Male hypogonadism may be classified into three categories according to the level of the defect (Table 65-1). Diseases directly affecting the testes result in *primary* or *hypergonadotropic hypogonadism*, which is characterized by oligospermia or azoospermia and low testosterone levels but exhibits elevations of LH and FSH because of a decrease in the negative feedback regulation on the pituitary and hypothalamus by androgens, estrogens, and inhibin. In contrast, hypogonadism from lesions in the hypothalamus or pituitary gives rise to *secondary* or *hypogonadotropic hypogonadism*; the low testosterone level or ineffective spermatogenesis results from inadequate concentrations of the gonadotropins. The third category of hypogonadism is the result of defects in androgen action.

Hypothalamic-Pituitary Disorders

Panhypopituitarism occurs congenitally from structural defects or from inadequate production or release of the hypothalamic-releasing factors. The condition may also be acquired through replacement by tumors, infarction from vascular insufficiency, infiltrative disorders, autoimmune diseases, trauma, and infections.

Kallmann syndrome is a form of hypogonadotropic hypogonadism that is associated with problems in the ability to discriminate odors, either incompletely (*hyposmia*) or completely (*anosmia*). This syndrome results from a defect in the migration of the GnRH neurons from the olfactory placode into the hypothalamus. Therefore, it represents a GnRH deficiency. Patients remain prepubertal, with small, rubbery testes, and they develop eunuchoidism (E-Fig. 65-1).

Hyperprolactinemia may result in hypogonadotropic hypogonadism because prolactin elevation inhibits normal release of GnRH, decreases the effectiveness of LH at the Leydig cell level, and also inhibits some of the actions of testosterone at the level of the target organ. Normalization of prolactin levels through withdrawal of an offending drug, by surgical removal of the pituitary adenoma, or with the use of dopamine agonists reverses this form of hypogonadism.

TABLE 65-1 CLASSIFICATION OF MALE HYPOGONADISM

HYPOTHALAMIC-PITUITARY DISORDERS (SECONDARY HYPOGONADISM)
Panhypopituitarism
Isolated gonadotropin deficiency
Complex congenital syndromes
Hyperprolactinemia
Hypothalamic dysfunction
GONADAL DISORDERS (PRIMARY HYPOGONADISM)
Klinefelter's syndrome and associated chromosomal defects
Myotonic dystrophy
Cryptorchidism
Bilateral anorchia
Seminiferous tubular failure
Adult Leydig cell failure
Androgen biosynthesis enzyme deficiency
DEFECTS IN ANDROGEN ACTION
Testicular feminization (complete androgen insensitivity)
Incomplete androgen insensitivity
5α-Reductase deficiency

Weight loss or systemic illness in male patients can cause another form of secondary hypogonadism, *hypothalamic dysfunction.* Weight loss or illness induces a defect in the hypothalamic release of GnRH and results in low levels of gonadotropin and testosterone. This condition is commonly observed in patients with cancer, AIDS, or chronic inflammatory processes.

Primary Gonadal Abnormalities

The most common congenital cause of primary testicular failure is *Klinefelter's syndrome*, which occurs in about 1 of every 600 live male births and is usually caused by a maternal meiotic chromosomal nondisjunction that results in an XXY genotype. At puberty, clinical findings include the following: a variable degree of hypogonadism; gynecomastia; small, firm testes measuring less than 2 cm in the longest axis (normal testes, 3.5 cm or greater); azoospermia; eunuchoid skeletal proportions; and elevations of FSH and LH (E-Fig. 65-2). Primary gonadal failure is also found in patients with another congenital condition, *myotonic dystrophy*, which is characterized by progressive weakness; atrophy of the facial, neck, hand, and lower extremity muscles; frontal baldness; and myotonia.

About 3% of full-term male infants have *cryptorchidism*, which spontaneously corrects during the first year of life in most cases; consequently, by 1 year of age, the incidence of this condition is about 0.75%. When the testes are maintained in the intra-abdominal position, the increased temperature leads to defective spermatogenesis and oligospermia. Leydig cell function usually remains normal, resulting in normal levels of adult testosterone.

Bilateral anorchia, also known as the vanishing testicle syndrome, is a rare condition in which the external genitalia are fully formed, indicating that ample quantities of testosterone and DHT were produced during early embryogenesis. However, the testicular tissue disappears before or shortly after birth, and the result is an empty scrotum. This condition is differentiated from cryptorchidism by an HCG stimulation test. Patients with cryptorchidism have an increase in serum testosterone level after an injection of HCG, whereas patients with bilateral anorchia do not.

Acquired gonadal failure has numerous causes. The adult seminiferous tubules are susceptible to a variety of injuries, and seminiferous tubular failure is found after infections such as mumps, gonococcal or lepromatous orchitis, irradiation, vascular injury, trauma, alcohol ingestion, and use of chemotherapeutic drugs, especially alkylating agents. The serum FSH concentration may be normal or elevated, depending on the degree of damage to the seminiferous tubules. The Leydig cell compartment may also be damaged by these same conditions. In addition, some men experience a gradual decline in testicular function as they age, possibly because of microvascular insufficiency. Patients with decreased testosterone production may clinically exhibit lowered libido and potency, emotional lability, fatigue, and vasomotor symptoms such as hot flushes. The serum LH concentration is usually elevated in this situation.

Defects in Androgen Action

When either testosterone or its metabolite, DHT, binds to the androgen receptor in target cells, the receptor is activated and binds DNA; the resulting stimulation of transcription, protein synthesis, and cell growth collectively constitutes androgen