvesting and cryopreservation of sperm.

DISORDERS OF THE MALE REPRODUCTIVE AXIS DURING ADULTHOOD ■ ■HYPOGONADOTROPIC HYPOGONADISM Because LH and FSH are trophic hormones for the testes, impaired secretion of these pituitary gonadotropins results in secondary hypogonadism, which is characterized by low testosterone in the setting of low or inappropriately normal LH and FSH. Hypogonadotropic hypogonadism can be classified into congenital and acquired disorders. Congenital disorders most commonly involve GnRH deficiency, which leads to gonadotropin deficiency. Acquired disorders are more common than congenital disorders and may result from sellar mass lesions, infiltrative diseases of the hypothalamus or pituitary, drugs, nutritional or psychiatric disorders, or systemic diseases. Those with the most severe congenital gonadotropin deficiency have complete absence of pubertal development, and, in some cases, hypospadias, undescended

TABLE 403-2 Causes of Congenital Hypogonadotropic Hypogonadism

Gene	Locus	Inheritance	Associated Features
GnRH Deficiency			
Commonly Associated with			
Hyposmia or Anosmia			
ANOS1 (KAL1)	Xp22	X-linked	Anosmia, renal agenesis, synkinesia, cleft lip/palate, oculomotor/visuospatial defects, gut malformations
NELF (NCMF)	9q34.3	AR	Anosmia, hypogonadotropic hypogonadism (some may be normosmic)
FGF8	10q24	AR	Anosmia (some patients may be normosmic), skeletal abnormalities
FGF17	8p21.3	AR	Anosmia (some patients may be normosmic)
FGFR1	8p11-p12	AD	Anosmia, cleft lip/palate, synkinesia, syndactyly
PROK2	3p21	AR	Anosmia/sleep dysregulation
PROKR2	20p12.3	AR	Variable
CHD7	8q12.1		Anosmia, other features of CHARGE syndrome
FEZ1	8p22	AR	Anosmia, olfactory bulb aplasia
WDR11	10q26	AD	Anosmia
SOX10	22q13		Deafness (Wardenburg Syndrome)
HS6ST1	2q14		Complex Anosmia

testes, and micropenis. Patients with congenital or prepubertal onset of partial gonadotropin deficiency have delayed or arrested sex development. The 24-h LH secretory profiles are heterogeneous in patients with hypogonadotropic hypogonadism, reflecting variable abnormalities of LH pulse frequency or amplitude. In severe cases, basal LH is low, and there are no LH pulses. A smaller subset of patients has low-amplitude LH pulses or markedly reduced pulse frequency. Occasionally, only sleep-entrained LH pulses occur, reminiscent of the pattern seen in the early

stages of puberty.

Congenital Disorders Associated with Gonadotropin Deficiency (See Chap. 391) Congenital hypogonadotropic hypogonadism is a heterogeneous group of disorders characterized by decreased gonadotropin secretion and testicular dysfunction either due to impaired function of the GnRH pulse generator or the gonadotrope. The disorders characterized by GnRH deficiency represent a family of monogenic or oligogenic disorders whose phenotype spans a wide spectrum. Some individuals with GnRH deficiency may suffer from complete absence of pubertal development, while others may manifest varying degrees of gonadotropin deficiency and pubertal delay, and a subset that carries the same mutations as their affected family members may even have normal reproductive function. In ~10% of men with congenital isolated hypogonadotropic hypogonadism (IHH), reversal of gonadotropin deficiency may occur in adult life after sex steroid therapy. Also, a small fraction of men with IHH may present with testosterone deficiency and infertility in adult life after having gone through apparently normal pubertal development. Nutritional, emotional, or metabolic stress may unmask gonadotropin deficiency and reproductive dysfunction (e.g., hypothalamic amenorrhea) in some patients who harbor mutations in the candidate genes but who previously had normal reproductive function. Oligogenicity and gene-gene and gene-environment interactions may contribute to variations in clinical phenotype. Disorders of the Testes and Male Reproductive System CHAPTER 403 Mutations in >60 genes involved in the development and migration of GnRH neurons (e.g., ANOS1, PROK2, PROKR2, FGFR1, FGF8, FGF17, WDR11, CHD7), GnRH secretion (KISS1, KISS1R, TAC3, TACR3), or GnRH function (e.g., GNRH1, RNRHR) have been linked to congenital IHH. The genetic defect remains elusive in nearly two-thirds of cases. Familial hypogonadotropic hypogonadism can be transmitted as an X-linked (20%), autosomal recessive (30%), or autosomal dominant (50%) trait. Some individuals with IHH have sporadic mutations in the same genes that cause inherited forms of the disorder. The genetic defects associated with GnRH deficiency can be classified as anosmic (Kallmann syndrome) or normosmic (Table 403-2), although the occurrence of both anosmic and normosmic forms of GnRH deficiency in the same families suggests commonality of pathophysiologic mechanisms. Kallmann syndrome, the anosmic form (Continued)

PART 12 Endocrinology and Metabolism TABLE 403-2 Causes of Congenital Hypogonadotropic Hypogonadism GENE LOCUS INHERITANCE ASSOCIATED FEATURES TUBB3 Tubulin β

AR Anosmia DUSP6 12q21.33 AR Anosmia GLCE 15q23 AR Anosmia (some patients may be normosmic) FLRT3 20p12.1 AR Anosmia (some patients may be normosmic) SPRY4 5q31.3 AR Anosmia (some patients may be normosmic) IL17RD 3p14.3 AR Anosmia SEMA3A 7q21.11 Anosmia SEMA7A 15q24.1 Anosmia as well as normosmia SEMA3E 7q21.11 Anosmia PLXNA1 3q21.3 Anosmia as well as normosmia DCC 18q21.2 AR Anosmia NTN1 17p13.1 AR Anosmia KLB 4p14 AR Metabolic disorders A2. GnRH Deficiency with Normal Sense of Smell GNRHR 4q21 AR None GnRH1 8p21 AR None KISS1 1q32.1 AR None KISS1R 19p13 AR None TAC3 12q13 AR Microphallus, cryptorchidism, reversal of GnRH deficiency TAC3R 4q25 AR Microphallus, cryptorchidism, reversal of GnRH deficiency LEPR 1p31 AR Obesity LEP 7q31 AR Obesity DMXL2 15q21.2 AR Polyendocrine polyneuropathy syndrome OTUD4 4q31.21 AR Ataxia (Gordon Holmes syndrome) RNF216 7p22.1 AR Ataxia (Gordon Holmes syndrome) STUB1 16p13.3 AR Ataxia POLR3B 12q23.3 AR Ataxia (hypomyelinating leukodystrophy-8 with hypogonadotropic hypogonadism [4H] syndrome) PNPLA6 19p13.2 AR Ataxia (Laurence-Moon syndrome) NR0B1

(Dax1) Xp21.2 X-linked Primary adrenal failure CCDC141 2q31.2 AR Normosmia IGSF10 3q25.1 AR Reversible and normosmic form of hypogonadotropic hypogonadism RNF216 7p22.1 AR Atxia, dementia, and hypogonadotropic hypogonadism (Gordon Holmes syndrome) B. Hypogonadotropic Hypogonadism Not Due to GnRH Deficiency PCSK1 5q15-21 AR Obesity, diabetes mellitus, ACTH deficiency HESX1 3p21 AR Septo-optic dysplasia, CPHD LHX3 9q34 AR CPHD (ACTH spared), cervical spine rigidity PROP1 5q35 AR CPHD (ACTH usually spared) FSHb 11p13 AR ↑ LH LHb 19q13 AR ↑ FSH SF1 (NR5A1) 9p33 AD/AR Primary adrenal failure, XY sex reversal Abbreviations: ACTH, adrenocorticotrophic hormone; AD, autosomal dominant; AR, autosomal recessive; CCDC141, coiled-coil domain containing 141; CHARGE syndrome, eye coloboma, heart defects, choanal atresia, growth and developmental retardation, genitourinary anomalies, ear anomalies; CPHD, combined pituitary hormone deficiency; DAX1, dosage-sensitive sex-reversal, adrenal hypoplasia congenita, X chromosome; DCC, deleted in colon cancer; DMXL2, DMX like 2; DUSP6, dual specificity phosphatase 6; FGFR1, fibroblast growth factor receptor 1; FGF17, fibroblast growth factor 17; FSHb, follicle-stimulating hormone β-subunit; FLRT3, fibronectin like domain containing leucine rich transmembrane protein 3; GH, growth hormone; GLCE, glucuronic acid epimerase; GNRHR, gonadotropin-releasing hormone receptor; GPR54, G protein- coupled receptor 54; HESX1, homeobox gene expressed in embryonic stem cells 1; IGSF10, immunoglobulin superfamily member 10; KAL1, Kallmann syndrome interval gene 1, also known as anosmin 1; KISS1, kisspeptin 1; KLB, klotho-1; LEP, leptin; LEPR, leptin receptor; LHX3, LIM homeobox gene 3; LHb, luteinizing hormone β-subunit; NELF, nasal embryonic luteinizing hormone-releasing hormone factor; NSMF, NMDA receptor synaptonuclear signaling and neuronal migration factor; NR0B1, nuclear receptor subfamily 0, group B, member 1; NTN1, netrin-1; OTUD4, OUT domain containing protein 4; PCSK1, proprotein convertase subtilisin/kexin type 1; PLXNA1, plexin A1; PNPLA6, patatin-like phospholipase domain-containing protein 6; PC1, prohormone convertase 1; PROK2, prokineticin 2; PROKR2, prokineticin 2 receptor; PROP1, prophet of pit 1; RNF216, ring finger protein 216; POLR3B, polymerase III RNA subunit B; SEMA3A, semaphorin 3A; SEMA7A, semaphorin 7A; SEMA3E, semaphorin 3E; SF1, steroidogenic factor 1; SPRY4, sprouty RTK signaling antagonist 4; STUB1, srip 1 homologous and U box containing protein 1; TUBB3, tubulin beta 3; IL17RD, interleukin 17 receptor D. (Continued) of GnRH deficiency, can result from mutations in one or more neuro developmental genes associated with olfactory bulb morphogenesis or the migration of GnRH neurons from their origin in the region of the olfactory placode, along the scaffold established by the olfactory nerves, through the cribriform plate into their final location into the preoptic region of the hypothalamus. Thus, mutations in KAL1, NMDA receptor synaptonuclear signaling and neuronal migration factor (NSMF), genes involved in fibroblast growth factor (FGF) signaling (FGF8, FGFR1, FGF17, IL17RD, DUSP6, SPRY4, and FLRT3), NELF, genes involved in PROK signaling (PROK2 and PROKR2), WDR11, SOX10, TUBB3 SEMA3, HS6ST1, CHD7, and FEZF1 have been described in patients with Kallmann syndrome; among these mutations in ANOS1, CHD7, FGF8, FGFR1, PROKR2, and PROLR2 are the most common. An X-linked form of IHH is caused by mutations in the ANOS1 gene,

Disorders of the Testes and Male Reproductive System CHAPTER 403 which encodes anosmin, a protein that mediates the migration of neural progenitors of the olfactory bulb and GnRH-producing neurons. These individuals have GnRH deficiency and variable combinations of anosmia or hyposmia. Proteins such as those involved in FGF and prokineticin signaling and KAL1, which account for the great majority of Kallmann syndrome cases, interact with heparin sulfate glycosaminoglycan compounds within the extracellular matrix in supporting GnRH neuronal

migration. Mutations in the FGFR1 gene cause an autosomal dominant form of hypogonadotropic hypogonadism that clinically resembles Kallmann syndrome; mutations in its putative ligand, the FGF8 gene product, have also been associated with IHH. Craniofacial tissues and olfactory ensheathing cells also play important roles in neurogenesis and migration of the GnRH neurons, and additional proteins that regulate these cell types may also be involved in the pathogenesis of Kallmann syndrome. The co-occurrence of tooth anomalies, cleft palate, craniofacial anomalies, pigmentation, and neurologic defects in patients with Kallmann syndrome suggests that the syndrome may be a part of the spectrum of neurocristopathies. Other dysmorphic features associated with some forms of IHH include renal agenesis, hearing loss, synkinesia, short metacarpals, eye movement abnormalities, cerebellar ataxia, and dental agenesis. The presence of these dysmorphic features can offer clues to the underlying genetic abnormality and guide genetic testing. Normosmic GnRH deficiency results from defects in pulsatile GnRH secretion, its regulation, or its action on the gonadotrope and has been associated with mutations in GnRHR, GNRH1, KISS1R, TAC3, TACR3, NROB1 (DAX1), leptin, or leptin receptor. Some mutations, such as those in PROK2, PROKR2, NSMF, FGFR1, FGF8, SEMA3A, WDR11, and CHD7, have been associated with both anosmic and normosmic forms of IHH; it is possible that these genes are involved in GnRH neuronal migration as well in regulation of GnRH secretion. GnRHR mutations, the most frequent identifiable cause of normosmic IHH, account for ~40% of autosomal recessive and 10% of sporadic cases of hypogonadotropic hypogonadism. These patients have decreased LH response to exogenous GnRH. Some receptor mutations alter GnRH binding affinity, allowing apparently normal responses to pharmacologic doses of exogenous GnRH, whereas other mutations may alter signal transduction downstream of hormone binding. Mutations of the GnRH1 gene have also been reported in patients with hypogonadotropic hypogonadism, although they are rare. The G protein-coupled receptor KISS1R (GPR54) and its cognate ligand, kisspeptin (KISS1), are important regulators of sexual maturation in primates. Recessive mutations in GPR54 cause gonadotropin deficiency without anosmia. The genes encoding NKB (TAC3), which is involved in preferential activation of GnRH release in early development, and its receptor (TACR3) have been implicated in some families with normosmic IHH. The tachykinin pathway plays an important role in GnRH activation during “mini-puberty” as well as in puberty. Prokineticin 2 (PROK2) and its receptor (PROK2R) are highly expressed in the olfactory ventricle and subventricular zone of the lateral ventricle and are associated with neurogenesis of the olfactory bulbs and the migration of the olfactory neuronal cells. Mutations in the CHD7 gene that encodes for the chromodomain helicase DNA binding protein 7 causes CHARGE syndrome characterized by eye coloboma, heart anomalies, choanal atresia, growth and developmental retardation, genitourinary anomalies, hypogonadism, and ear abnormalities. X-linked hypogonadotropic hypogonadism also occurs in adrenal hypoplasia congenita, a disorder caused by mutations in the DAX1 gene, which encodes a nuclear receptor in the adrenal gland and reproductive axis. Adrenal hypoplasia congenita is characterized by absent development of the adult zone of the adrenal cortex, leading to neonatal adrenal insufficiency. Puberty usually does not occur or is arrested, reflecting variable degrees of gonadotropin deficiency. Although sexual differentiation is normal, some patients have testicular dysgenesis and impaired spermatogenesis despite gonadotropin replacement. Less commonly, adrenal hypoplasia congenita, sex reversal, and hypogonadotropic hypogonadism can be caused by mutations of steroidogenic factor 1 (SF1). Rarely, recessive mutations in the LH β or FSH β genes have been described in patients with selective deficiencies of these gonadotropins. A number of homeodomain transcription factors are involved in the development and differentiation of the specialized hormoneproducing cells within the pituitary gland (Table 403-2). Patients with

mutations of PROP1 have combined pituitary hormone deficiency that includes GH, prolactin (PRL), thyroid-stimulating hormone (TSH), LH, and FSH, but not ACTH. LHX3 mutations cause combined pituitary hormone deficiency in association with cervical spine rigidity. HESX1 mutations cause septo-optic dysplasia and combined pituitary hormone deficiency. Mutations of ARNT1, inherited as an autosomal recessive disorder, are associated with diabetes insipidus; ACTH, GH, LH, and FSH deficiency; anterior pituitary hypoplasia; hypoplastic frontal and temporal lobes; thin corpus callosum; prominent forehead; and retrognathia. Patients with SOX2 mutations can have gonadotropin deficiency, variable deficiencies of TSH and ACTH, pituitary hypoplasia, microphthalmia, and intellectual disability. Prader-Willi syndrome (PWS) is a genomic imprinting disorder caused by deletions of the proximal portion of the paternally derived chromosome 15q11-15q13 region, which contains a bipartite imprinting center (65–75%); uniparental disomy of the maternal alleles (20–30%); or mutations of the genes/loci involved in imprinting (1–3%) (Chap. 479). The imprinting gene implicated in PWS is a ubiquitin pathway gene known as UBE3A, for which the maternal allele is normally expressed while the paternal allele is silenced. PWS is characterized by obesity, hypotonic musculature, intellectual disability, hypogonadism, short stature, and small hands and feet. Some of the major manifestations of PWS may be due to reduced expression of prohormone convertase 1. Laurence-Moon syndrome is an autosomal recessive disorder characterized by obesity, hypogonadism, mental retardation, polydactyly, and retinitis pigmentosa. Recessive mutations of leptin, or its receptor, cause severe obesity and pubertal arrest, apparently because of hypothalamic GnRH deficiency (Chap. 413).

Acquired Hypogonadotropic Disorders • SEVERE ILLNESS, STRESS, MALNUTRITION, AND EXERCISE These may cause reversible gonadotropin deficiency. Although gonadotropin deficiency and reproductive dysfunction are well documented in these conditions in women, men exhibit similar but less pronounced responses. Unlike women, most male runners and other endurance athletes have normal gonadotropin and sex steroid levels, despite low body fat and frequent intensive exercise. Testosterone levels fall at the onset of illness and recover during recuperation. The magnitude of gonadotropin suppression generally correlates with the severity of illness. Although hypogonadotropic hypogonadism is the most common cause of testosterone deficiency in patients with acute illness, some have elevated levels of LH and FSH, which suggests primary gonadal dysfunction. The pathophysiology of reproductive dysfunction during acute illness is unknown but likely involves the combined effects of reductive stress, inflammation, cytokines, and/or glucocorticoid effects. There is a high frequency of low testosterone levels in patients with chronic illnesses such as HIV infection, end-stage renal disease, chronic obstructive lung disease, and many types of cancer and in patients receiving glucocorticoids. About 20% of HIV-infected men with low testosterone levels have elevated LH and FSH levels; these patients presumably have primary testicular dysfunction. The remaining 80% have either normal or low LH and FSH levels; these men have a central hypothalamic-pituitary defect or a dual defect involving both the testis and the hypothalamic-pituitary centers. Muscle wasting is common in chronic diseases associated with hypogonadism, which also leads to debility, poor quality of life, and adverse outcome of disease. Men using opioids for relief of cancer or noncancerous pain or because of addiction often have suppressed testosterone and LH levels and high prevalence of sexual dysfunction and osteoporosis; the degree of suppression is dose-related and particularly severe with long-acting opioids such as methadone. Exogenous opioids bind to the κ -opioid receptors on the KNDy neurons, suppress GnRH secretion, and alter the sensitivity to feedback inhibition by gonadal steroids. Heavy marijuana use has been associated with reduced sperm density, motility, morphology, and capacitation, and increased risk of subfertility.

The effects of marijuana use on circulating testosterone levels have been inconsistent in humans. Gynecomastia observed in marijuana users can be caused by plant estrogens in crude preparations. Androgen deprivation therapy in men with prostate cancer has been associated with increased risk of bone fractures, diabetes mellitus, cardiovascular events, fatigue, sexual dysfunction, tender gynecomastia, and poor quality of life.

OBESITY In men with mild to moderate obesity, SHBG levels decrease in proportion to the degree of obesity, resulting in lower total testosterone levels. However, free testosterone levels usually remain within the normal range. SHBG production in the liver is inhibited by hepatic lipids and by tumor necrosis factor α and interleukin 1, but it is not affected by insulin. Thus, the low SHBG levels seen in obesity and diabetes are likely the result of low-grade inflammation and the increased amount of hepatic lipids rather than high insulin levels. Inflammation and gliosis in the pituitary, hypothalamic leptin resistance, and increased estradiol levels because of aromatization of testosterone to estradiol in adipose tissue may impair hypothalamic-pituitary function; obesity also may directly affect testicular function. Weight gain in adult men can accelerate the rate of age-related decline in testosterone levels. Weight loss is associated with reversal of these abnormalities including an increase in total and free testosterone levels and a decrease in estradiol levels.

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HYPERPROLACTINEMIA (See also Chap. 392) Elevated PRL levels are associated with hypogonadotropic hypogonadism. PRL inhibits hypothalamic GnRH secretion either directly or through modulation of tuberoinfundibular dopaminergic pathways and also attenuates LH and FSH response to GnRH. A PRL-secreting tumor may also destroy the surrounding gonadotropes by invasion or compression of the pituitary stalk. Treatment with dopamine agonists reverses gonadotropin deficiency, although there may be a delay relative to PRL suppression.

SELLAR MASS LESIONS Neoplastic and nonneoplastic lesions in the hypothalamus or pituitary can directly or indirectly affect gonadotrope function. In adults, pituitary adenomas constitute the largest category of space-occupying lesions affecting gonadotropin and other pituitary hormone production. Pituitary adenomas that extend into the suprasellar region can impair GnRH secretion and mildly increase PRL secretion (usually $<50 \mu\text{g/L}$) because of impaired tonic inhibition by dopaminergic pathways. These tumors that cause hyperprolactinemia by stalk compression should be distinguished from prolactinomas, which typically are associated with higher PRL levels. The presence of diabetes insipidus suggests the possibility of a craniopharyngioma, infiltrative disorder, or other hypothalamic lesions (Chap. 393).

HEMOCHROMATOSIS (See also Chap. 426) Both the pituitary and testis can be affected by excessive iron deposition. However, the pituitary defect is the predominant lesion in most patients with hemochromatosis and hypogonadism. The diagnosis of hemochromatosis is suggested by the association of characteristic skin discoloration, hepatic enlargement or dysfunction, diabetes mellitus, arthritis, cardiac conduction defects, hypogonadism, and increased serum ferritin ($>300 \text{ ng/mL}$ for men) and transferrin saturation ($>45\%$, threshold varies in different guidelines).

■ ■ **PRIMARY TESTICULAR CAUSES OF HYPOGONADISM** Common causes of primary testicular dysfunction include Klinefelter syndrome, uncorrected cryptorchidism, cancer chemotherapy, radiation to the testes, trauma, torsion, infectious orchitis, HIV infection, anorchia syndrome, and myotonic dystrophy. Primary testicular disorders may be associated with impaired spermatogenesis, decreased androgen production, or both. See Chap. 402 for disorders of testis development, androgen synthesis, and androgen action.

Klinefelter Syndrome (See also Chap. 402) Klinefelter syndrome is the most common chromosomal disorder associated with 47,XXY karyotype, testicular dysfunction, and male infertility. It occurs in about 1 in 600 live-born males. Azoospermia is the rule in men with Klinefelter syndrome who have the 47,XXY karyotype

due to the progressive loss of 47,XXY spermatogonial stem cells; however, men with

mosaicism (46,XY/47,XXY) and even some with 47,XXY karyotype may have germ cells, especially at a younger age. The clinical phenotype of Klinefelter syndrome can be variable, possibly because of mosaicism, polymorphisms in AR gene, the parental origin of the X chromosome, X-linked copy number variations, gene-dosage effects in conjunction with X chromosome inactivation, variable testosterone levels, and variable changes in the transcriptome and methylome in various tissues. Testicular histology shows hyalinization of seminiferous tubules and germ cell aplasia. However, spermatogenesis can be observed in a small number of tubules from which sperm can be harvested during testicular sperm extraction for IVF. Although their function is impaired, the number of Leydig cells appears to increase. Testosterone is decreased and estradiol is increased, leading to clinical features of undervirilization and gynecomastia. Men with Klinefelter syndrome are at increased risk of systemic lupus erythematosus, Sjögren's syndrome, breast cancer, diabetes mellitus, osteoporosis, nonHodgkin's lymphoma, and some types of lung cancers and at reduced risk of prostate cancer. Periodic mammography for breast cancer surveillance is recommended for men with Klinefelter syndrome. Fertility can be achieved by intracytoplasmic injection of sperm retrieved surgically from the testes of men with Klinefelter syndrome, including some men with nonmosaic form of Klinefelter syndrome. Although sperm retrieval in adolescence for fertility preservation offers no benefit over harvesting in adulthood, fertility counseling, including the potential for sperm retrieval, should be offered prior to starting testosterone replacement therapy. The karyotypes 48,XXXY and 49,XXXXY are associated with a more severe phenotype, increased risk of congenital malformations, and lower intelligence than 47,XXY individuals. Cryptorchidism Cryptorchidism occurs when there is incomplete descent of the testis from the abdominal cavity into the scrotum. About 1–4% of full-term and 30% of premature male infants have at least one undescended testis at birth, but descent is usually complete by the first few weeks of life. Fifty percent of undescended testes at birth will descend spontaneously within the first 6–18 months of life. Consequently, the incidence of cryptorchidism is <1% by 9 months of age. Cryptorchidism should be distinguished from retractile testes that can be pulled down into the scrotum during physical examination and require no treatment. Testosterone and insulin-like 3 (INSL3) and their cognate receptors, androgen receptor and relaxin/insulin-like family peptide receptor 2 (RXFP2), regulate the development and growth of the fetal gubernaculum-cremaster muscle complex and the inguinoscrotal descent of the testes. Mutations in INSL3 and RXFP2 have been found in some patients with nonsyndromic cryptorchidism. However, genome-wide association studies have not found a consistent relation of nonsyndromic cryptorchidism with any single locus, suggesting complex, multilocus genetic susceptibility. Cryptorchidism is associated with increased risk of malignancy, infertility, inguinal hernia, and torsion. Unilateral cryptorchidism, even when corrected before puberty, is associated with decreased sperm count, possibly reflecting unrecognized damage to the fully descended testis or other genetic factors. Surgical correction is usually performed between 6 and 18 months of age depending on the location of the testes, the child's body size, and parental preference. Epidemiologic, clinical, and molecular evidence supports the idea that cryptorchidism, hypospadias, impaired spermatogenesis, and testicular cancer may be causally related to common genetic and environment perturbations and are components of the testicular dysgenesis syndrome. Acquired Testicular Defects Viral orchitis may be caused by the mumps virus, echovirus, lymphocytic choriomeningitis virus, and group B arboviruses. Orchitis occurs in as many as one-fourth of adult men with mumps; the orchitis is unilateral in about two-thirds and bilateral in the remainder. Orchitis usually develops a few days

after the onset of parotitis but may precede it. The testis may return to normal size and function or undergo atrophy. Semen analysis returns to normal for three-fourths of men with unilateral involvement but for only one-third of men with bilateral orchitis. Trauma, including testicular torsion, can also cause secondary

atrophy of the testes. The exposed position of the testes in the scrotum renders them susceptible to both thermal and physical trauma, particularly in men with hazardous occupations. The late-term adverse effects of cancer treatment on reproductive health have emerged as an important concern among cancer survivors. Many professional cancer societies have published guidelines on the fertility preservation in patients with cancer and strongly endorsed consideration of fertility preservation measures prior to initiation of cancer treatment. The testes are sensitive to radiation damage due to the direct effects of ionized radioactive particles as well as indirect effects of free radicals generated from water. Radiation doses <1.0 Gy are associated with only a transient decline in sperm density; doses between 1.0 and 2.0 Gy are associated with temporary azoospermia, and doses >2.0 Gy are generally associated with permanent azoospermia. Leydig cells are relatively resistant to the effects of radiation and only doses >20 Gy are associated with Leydig cell dysfunction and increased FSH and LH levels. Permanent testosterone deficiency in adult men is uncommon after therapeutic radiation; however, most boys given direct testicular radiation therapy for acute lymphoblastic leukemia have permanently low testosterone levels. Direct testicular radiation and whole-body radiation before bone marrow transplantation pose the greatest risk of permanent testicular damage. Combination chemotherapy for acute leukemia, Hodgkin's disease, and testicular and other cancers may impair Leydig cell function and cause infertility. The degree of gonadal dysfunction depends on the type of chemotherapeutic agent and the dose and duration of therapy. Because of the high response rates and the young age of these men, infertility and testosterone deficiency have emerged as important long-term complications of cancer chemotherapy. Cyclophosphamide, procarbazine, ifosfamide, busulfan, chlorambucil, chlormethine cisplatin, carboplatin, and doxorubicin are associated with moderate to high risk of infertility. Azoospermia is uncommon with cyclophosphamide equivalent doses of <4000 mg/m², and higher doses of alkylating agents are generally associated with varying degree of damage to germ cells. The outcomes of assisted reproductive technologies in cancer survivors using cryopreserved sperm collected prior to cancer treatment are similar to those in infertile men who do not have cancer. A smaller subset of cancer survivors treated with large doses of alkylating agents may also suffer from testosterone deficiency and sexual dysfunction. Drugs interfere with testicular function by several mechanisms, including inhibition of testosterone synthesis (e.g., ketoconazole, abiraterone, GnRH agonists and antagonists), blockade of androgen action (e.g., spironolactone), increased estrogen (e.g., marijuana), and toxic effects on spermatogenesis (e.g., chemotherapy). Alcohol, when consumed in small to moderate amounts, modestly increases testosterone levels, but ingestion of large quantities decreases testosterone, independent of liver disease or malnutrition. Chronic ethanol use in large amounts lowers testosterone levels by inducing inflammation and reductive stress and by its effects on the hypothalamus, pituitary, and liver. The occupational and recreational history should be evaluated in all men with infertility because of the toxic effects of many chemical agents on spermatogenesis. Known environmental hazards include pesticides (e.g., vinclozolin, dicofol, atrazine), sewage contaminants (e.g., ethinyl estradiol in birth control pills, surfactants such as octylphenol, nonylphenol), plasticizers (e.g., phthalates), flame retardants (e.g., polychlorinated biphenyls, polybrominated diphenol ethers), industrial pollutants (e.g., heavy metals such as cadmium and lead, dioxins, polycyclic aromatic

hydrocarbons), microwaves, and ultrasound. In some populations, sperm density is said to have declined by as much as 40% in the past 50 years. Environmental estrogens or antiandrogens may be partly responsible. Sperm antibodies can cause isolated male infertility. In some instances, these antibodies are secondary phenomena resulting from duct obstruction or vasectomy. Granulomatous diseases can affect the testes, and testicular atrophy occurs in 10–20% of men with lepromatous leprosy because of direct tissue invasion by the mycobacteria. The tubules are involved initially, followed by endarteritis and destruction of Leydig cells.

Systemic disease can cause primary testis dysfunction in addition to suppressing gonadotropin production. In cirrhosis, a combined testicular and pituitary abnormality leads to decreased testosterone production independent of the direct toxic effects of ethanol. Impaired hepatic extraction of adrenal androstenedione leads to extraglandular conversion to estrone and estradiol, which partially suppresses LH. Testicular atrophy and gynecomastia are present in approximately one-half of men with cirrhosis. In chronic renal failure, testosterone synthesis and sperm production decrease despite elevated gonadotropins. The elevated LH level is due to reduced clearance. About one-fourth of men with renal failure have hyperprolactinemia. Improvement in testosterone production with hemodialysis is incomplete, but successful renal transplantation may return testicular function to normal. Testicular atrophy is present in one-third of men with sickle cell anemia. The defect may be at either the testicular or the pituitary level, although hypogonadotropic hypogonadism is more common. Sperm density can decrease temporarily after acute febrile illness in the absence of a change in testosterone production. Infertility in men with celiac disease is associated with a hormonal pattern typical of androgen resistance, namely, elevated testosterone and LH levels.

Disorders of the Testes and Male Reproductive System CHAPTER 403 Neurologic diseases such as myotonic dystrophy, spinobulbar muscular atrophy (Kennedy's disease), and spinal cord injury are often associated with impaired testicular function. In myotonic dystrophy, small testes may be associated with impairment of both spermatogenesis and Leydig cell function. Spinobulbar muscular atrophy (Kennedy's disease) is caused by an expansion of the glutamine repeat tract in the amino-terminal region of the AR; this expansion impairs function of the AR. Men with spinobulbar muscular atrophy often have undervirilization and infertility as a late manifestation. Spinal cord injury that causes paraplegia is often associated with low testosterone levels and may cause persistent defects in spermatogenesis; some patients retain the capacity for penile erection and ejaculation. ■ ■ ANDROGEN INSENSITIVITY SYNDROMES Mutations in the AR cause resistance to the action of testosterone and DHT. These X-linked mutations are associated with variable degrees of defective male phenotypic development and undervirilization (Chap. 402). Although not technically hormone-insensitivity syndromes, two genetic disorders associated with mutations in the steroid 5 α -reductase type 2 or the CYP19 (aromatase) gene impair testosterone conversion to active sex steroids. Mutations in the SRD5A2 gene, which encodes the steroid 5 α -reductase type 2, prevent the conversion of testosterone to DHT, which is necessary for the normal development of the male external genitalia. Mutations in the CYP19 gene, which encodes aromatase, prevent testosterone conversion to estradiol. Males with CYP19 mutations have delayed epiphyseal fusion, tall stature, eunuchoid proportions, visceral adiposity, and osteoporosis, consistent with evidence from an estrogen receptor-deficient individual that these testosterone actions are mediated via estrogen. GYNECOMASTIA Gynecomastia refers to enlargement of the male breast. It is caused by excess estrogen action and is usually the result of an increased estro

gen/androgen ratio. True gynecomastia is associated with glandular breast tissue that is >4 cm in diameter and often tender. Glandular tissue enlargement should be distinguished from excess adipose tissue: glandular tissue is firmer and contains fibrous-like cords. Gynecomastia occurs as a normal physiologic phenomenon in the newborn (due to transplacental transfer of maternal and placental estrogens), during puberty (high estrogen-to-androgen ratio in early stages of puberty), and with aging (increased fat tissue and increased aromatase activity along with the age-related decline in testosterone levels), but it can also result from pathologic conditions associated with testosterone deficiency or estrogen excess. The prevalence of gynecomastia increases with age and body mass index (BMI), likely because of increased aromatase activity in adipose tissue. Medications that alter androgen metabolism or action may also cause gynecomastia. The relative risk of breast cancer is increased in men with gynecomastia, although the absolute risk is relatively small.

■ ■ **PATHOLOGIC GYNECOMASTIA** Any cause of androgen deficiency can lead to gynecomastia, reflecting an increased estrogen/androgen ratio, as estrogen synthesis still occurs by aromatization of residual adrenal and gonadal androgens. Gynecomastia is a characteristic feature of Klinefelter syndrome (Chap. 402). Androgen insensitivity disorders also cause gynecomastia. Androgen deprivation therapy using GnRH analogues with and without androgen receptor blockers in men with prostate cancer is often associated with painful breast enlargement. Excess estrogen production may be caused by tumors, including Leydig cell tumors; Sertoli cell tumors in isolation or in association with Peutz-Jeghers syndrome or Carney complex; granulosa cell tumors; and adrenal tumors producing estrogen precursors. Tumors that produce hCG, including some testicular germ cell tumors, stimulate Leydig cell estrogen synthesis. Increased conversion of androgens to estrogens can be a result of increased availability of substrate (androstenedione) for extraglandular estrogen formation (CAH, hyperthyroidism, and most feminizing adrenal tumors) or of diminished catabolism of androstenedione (liver disease) so that estrogen precursors are shunted to aromatase in peripheral sites. Obesity is associated with increased aromatization of androgen precursors to estrogens. Extraglandular aromatase activity can also be increased in tumors of the liver or adrenal gland or rarely as an inherited disorder. Several families with increased peripheral aromatase activity inherited as an autosomal dominant or as an X-linked disorder have been described. In some families with this disorder, a chimeric CYP19 due to an inversion in chromosome 15q21.2-3 causes the CYP19 gene to be activated by the regulatory elements of contiguous genes (e.g., transient

PART 12 Endocrinology and Metabolism Breast enlargement True glandular enlargement Hard tissue, fixed to underlying tissue Recent onset, rapid growth Onset in neonatal or peripubertal period Known causative drugs or diseases readily apparent Longstanding, size <4 cm Glandular tissue >4 cm, cause not apparent, Clinical features of testosterone deficiency, Breast tenderness Small testes Increased E2, normal or low T, increased E2 to T ratio Low total and free T, increased E2 to T ratio T deficiency syndrome, further evaluation to determine cause of T deficiency Ultrasound of testes to locate E2 producing tumor, search for other sources of increased E2 **FIGURE 403-7 Evaluation of gynecomastia.** E2, 17 β -estradiol; FSH, follicle-stimulating hormones; hCG β , human chorionic gonadotropin β ; LH, luteinizing hormone; T, testosterone.

receptor potential cation channel subfamily M member 7 [TRPM7], TMOD3, or FLJ14957), resulting in excessive estrogen production in the fat and other extragonadal tissues. The familial aromatase

excess syndrome due to CYP19 mutation or chromosomal rearrangement is characterized by pre- or peripubertal onset of gynecomastia, advanced bone age, short adult height due to premature epiphyseal closure, and hypogonadotropic hypogonadism. Peutz-Jeghers syndrome is characterized by intestinal hamartomas, mucocutaneous pigmentation, calcifying Sertoli cell tumors, premature epiphyseal closure, and prepubertal gynecomastia due to increased aromatization. Hyperthyroidism is associated with elevated SHBG levels, which increase the free estradiol-to-free testosterone ratio even though total testosterone and estradiol levels are often normal. Drugs can cause gynecomastia by acting directly as estrogenic substances (e.g., oral contraceptives, phytoestrogens, digitalis) or inhibiting androgen synthesis (e.g., GnRH agonists, ketoconazole) or action (e.g., spironolactone, AR blockers such as enzalutamide); for many drugs, such as cimetidine, imatinib, or some antiretroviral drugs for HIV, the precise mechanism is unknown. Unintentional exposure to estrogenic agents in skin care products has been reported as a cause of gynecomastia in prepubertal children. Because up to two-thirds of pubertal boys and about half of hospitalized men have palpable glandular tissue that is benign, detailed investigation or intervention is not indicated in all men presenting with gynecomastia (Fig. 403-7). In addition to the extent of gynecomastia, recent onset, rapid growth, tender tissue, and occurrence in a lean subject should prompt more extensive evaluation. This should include a careful drug history, examination of the testes, assessment of increased adipose tissue. Mammography with or without additional corroboratory imaging studies and biopsy. Follow-up with serial examinations. Total and free T, SHBG, LH, FSH, E2, TSH, and hCG. Very high SHBG, normal or high total T, normal E2. Increased hCG β . Ultrasound of the testis, CT scan of adrenal and chest to locate an hCG producing tumor. Measure free T and E2, search for a cause of high SHBG.

of virilization, evaluation of liver function, and hormonal measurements including testosterone, estradiol, estrone, androstenedione, LH, and hCG. Markedly elevated estradiol concentrations along with suppressed LH should prompt a search for a testicular or adrenal estrogen-secreting tumor. A karyotype should be obtained in men with very small testes to exclude Klinefelter syndrome. Despite extensive evaluation, the etiology is established in only a small proportion of patients.

TREATMENT Gynecomastia When the primary cause can be identified and corrected shortly after the onset of gynecomastia, breast enlargement usually subsides over several months. However, if gynecomastia is of long duration, surgery is the most effective therapy. Indications for surgery include severe psychological distress, continued growth or tenderness, failure to respond to medical therapy, or suspected malignancy. In patients who have painful gynecomastia and in whom surgery cannot be performed, treatment with antiestrogens such as tamoxifen (20 mg/d) can reduce pain and breast tissue size in over half the patients. The estrogen receptor antagonists tamoxifen and raloxifene have been reported in small trials to reduce breast size in men with pubertal gynecomastia, although complete regression of breast enlargement is unusual with the use of estrogen receptor antagonists. Aromatase inhibitors can be effective in the early proliferative phase of the disorder. However, in a randomized trial in men with established gynecomastia, anastrozole proved no more effective than placebo in reducing breast size. Tamoxifen is effective in prevention and treatment of breast enlargement and breast pain in men with prostate cancer who are receiving androgen deprivation therapy. Long-standing gynecomastia is usually not responsive to drug therapy and requires mastoplasty if it is associated with pain and distress.

AGING-RELATED CHANGES IN MALE REPRODUCTIVE FUNCTION A number of cross-sectional and longitudinal studies (e.g., the Baltimore Longitudinal Study of Aging, the Framingham Heart Study, the Massachusetts Male Aging Study, and the European Male Aging

Study [EMAS]) have established that testosterone concentrations decrease with advancing age. This age-related decline starts in the third decade of life and progresses slowly; the rate of decline in testosterone concentrations is greater in men with obesity, chronic illness, and in those taking medications. Because SHBG concentrations are higher in older men than in younger men, free or bioavailable testosterone concentrations decline with aging to a greater extent than total testosterone concentrations. The age-related decline in testosterone is due to defects at all levels of the hypothalamic-pituitary-testicular axis: pulsatile GnRH secretion is attenuated, LH response to GnRH is reduced, and testicular response to LH is impaired. However, the gradual rise of LH with aging suggests that testis dysfunction is the main cause of declining androgen levels. The term andropause has been used to denote age-related decline in testosterone concentrations; this term is a misnomer because there is no discrete time when testosterone concentrations decline abruptly. Several epidemiologic studies, such as the Framingham Heart Study, the EMAS, and the Study of Osteoporotic Fractures in Men (MrOS), that used mass spectrometry for measuring testosterone levels have reported ~10% prevalence of low testosterone levels in middle-aged and older men; the prevalence of unequivocally low testosterone and sexual symptoms in men aged 40–70 years in the EMAS was 2.1% and increased with age from 0.1% for men aged 40–49 years of age to 5.1% for those aged 70–79 years. Low total and bioavailable testosterone concentrations have been associated with decreased sexual desire, decreased appendicular skeletal muscle mass and strength, decreased self-reported physical function, higher whole body and visceral fat mass and insulin resistance, and increased risk of type 2 diabetes, coronary artery disease, and all-cause mortality. An analysis of signs and

symptoms in older men in the EMAS revealed a syndromic association of sexual symptoms with total testosterone levels <320 ng/dL and free testosterone levels <64 pg/mL in community-dwelling older men.

Two placebo-controlled randomized trials—the Testosterone Trials (TTrials) and the Testosterone Replacement Therapy for Assessment of Long-Term Vascular Events and efficacy Response in Hypogonadal Men (TRAVERSE) study—have provided important information about the efficacy and safety of testosterone replacement therapy (TRT) in middle-aged and older men with hypogonadism. In these and other randomized trials, TRT of men with hypogonadism consistently improved sexual activity and sexual desire and alleviated hypogonadal symptoms. TRT also improves mood and energy level. TRT increases hemoglobin levels and corrects anemia in a greater proportion of middle-aged and older men with hypogonadism who have unexplained anemia, compared to placebo. Testosterone treatment significantly increases vertebral as well as femoral volumetric and areal bone mineral density and estimated bone strength. Testosterone treatment does not improve memory or other measures of cognition in men who do not have cognitive deficits. Testosterone treatment increases lean body mass, maximal voluntary muscle strength and muscle power, and self-reported mobility, and reduces whole body and visceral fat mass. In men with hypogonadism, testosterone treatment has not been shown to prevent progression from prediabetes to diabetes or induce glycemic remission in those with diabetes. In systematic reviews of randomized controlled trials, testosterone therapy of healthy older men with low or low-normal testosterone levels was associated with greater increments in lean body mass, grip strength, and self-reported physical function than that associated with placebo. Disorders of the Testes and Male Reproductive System CHAPTER 403 Neither the testosterone trials nor a randomized trial of the effects of testosterone on atherosclerosis progression in aging men (TEAAM

trial) with low or low normal testosterone levels found significant differences between testosterone and placebo arms in the rates of change in either the coronary artery calcium scores or the common carotid artery intima-media thickness. However, in the TTrial, testosterone treatment was associated with a significantly greater increase in coronary artery noncalcified plaque volume, as measured by coronary artery computed tomography angiography. Neither of the trials was long enough or large enough to determine the effects of TRT on prostate or major adverse cardiovascular events. The TRAVERSE trial compared the effects of TRT and placebo on major adverse cardiovascular events (MACE) in middle-aged and older men with hypogonadism and either preexisting cardiovascular disease (CVD) or increased risk of CVD. During a mean follow-up period of 33 months, the incidence of MACE did not differ between the testosterone and placebo groups. Testosterone treatment was associated with higher incidence of venous thromboembolism and atrial fibrillation than placebo. The incidences of high-grade prostate cancer (Gleason grade 4+3 or higher) or any prostate cancer, acute urinary retention, invasive surgical procedures for benign prostatic hyperplasia, and initiation of new pharmacologic therapy for benign prostatic hyperplasia were low and did not differ between the testosterone and placebo groups. Testosterone treatment was associated with significantly greater increase in serum prostate-specific antigen (PSA) level in the first 12 months of testosterone but the rate of change in PSA after 12 months of treatment was similar in the testosterone and placebo-treated men. Testosterone treatment did not worsen lower urinary tract symptoms. Testosterone treatment, by increasing PSA levels, could increase the risk of referral for prostate biopsy and detection of low-grade prostate cancer. Population screening of all older men for low testosterone levels is not recommended, and testing should be restricted to men who have symptoms or signs attributable to androgen deficiency. Testosterone therapy is not recommended for all older men with low testosterone levels. In older men with significant symptoms of testosterone deficiency who have unequivocally low testosterone levels, testosterone treatment should be individualized based on consideration of the burden of symptoms, the presence of comorbid conditions that may increase the risk of harm from testosterone treatment, the risks versus benefits of treatment and monitoring, and clinician and patient values (see “Testosterone Replacement,” below).

PART 12 Endocrinology and Metabolism Testicular morphology, semen production, and fertility are maintained up to a very old age in men. Although concern has been expressed about age-related increases in germ cell mutations and impairment of DNA repair mechanisms, there is no clear evidence that the frequency of chromosomal aneuploidy is increased in the sperm of older men. However, the incidence of autosomal dominant diseases, such as achondroplasia, polyposis coli, Marfan syndrome, and Apert syndrome, increases in the offspring of men who are advanced in age, consistent with transmission of sporadic missense mutations. Advanced paternal age may be associated with increased rates of de novo mutations, which may contribute to an increased risk of neurodevelopmental diseases such as schizophrenia and autism. The somatic mutations in male germ cells that enhance the proliferation of germ cells could lead to within-testis expansion of mutant clonal lines, thus favoring the propagation of germ cells carrying these pathogenic mutations and increasing the risk of mutations in the offspring of older fathers (the “selfish spermatogonial selection” hypothesis).

APPROACH TO THE PATIENT Testosterone Deficiency Hypogonadism is often characterized by decreased sex drive, reduced frequency of sexual activity, inability to maintain erections, fatigue, low mood, hot flashes, reduced beard growth, loss of muscle mass, decreased testicular size, and gynecomastia. Erectile dysfunction and testosterone deficiency are two distinct clinical disorders that can coexist in middle-aged and older men. Some,

but not all, patients with erectile dysfunction have testosterone deficiency. Thus, it is useful to evaluate men presenting with erectile dysfunction for testosterone deficiency. Except when extreme, these clinical features of testosterone deficiency may be difficult to ascertain signs and symptoms; exclude systemic causes, eating and body image disorders, medications, and substance use. Measure fasting, early morning total T and, if indicated, free T. Measure LH and FSH. Low T, low or inappropriately normal LH (hypogonadotropic) Low T, high LH (hypergonadotropic) • Rule out systemic illness • Measure prolactin and ferritin • Evaluate other pituitary hormones • MRI scan of the pituitary. Primary testicular dysfunction • Karyotype to exclude Klinefelter syndrome. Low <200 ng/dL Borderline 200–350 ng/dL

“ 350 ng/dL Total and/or free T low Total and free T normal Evaluate for other causes of symptoms; follow, if indicated Repeat total T and free T FIGURE 403-8 Evaluation of hypogonadism. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; T, testosterone. distinguish from changes that occur with normal aging. Moreover, testosterone deficiency may develop gradually. When symptoms or clinical features suggest possible testosterone deficiency, the laboratory evaluation is initiated by the measurement of total testosterone in a fasting specimen, preferably in the morning using a reliable assay, such as LC-MS/MS, that has been calibrated to an international testosterone standard (Fig. 403-8). A consistently low total testosterone level below the lower limit of the normal male range, measured by an LC-MS/MS assay in a CDC-certified laboratory, in association with symptoms, is evidence of testosterone deficiency. An early-morning testosterone level >400 ng/dL makes the diagnosis of androgen deficiency unlikely. In men with testosterone levels between 200 and 400 ng/dL, the total testosterone level should be repeated, and a free testosterone level should be measured. In older men and in patients with other clinical states that are associated with alterations in SHBG levels, a direct measurement of free testosterone level by equilibrium dialysis is needed to diagnose testosterone deficiency. When testosterone deficiency has been confirmed by the consistently low testosterone concentrations, LH should be measured to determine whether the patient has primary (high LH) or secondary (low or inappropriately normal LH) hypogonadism. Elevated LH and FSH levels indicate a defect at the testicular level. Common causes of primary testicular failure include Klinefelter syndrome, HIV infection, uncorrected cryptorchidism, cancer chemotherapeutic agents, radiation, surgical orchiectomy, or prior infectious orchitis. A karyotype should be performed in men with low testosterone and elevated LH to diagnose Klinefelter syndrome. Men who have a low testosterone but “inappropriately normal” or low LH levels have secondary hypogonadism; their defect resides at the hypothalamic-pituitary level. Common causes of acquired secondary hypogonadism include space-occupying lesions of the sella,

hyperprolactinemia, chronic illness, hemochromatosis, excessive exercise, and the use of anabolic-androgenic steroids, opioids, marijuana, glucocorticoids, and alcohol. Measurement of PRL and MRI

scan of the hypothalamic-pituitary region can help exclude the presence of a space-occupying lesion. Patients in whom known causes of hypogonadotropic hypogonadism have been excluded are classified as having IHH. It is not unusual for congenital causes of hypogonadotropic hypogonadism, such as Kallmann syndrome, to be diagnosed in young adults.

TREATMENT

Testosterone Deficiency

GONADOTROPINS

Gonadotropin therapy is used to establish or restore fertility in patients with gonadotropin deficiency of any cause. Several gonadotropin preparations are available. Human menopausal gonadotropin (hMG; purified from the urine of postmenopausal women) contains 75 IU of FSH and 75 IU of LH per vial. hCG (purified from the urine of pregnant women) has minimal FSH activity and resembles LH in its ability to stimulate testosterone production by Leydig cells. Recombinant LH is also available, but its half-life is relatively short (10 h). Treatment is usually begun with hCG alone. If hCG alone does not induce spermatogenesis, hMG is added to promote the FSH-dependent stages of spermatid development. Recombinant human FSH (hFSH) is available and is indistinguishable from purified urinary hFSH in its biologic activity and pharmacokinetics in vitro and in vivo, although the mature β subunit of recombinant hFSH has seven fewer amino acids. Recombinant hFSH is available in ampoules containing 75 IU ($\sim 7.5 \mu\text{g}$ FSH), which accounts for $>99\%$ of protein content. Once spermatogenesis is restored using combined FSH and LH therapy, hCG alone is often sufficient to maintain spermatogenesis. Although a variety of treatment regimens are used, 1500 IU of hCG administered intramuscularly three times weekly is a reasonable starting dose. Testosterone levels should be measured 6–8 weeks later and 48–72 h after the hCG injection; the hCG dose should be adjusted to achieve testosterone levels in the mid-normal range. Sperm counts should be monitored on a monthly basis. It may take several months for spermatogenesis to be restored; therefore, it is important to forewarn patients about the potential length and expense of the treatment and to provide conservative estimates of success rates. If testosterone levels are in the mid-normal range but the sperm concentrations are low after 6 months of therapy with hCG alone, FSH should be added. This can be done by using hMG, highly purified urinary hFSH, or recombinant hFSH. A common practice is to start with the addition of 75 IU FSH three times each week in conjunction with the hCG injections. If sperm densities are still low after 3 months of combined treatment, the FSH dose should be increased to 150 IU. Occasionally, it may take ≥ 18 –24 months for spermatogenesis to be restored. The two best predictors of the success of gonadotropin therapy in hypogonadotropic men are testicular volume at presentation and time of onset of gonadotropin deficiency. In general, men with testicular volumes >8 mL have better response rates than those who have testicular volumes <4 mL. Patients who develop gonadotropin deficiency after puberty experience higher success rates than those who have never undergone pubertal changes. Spermatogenesis can usually be reinitiated by hCG alone, with high rates of success for men with postpubertal onset of hypogonadotropism. The presence of a primary testicular abnormality, such as cryptorchidism, will attenuate testicular response to gonadotropin therapy. Prior testosterone therapy does not preclude subsequent response to gonadotropin therapy, although some studies suggest that it may attenuate response to subsequent gonadotropin therapy.

TESTOSTERONE REPLACEMENT TRT is indicated to restore testosterone levels to normal and correct features of testosterone deficiency in men with hypogonadism. TRT induces secondary sex characteristics; improves libido and overall sexual activity; relieves symptoms of hypogonadism; improves mood and energy level; increases skeletal muscle mass, muscle strength and power, and some measures of physical function; hemoglobin and hematocrit; and volumetric and areal bone mineral density; corrects the mild anemia associated with testosterone deficiency; and decreases

fat mass. The benefits of TRT have only been proven in men with confirmed hypogonadism, as demonstrated by testosterone levels that are below the lower limit of normal and one or more symptoms of hypogonadism.

Disorders of the Testes and Male Reproductive System CHAPTER 403 Testosterone is available in a variety of formulations with distinct pharmacokinetics (Table 403-3). Testosterone serves as a prohormone and is converted to 17β -estradiol by aromatase and to 5α -DHT by steroid 5α -reductase. Therefore, when evaluating testosterone formulations, it is important to consider whether the formulation being used can achieve physiologic estradiol and DHT concentrations, in addition to normal testosterone concentrations. The current recommendation is to restore testosterone levels to the mid-normal range.

Oral Derivatives of Testosterone Testosterone is well absorbed after oral administration but is quickly degraded during the first pass through the liver. Therefore, it is difficult to achieve sustained blood levels of testosterone after oral administration of crystalline testosterone. 17α -Alkylated derivatives of testosterone (e.g., 17α -methyl testosterone, oxandrolone, fluoxymesterone) are relatively resistant to hepatic degradation and can be administered orally; however, because of the potential for hepatotoxicity, including cholestatic jaundice, peliosis, and hepatocellular neoplasms, these formulations should not be used for testosterone replacement. Hereditary angioedema due to C1 esterase deficiency is the only exception to this general recommendation; in this condition, oral 17α -alkylated androgens are useful because they stimulate hepatic synthesis of the C1 esterase inhibitor.

Injectable Forms of Testosterone The esterification of testosterone at the 17β -hydroxy position makes the molecule hydrophobic and extends its duration of action. The slow release of testosterone ester from an oily depot in the muscle accounts for its extended duration of action. The longer the side chain, the greater is the hydrophobicity of the ester and longer the duration of action. Thus, testosterone enanthate, cypionate, and undecanoate with longer side chains have longer durations of action than testosterone propionate. Within 24 h after intramuscular administration of 200 mg testosterone enanthate or cypionate, testosterone levels rise into the high-normal or supra-physiologic range and then gradually decline into the hypogonadal range over the next 2 weeks. A bimonthly regimen of testosterone enanthate or cypionate therefore results in peaks and troughs in testosterone levels that may be accompanied by changes in a patient's mood, sexual desire, and energy level; weekly administration of testosterone enanthate or cypionate can reduce these variations in testosterone levels during the dosing interval. The kinetics of testosterone enanthate and cypionate are similar. Estradiol and DHT levels are normal if testosterone replacement is physiologic. A long-acting testosterone undecanoate in oil, administered at an initial priming dose of 750 mg intramuscularly followed by a second dose of 750 mg 4 weeks later, and then at a maintenance dose of 750 mg every 10 weeks, maintains serum testosterone, estradiol, and DHT in the normal male range and corrects symptoms of testosterone deficiency in a majority of treated men. Its relative drawbacks are the large injection volume and the risk of pulmonary oil microembolism (POME) reaction in a small proportion of patients.

Testosterone Gel Several transdermal testosterone gels, such as Androgel, Testim, Fortesta, and Axiron, and some generic versions, when applied topically to the skin in appropriate doses (Table 403-3), can maintain total and free testosterone concentrations in the normal range in men with hypogonadism. The current

TABLE 403-3 Clinical Pharmacology of Some Testosterone Formulations

FORMULATION	REGIMEN	PHARMACOKINETIC PROFILE	DHT AND E2	ADVANTAGES	DISADVANTAGES
T enanthate or cypionate	140–200 mg IM q2wk or 70–100 mg/wk	After a single IM injection, serum T levels rise into the			

supraphysiologic range, then decline gradually into the low-normal or the hypogonadal range by the end of the dosing interval

Topical T gels Available in sachets, tubes, and pumps When used in appropriate doses, these topical formulations restore serum T and E2 levels to the physiologic male range

PART 12 Endocrinology and Metabolism T pellets Several pellets implanted SC; dose and regimen vary with formulation Serum T peaks at 1 month and then is sustained in normal range for 3–4 months, depending on formulation

Oral T undecanoate (TU) Two different formulations of oral testosterone are available each taken orally bid with food TU formulated in a self-emulsifying drug delivery system that includes hydrophilic and lipophilic excipients to enable the solubilization of TU and its absorption through the lymphatics after oral ingestion with a typical meal. After each administration, serum T levels rise and return to baseline by 12 h. When administered at the recommended dose, average serum T levels are maintained in the normal range in a majority of treated men

Injectable longacting TU in oil U.S. regimen 750 mg IM, followed by 750 mg at 4 weeks, and 750 mg every 10 weeks When administered at the recommended dose, serum T levels are maintained in the normal range in a majority of treated men

Intranasal T 2 actuations of the metered-dose pump (11 mg) applied into the nostrils 3 times daily Restores T into the normal male range

Abbreviations: DHT, dihydrotestosterone; E2, estradiol; T, testosterone. recommendations are to begin with an initial U.S. Food and Drug Administration–recommended dose and adjust the dose based on testosterone and hematocrit levels. The advantages of the testosterone gel include the ease of application. A major concern is the potential for transfer of the gel to a sexual partner or to children who may come in close contact with the patient. The ratio of DHT to testosterone concentrations is higher in men treated with the testosterone gel than in healthy men. Also, there is considerable intra- and inter individual variation in serum testosterone levels in men treated with the transdermal gel due to variations in transdermal absorption and plasma clearance of testosterone. Therefore, monitoring of serum testosterone levels and multiple dose adjustments are required to achieve and maintain testosterone levels in the target range. Pellets of crystalline testosterone can be inserted in the subcutaneous tissue through a small skin incision. Testosterone is released by surface erosion of the implanted pellets and absorbed into the systemic circulation, and testosterone levels can be maintained in the normal range for 3–4 months. Potential drawbacks include the need for skin incision for insertion and removal and spontaneous extrusions and fibrosis at the insertion.

DHT and E2 levels rise in proportion to the increase in T levels; T:DHT and T:E2 ratios do not change Corrects symptoms of testosterone deficiency; relatively inexpensive if self-administered; flexibility of dosing Requires IM injection; peaks and valleys in serum T levels that are associated with fluctuations in patient's mood, energy level, and sex drive Serum DHT levels and DHT:T ratio are higher in hypogonadal men treated with the transdermal gels than in healthy eugonadal men Corrects symptoms of testosterone deficiency, ease of application, good skin tolerability Potential of transfer to a female partner or child by direct skin-to-skin contact; skin irritation in a small proportion of treated men; moderately high DHT levels; considerable interindividual and intraindividual variation in on-treatment testosterone levels T:DHT and T:E2 ratios do not change Corrects symptoms of testosterone deficiency Requires surgical incision for insertions; pellets may extrude spontaneously High DHT:T ratio Convenience of oral administration High DHT:T ratio DHT and E2 levels rise in proportion to the increase in T levels; T:DHT and T:E2 ratios do not change Corrects symptoms of testosterone deficiency; requires infrequent administration Requires IM injection of a large volume; serious pulmonary oil microembolism (POME) reactions, characterized by cough, dyspnea, throat tightening, chest pain, dizziness, and syncope, and episodes of

anaphylaxis have been reported to occur during or immediately after the injection in a very small number of patients; patients should be watched for POME reaction for 30 min after each injection. T:DHT and T:E2 ratio in the physiologic range. Requires 3 times daily application; nasal irritation, epistaxis, nasopharyngitis. Testosterone undecanoate, formulated in a self-emulsifying drug delivery system that includes hydrophilic and lipophilic excipients to enable its solubilization in the gut, is absorbed through the lymphatics after oral ingestion with a fatty meal and is spared the first-pass degradation in the liver. After each administration, serum testosterone levels rise and return to baseline by 12 h. When administered at the recommended dose, average serum testosterone levels are maintained in the normal range in a majority of treated men, but DHT-to-testosterone ratios are higher in men with hypogonadism treated with oral testosterone undecanoate, as compared to eugonadal men. An intranasal testosterone gel is available as a metered-dose pump and is administered typically at a starting dose of 11 mg testosterone in the form of two pump actuations, one in each nostril three times daily. Formulation-specific adverse effects include rhinorrhea, nasal discomfort, epistaxis, nasopharyngitis, and nasal scab. Novel Androgen Formulations Selective AR modulators (SARMs) are a class of AR ligands that bind the AR and display tissue-selective actions. A number of nonsteroidal SARMs that act as

agonists on the muscle and bone and that spare the prostate to varying degrees have advanced to phase 3 human trials. Nonsteroidal SARMs do not serve as substrates for either the steroid 5α -reductase or the CYP19 (aromatase). SARM binding to AR induces specific conformational changes in the AR protein, which then modulates protein-protein interactions between AR and its coregulators, resulting in tissue-specific regulation of gene expression. SARMs that are strong agonists for the muscle, bone, and sexual function and antagonists for the prostate may be valuable in treating men with prostate cancer who are receiving androgen deprivation therapy. 7α -Methyl-19-nortestosterone is an androgen that cannot be 5α -reduced; therefore, compared to testosterone, it has relatively greater agonist activity in muscle and gonadotropin suppression but lesser activity on the prostate. Pharmacologic Uses of Androgens Androgens and SARMs are being evaluated as anabolic therapies for functional limitations associated with aging and chronic illness. Testosterone supplementation increases skeletal muscle mass, maximal voluntary strength, and muscle power in healthy men, hypogonadal men, older men with low testosterone levels, HIV-infected men with weight loss, and men receiving glucocorticoids. These anabolic effects of testosterone are related to testosterone dose and circulating concentrations. Systematic reviews have confirmed that testosterone therapy of HIV-infected men with weight loss promotes improvements in body weight, lean body mass, muscle strength, and depression indices, leading to the recommendation that testosterone may be considered as an adjunctive therapy in HIV-infected men who are experiencing unexplained weight loss and who have low testosterone levels. It is unknown whether testosterone therapy of older men with functional limitations is safe and effective in improving physical function and reducing disability. Testosterone administration induces hypertrophy of both type 1 and 2 fibers and increases satellite cell (muscle progenitor cells) and myonuclear number. Androgens promote the differentiation of mesenchymal, multipotent progenitor cells into the myogenic lineage and inhibit their differentiation into the adipogenic lineage. Testosterone binding to AR promotes the association of liganded AR with β -catenin and its translocation into the nucleus where it binds TCF-4 and activates Wnt-target genes, including follistatin, which blocks signaling through the transforming growth factor β pathway, thereby promoting myogenic differentiation of muscle progenitor cells. Testosterone may have additional effects on satellite cell replication and polyamine pathway, which may contribute to an

increase in skeletal muscle mass. Other indications for androgen therapy are in selected patients with anemia due to bone marrow failure (an indication largely supplanted by erythropoietin) and hereditary angioedema. Recommended Regimens for Testosterone Replacement Therapy

Testosterone esters are administered typically at doses of 70–100 mg intramuscularly every week or 140–200 mg every 2 weeks. Testosterone undecanoate is administered at an initial dose of 750 mg followed 4 weeks later by a second injection of 750 mg and then 750 mg every 10 weeks. Testosterone gels are typically applied over a covered area of skin at initial doses that vary with the formulation. Patients should wash their hands after gel application and keep the area of gel application covered with clothing to minimize the risk of gel transfer to another person. Oral testosterone undecanoate is taken with meals at a starting dose of 237 mg twice daily. Intranasal testosterone is administered as a spray in each nostril three times a day (33 mg/d). Evaluating Efficacy of Testosterone Replacement Therapy The goals of TRT are to restore serum testosterone levels into the midnormal range for healthy young men, correct symptoms of hypogonadism, and induce and maintain secondary sex characteristics. Testosterone should be measured 3 months after initiating therapy to assess adequacy of therapy. There is substantial interindividual variability in serum testosterone levels, especially with transdermal gels, presumably due to genetic differences in testosterone clearance

and substantial variation in transdermal absorption. In patients who are treated with testosterone enanthate or cypionate, testosterone levels should be 350–550 ng/dL 1 week after the injection. If testosterone levels are outside this range, adjustments should be made either in the dose or in the interval between injections. In men on transdermal testosterone patch or gel, testosterone levels should be in the mid-normal range (400–750 ng/dL) 4–12 h after application. If testosterone levels are outside this range, the dose should be adjusted. Multiple dose adjustments are often necessary to achieve testosterone levels in the desired therapeutic range.

Disorders of the Testes and Male Reproductive System CHAPTER 403 Restoration of sexual function, induction and maintenance of secondary sex characteristics, well-being, and maintenance of muscle and bone health are important objectives of TRT. The patient should be asked about sexual desire and activity, the presence of early morning erections, and the ability to achieve and maintain erections adequate for sexual intercourse. The hair growth in response to androgen replacement is variable and depends on ethnicity. Men with prepubertal onset of testosterone deficiency who begin testosterone therapy in their late twenties or thirties may find it difficult to adjust to their newly found sexuality and may benefit from counseling. If the patient has a sexual partner, the partner should be included in counseling because of the dramatic physical and sexual changes that occur with TRT. Contraindications for Testosterone Administration Testosterone administration is contraindicated in men with prostate or breast cancer (Table 403-4). Testosterone therapy should not be administered without further urologic evaluation to men with a palpable prostate nodule or induration, a PSA >3 ng/mL, or severe lower urinary tract symptoms (American Urological Association lower urinary tract symptom score >19). Testosterone should not be administered to men with a hypercoagulable condition, baseline hematocrit $\geq 50\%$, severe untreated obstructive sleep apnea, or uncontrolled or poorly controlled congestive heart failure, or with myocardial infarction, stroke, or acute coronary syndrome in the preceding 4 months. Monitoring Potential Adverse Experiences The clinical effectiveness and safety of TRT should be assessed 3–6 months after initiating testosterone therapy and annually thereafter (Table 403-5).

Potential adverse effects include acne, oiliness of skin, erythrocytosis, venous thromboembolism, breast tenderness, leg edema, and increased risk of detection of prostate events. In addition, there may be formulation-specific adverse effects such as skin irritation with transdermal patch; risk of gel transfer to a sexual partner with testosterone gels; pain and mood fluctuation with injectable testosterone esters; cough and injection site pain with long-acting testosterone esters.

TABLE 403-4 Conditions in Which Testosterone Administration Should not be Used or Used with Increased Caution

Conditions in which testosterone administration is associated with very high risk of serious adverse outcomes: Metastatic prostate cancer, Some types of breast cancers, Thrombophilia.

Conditions in which testosterone administration is associated with moderate to high risk of adverse outcomes and should be used with increased caution and only after further evaluation: Undiagnosed prostate nodule or induration, PSA >3, Erythrocytosis (hematocrit >50%), Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by American Urological Association/International prostate symptom score >19, Uncontrolled or poorly controlled congestive heart failure, Myocardial infarction, stroke, or acute coronary syndrome in the preceding 4 months.

Abbreviation: PSA, prostate-specific antigen.

TABLE 403-5 Monitoring Men Receiving Testosterone Therapy

1. Evaluate the patient 3–6 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects.
2. Monitor testosterone level 3–6 months after initiation of testosterone therapy:
 - Therapy should aim to raise average serum testosterone level into the midnormal range (~400–750 ng/dL).
 - Injectable testosterone enanthate or cypionate: Measure serum testosterone level midway between injections. If testosterone is >750 ng/dL (26.2 nmol/L) or <400 ng/dL (14.0 nmol/L), adjust dose or frequency.
 - Transdermal gels and solution: Assess testosterone level 2–12 h after patient has been on treatment for at least 2 weeks; adjust dose to achieve serum testosterone level in the mid-normal range (400–750 ng/dL).
 - Testosterone pellets: Measure testosterone levels at the end of the PART 12 Endocrinology and Metabolism dosing interval. Adjust the number of pellets and/or the dosing interval to achieve serum testosterone levels in the normal range.
 - Oral testosterone undecanoate: Measure testosterone levels 6–8 h after an oral dose.
 - Injectable testosterone undecanoate: Measure serum testosterone level just prior to each subsequent injection and adjust the dosing interval to maintain serum testosterone in mid-normal range.
3. Check hematocrit at baseline, at 3–6 months, and then annually. If hematocrit is >54%, stop therapy until hematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea; reinstitute therapy with a reduced dose.
4. Measure bone mineral density of lumbar spine and/or femoral neck after 1–2 years of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture, consistent with regional standard of care.
5. In men aged ≥55 years, perform digital rectal examination and check PSA level before initiating treatment, at 3–6 months, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient.
6. Obtain urologic consultation if there is:
 - An increase in serum PSA concentration >1.4 ng/mL within the first 12 months after starting testosterone treatment, confirmed by

repeating the test. • A PSA level >4 ng/mL any time during treatment, confirmed by repeating the test. • Detection of a prostatic abnormality on digital rectal examination. • Severe lower urinary tract symptoms

7. Evaluate formulation-specific adverse effects at each visit: • Injectable testosterone esters (enanthate, cypionate, and undecanoate): Ask about fluctuations in mood or libido, and rarely cough after injections. • Testosterone gels: Advise patients to cover the application sites with a shirt and to wash the skin with soap and water before having skin-to-skin contact because testosterone gels leave a testosterone residue on the skin that can be transferred to a woman or child who might come in close contact. Serum testosterone levels are maintained when the application site is washed 4–6 h after application of the testosterone gel. • Testosterone undecanoate injection: Observe patients for POME reaction for 30 min after each injection. • Testosterone pellets: Look for signs of infection, fibrosis, or pellet extrusion. • Intranasal testosterone: Look for signs of nasal irritation or scab. Abbreviations: AUA/IPSS, American Urological Association International Prostate Symptom Score; POME, pulmonary oil microembolism; PSA, prostate-specific antigen. testosterone undecanoate; and nasal irritation, epistaxis, and nasal scab with intranasal formulation. In the TRAVERSE trial, a randomized controlled trial of TRT in middle-aged and older men with hypogonadism, TRT was associated with increased risk of atrial fibrillation, acute kidney injury, and bone fractures. Hemoglobin Levels Administration of testosterone to men with hypogonadism is typically associated with only a small (~3%) increase in hemoglobin levels, due to direct effects of testosterone on hematopoietic progenitors in the bone marrow, stimulation of erythropoietin, suppression of hepcidin, and increased iron availability for erythropoiesis. The magnitude of hemoglobin increase during TRT is greater in older men than younger men and in men who have sleep apnea, a significant smoking history, or chronic

obstructive lung disease or who live at high altitude. The frequency of erythrocytosis is higher in men with hypogonadism treated with injectable testosterone esters than in those treated with transdermal formulations, presumably due to the higher testosterone dose delivered by the typical regimens of testosterone esters. Erythrocytosis is a frequent adverse event reported in testosterone trials in middle-aged and older men and is also the most frequent cause of treatment discontinuation in these trials. If hematocrit rises above 54%, testosterone therapy should be stopped until hematocrit has fallen to <50%. After evaluation of the patient for hypoxia and sleep apnea, testosterone therapy may be reinitiated at a lower dose. Prostate and Serum PSA Levels TRT increases prostate volume to the size seen in age-matched controls. In the TRAVERSE trial, the incidences of high-grade or any prostate cancer were low and did not differ between the testosterone- and placebo-treated men. The incidences of acute urinary retention, invasive surgical procedure for benign prostatic hyperplasia, prostate biopsy, or initiation of new pharmacologic therapy for benign prostatic hyperplasia also were similar in the testosterone and placebo groups. Testosterone treatment did not worsen lower urinary tract symptoms. There is no evidence that TRT causes prostate cancer. However, testosterone treatment can exacerbate preexisting metastatic prostate cancer. Many older men harbor microscopic foci of cancer in their prostates. It is not known whether long-term TRT will induce these microscopic foci to grow into clinically significant cancers. PSA levels are lower in testosterone-deficient men and increase after initiation of TRT. An increase in PSA levels after starting TRT can lead to urologic referral, increased risk of prostate biopsy, and detection of a low-grade prostate cancer that is common among middle-aged and older

men. Increments in PSA levels after testosterone supplementation in androgen-deficient men are generally <0.5 ng/mL, and increments >1.0 ng/mL over a 3- to 6-month period are unusual. The 90% confidence interval for the change in PSA values in men with benign prostatic hyperplasia, measured 3–6 months apart, is 1.4 ng/mL. Therefore, the Endocrine Society expert panel suggested that an increase in PSA >1.4 ng/mL in the first year after starting TRT, if confirmed, should lead to urologic evaluation. There is considerable test-retest variability in PSA measurements. Therefore, PSA elevations after starting TRT should be confirmed by repeating the PSA test no sooner than 4 weeks after the first test. PSA level >4 ng/mL at any time during treatment, if confirmed by repeat testing, requires further urologic evaluation. Because prostate biopsy has the potential for harm (infection, bleeding, and diagnosis of a low-grade prostate cancer), the institution of PSA monitoring and urologic referral for a prostate biopsy should be a shared decision of the patient and the clinician. Cardiovascular Risk In 2015, the U.S. Food and Drug Administration (FDA), because of concerns about the cardiovascular risk of TRT, required the testosterone manufacturers to conduct a randomized controlled trial to compare the effects of TRT versus placebo on cardiovascular events. The TRAVERSE trial, a large prospective randomized controlled trial, conducted in response to the FDA's requirement, has provided strong evidence that testosterone treatment does not increase the risk of major cardiovascular events (death due to cardiovascular cause, nonfatal myocardial infarction, or nonfatal stroke) relative to placebo treatment in middle-aged and older men with hypogonadism and preexisting cardiovascular disease or increased risk of cardiovascular disease during a mean follow-up duration of 33 months. The incidence of a secondary composite cardiovascular endpoint that included death due to cardiovascular cause, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization procedure also did not differ between the testosterone and placebo groups. Testosterone-treated men experienced higher rates of venous thromboembolic events, nonfatal arrhythmias, clinical bone fractures, and acute kidney injury than placebo-treated men. The TRAVERSE trial also found a small

but statistically significantly greater increase in blood pressure in the testosterone than in the placebo group, similar to the findings of some other studies.

Androgen Use by Athletes and Recreational Bodybuilders

The illicit use of androgenic-anabolic steroids (AAS) to enhance athletic performance first surfaced in the 1950s among powerlifters and spread rapidly to other sports, professional as well as high school athletes, and recreational bodybuilders. In the early 1980s, the use of AAS spread beyond the athletic community into the general population, and now, as many as 3–4 million Americans—most of them men—have likely used these compounds. Most AAS users are not athletes, but rather recreational weightlifters, almost all men, who use these drugs to look lean and more muscular. A subset of AAS users suffers from muscle dysmorphia, a form of body image disorder characterized by excessive preoccupation with leanness and muscularity and poor functioning in social and occupational life. A secular transformation of idealized body image toward greater muscularity and leanness has contributed to increasing prevalence of body image disorders and the use of muscle-building anabolic drugs in young men. The most commonly used AAS include testosterone esters, nandrolone, trenbolone, stanozolol, methandienone, boldenone, and methenolone. AAS users generally use large doses of multiple steroids in cycles, a practice known as stacking. AAS users may also typically use other drugs that are perceived to be muscle building or performance enhancing, such as human GH; erythropoiesis-stimulating agents; insulin; stimulants such as amphetamine, clenbuterol, cocaine, ephedrine, and thyroxine; and drugs perceived to reduce adverse effects such as hCG, aromatase inhibitors, or estrogen antagonists. Recent years have witnessed increasing use of unapproved nonsteroidal SARMs and GH

secretagogues purchased from internet sites. Most of the information about the adverse effects of AAS has emerged from case reports, uncontrolled studies, or clinical trials that used replacement doses of testosterone. The adverse event data from clinical trials using physiologic replacement doses of testosterone have been extrapolated unjustifiably to AAS users, who may administer 10–100 times the replacement doses of testosterone over many years, to support the claim that AAS use is safe and manageable. The adverse events associated with AAS use may be due to AAS themselves, concomitant use of other drugs, high-risk behaviors, and host characteristics that may render these individuals more susceptible to AAS use or to other high-risk behaviors. Four categories of adverse events associated with AAS abuse are of particular concern: cardiovascular events, psychiatric disorders, prolonged suppression of the hypothalamic-pituitary-testicular axis, and potential neurotoxicity. The high rates of premature mortality observed in AAS users are alarming. One Finnish study reported 4.6 times the risk of death among elite powerlifters compared with age-matched men from the general population. The causes of death among powerlifters included suicides, myocardial infarction, and liver failure. A retrospective review of patient records in Sweden also reported higher standardized mortality ratios for AAS users than for nonusers and increased death rates due to suicide, homicide, and accidents. High doses of AAS may induce proatherogenic dyslipidemia, accelerate atherogenesis, increase thrombosis risk via effects on clotting factors and platelets, and induce vasospasm through their effects on vascular nitric oxide. Long-term AAS use may be associated with myocardial hypertrophy and fibrosis. Myocardial tissue of powerlifters using AAS has been shown to be infiltrated with fibrous tissue and fat droplets. Current AAS users display significantly reduced left ventricular systolic and diastolic function compared to previous users and nonusers. Additionally, studies using CT angiography have reported higher coronary artery plaque volume in AAS users than in nonusers. Lifetime AAS dose is strongly associated with coronary atherosclerotic burden. Power athletes using AAS often have short QT intervals but increased QT dispersion, which may predispose them to ventricular arrhythmias.

Unlike replacement doses of testosterone, which are associated with only a small decrease in high-density lipoprotein (HDL) cholesterol and little or no effect on total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels, supraphysiologic doses of testosterone and orally administered 17 α -alkylated, nonaromatizable AAS are associated with marked reductions in HDL cholesterol and increases in LDL cholesterol.

Some AAS users develop hypomanic and manic symptoms (irritability, aggressiveness, reckless behavior, and occasional psychotic symptoms, sometimes associated with violence) during AAS exposure, and depression, sometimes associated with suicidality, during AAS withdrawal. Users may also be susceptible to other forms of illicit drug use. Disorders of the Testes and Male Reproductive System CHAPTER 403 Long-term AAS use suppresses LH, FSH, and testosterone levels and spermatogenesis. Men who have used AAS for more than a few months experience marked suppression of the hypothalamic-pituitary-testicular (HPT) axis after stopping AAS that may be associated with sexual dysfunction, fatigue, infertility, depressed mood, and even suicidality. In some long-term AAS users, recovery of the HPT axis may take a long time, may be incomplete, or may never occur. The symptoms of testosterone deficiency caused by AAS withdrawal may cause some men to revert back to using AAS, leading to continued use and AAS dependence. As many as 30% of AAS users develop a syndrome of AAS dependence, characterized by long-term AAS use despite adverse medical and psychiatric effects. AAS withdrawal hypogonadism has emerged as an important cause of androgen deficiency, accounting for a substantial fraction of testosterone

prescriptions in many men's health clinics; therefore, AAS use should be considered in the differential diagnosis of hypo gonadism in young men. Supraphysiologic doses of testosterone may also impair insulin sensitivity. Orally administered androgens also have been associated with insulin resistance and diabetes. AAS users are more likely to engage in high-risk behaviors such as unsafe injection practices and have increased rates of incarceration that may render them at increased risk of HIV and hepatitis B and C. AAS users are more likely to report high-risk unprotected anal sex than nonusers. Elevated liver enzymes, cholestatic jaundice, hepatic neoplasms, and peliosis hepatis have been reported with oral, 17 α -alkylated AAS. AAS use may cause muscle hypertrophy without compensatory adaptations in tendons, ligaments, and joints, thus increasing the risk of tendon, ligament, and joint injuries. Upper extremity tendon ruptures are observed predominantly among weightlifters who use AAS. AAS use is associated with acne, baldness, and increased body hair.

APPROACH TO THE PATIENT

Androgenic-Anabolic Steroids Use

The suspicion of AAS use should be raised by increased hemoglobin and hematocrit levels, suppressed LH and FSH and testosterone levels, low HDL cholesterol and SHBG levels, and low testicular volume and sperm density in a person who looks highly muscular. In AAS users seeking medical attention, evaluation using the Appearance and Performance Enhancing Drug Use Schedule (APEDUS), a validated semi-structured interview, is sufficient to assess the associated body image or eating disorder, psychiatric symptoms, and the use of AAS and other substances; formal testing for AAS usually is rarely needed in clinical practice. History of AAS use should be obtained in all young men being evaluated for hypogonadism. As AAS use is often associated with the use of other substances, a urine drug screen for other substances is helpful in guiding treatment. If needed, accredited laboratories use gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry to detect anabolic steroid abuse. High-resolution mass spectrometry and tandem mass spectrometry have improved the sensitivity of

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