The treatment of other forms of CAH includes mineralocorticoid and glucocorticoid replacement for salt-losing conditions (e.g., *StAR*, *CYP11A1*, *HSD3β2*), suppression of ACTH drive with glucocorticoids in disorders associated with hypertension (e.g., *CYP17*, *CYP11B1*), and appropriate sex hormone replacement in adolescence and adulthood, when necessary.

OTHER CAUSES Increased androgen synthesis can also occur in CAH due to defects in *POR*, *11β-hydroxylase* (*CYP11B1*), and *3β-hydroxysteroid dehydrogenase type 2* (*HSD3B2*) and with mutations in the genes encoding *aromatase* (*CYP19*) and the glucocorticoid receptor. Increased androgen exposure in utero can occur with maternal virilizing tumors and with ingestion of androgenic compounds.

OTHER DISORDERS AFFECTING 46,XX FEMALES

Congenital absence of the vagina occurs in association with *müllerian agenesis* or *hypoplasia* as part of the Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome (rarely caused by *WNT4* mutations). This diagnosis should be considered in otherwise phenotypically normal females with primary amenorrhea. Associated features include renal (agenesis) and cervical spinal abnormalities.

GLOBAL CONSIDERATIONS

The approach to a child or adolescent with ambiguous genitalia or another DSD requires cultural sensitivity, as the concepts of sex and gender vary widely. Rare genetic DSDs can occur more frequently in specific populations (e.g., *5α-reductase type 2* in the Dominican Republic). Different forms of CAH also show ethnic and geographic variability. In many countries, appropriate biochemical tests may not be readily available, and access to appropriate forms of treatment and support may be limited.

411 Disorders of the Testes and Male Reproductive System

Shalender Bhasin, J. Larry Jameson

The male reproductive system regulates sex differentiation, virilization, 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, stimulation of 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. A variety of testosterone formulations now allow more physiologic androgen replacement. 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. 67, 115, and 116, respectively.**

DEVELOPMENT AND STRUCTURE OF THE TESTIS

The fetal testis develops from the undifferentiated gonad after expression of a genetic cascade that is initiated by the *SRY* (sex-related gene on the Y chromosome) **(Chap. 410)**. SRY 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. 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. Leydig cells produce testosterone, which 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. Testicular descent through the inguinal canal is controlled in part by Leydig cell production of insulin-like factor 3 (INSL3), which acts via a receptor termed *Great* (*G* protein–coupled *re*ceptor *a*ffecting *t*estis descent). 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

Although *puberty* commonly refers to the maturation of the reproductive axis and the development of secondary sex characteristics, it involves a coordinated response of multiple hormonal systems including the adrenal gland and the growth hormone (GH) axis **(Fig. 411-1)**. 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 greatly accelerated by the activation of the hypothalamic-pituitary axis and the production of gonadotropin-releasing hormone (GnRH). The GnRH pulse generator in the hypothalamus 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, γ-aminobutyric acid (GABA), and neuropeptide Y. Although the pathways that initiate reactivation of the GnRH pulse generator at the onset of puberty have been elusive, mounting evidence supports involvement of GPR54, a G protein–coupled receptor that binds an endogenous ligand, kisspeptin. Individuals with mutations of GPR54 fail to enter puberty, and experiments in primates demonstrate that infusion of the ligand is sufficient to induce premature puberty. 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. Leptin, a hormone produced by adipose cells, 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. 415e)**. The adipocyte hormone leptin, gut hormone ghrelin, neuropeptide Y, and kisspeptin integrate the signals

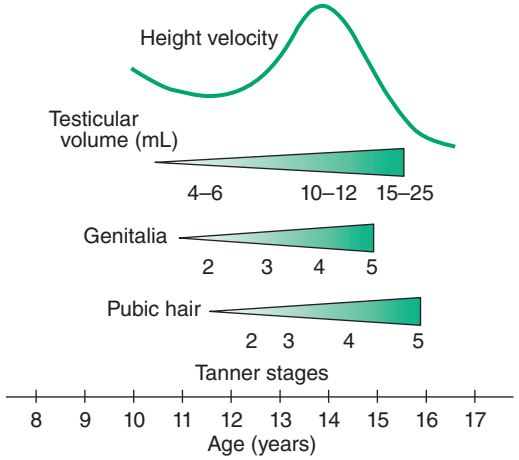

FIGURE 411-1 Pubertal events in males. Sexual maturity ratings for genitalia and pubic hair and divided into five stages. *(From WA Marshall, JM Tanner: Variations in the pattern of pubertal changes in boys. Arch Dis Child 45:13, 1970.)*