PART X Reproductive Physiology

CHAPTER 37

# The Male Reproductive System

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## CHAPTER OUTLINE



## KEY CONCEPTS

1. In the testes, luteinizing hormone (LH) controls the synthesis of testosterone by Leydig cells, and follicle-stimulating hormone (FSH) increases the production of
2. androgen-binding protein, inhibin, and estrogen by Sertoli cells.
3. Spermatozoa are produced within the seminiferous tubules of both testes. Sperm develop from spermatogonia through a series of developmental stages that include spermatocytes and spermatids.
4. The sperm mature and are stored in the epididymis. At the time of ejaculation, sperm are moved by muscular contractions of the epididymis and vas deferens through the ejaculatory ducts into the prostatic urethra. The sperm are finally moved out of the body through the urethra in the penis.
5. LH and FSH secretion by the anterior pituitary are controlled by gonadotropin-releasing hormone (GnRH).
6. Testosterone mainly reduces LH secretion, whereas inhibin reduces the secretion of FSH. The testicular hormones complete a negative-feedback loop with the hypothalamic-pituitary axis.
7. Androgens have several target organs and have roles in regulating the development of secondary sex characteristics, the libido, and sexual behavior.
8. The most potent natural androgen is dihydrotestosterone, which is produced from the precursor, testosterone, by the action of the enzyme 5α-reductase.
9. Male reproductive dysfunction is often due to a lack of LH and FSH secretion or abnormal testicular morphology.

The testes have two primary functions, spermatogenesis, the process of producing mature sperm, and steroidogenesis, the synthesis of testosterone. Both processes are regulated by the pituitary gonadotropins LH and FSH. Testosterone is the primary sex hormone in the male and is responsible for primary and secondary sex characteristics. The primary sex characteristics include those structures responsible for promoting the development, preservation, and delivery of sperm. The secondary sex characteristics are those structures and behavioral features that make men externally different from women and include the typical male hair pattern, deep voice, and large muscle and bone masses.

## AN OVERVIEW OF THE MALE REPRODUCTIVE SYSTEM

A diagram of reproduction regulation in the male is presented in Figure 37.1. The system is divided into factors affecting male function: brain centers, which control pituitary release of hormones and sexual behavior; gonadal

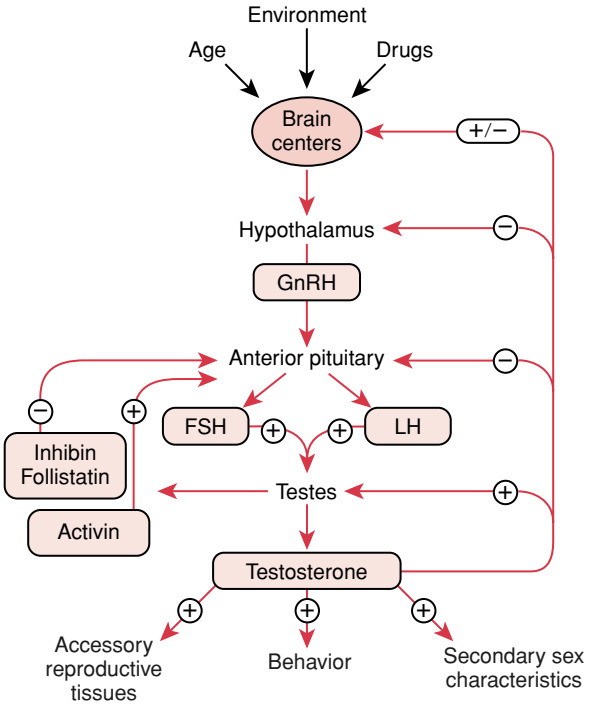


**FIGURE 37.1 Regulation of reproduction in the male.** The main reproductive hormones are shown in boxes. Positive and negative regulations are depicted by plus and minus signs, respectively.

structures, which produce sperm and hormones; a ductal system, which stores and transports sperm; and accessory glands, which support sperm viability.

The endocrine glands of the male reproductive system include the hypothalamus, anterior pituitary, and testes. The hypothalamus processes information obtained from the external and internal environment using neurotransmitters that regulate the secretion of gonadotropin-releasing hormone (GnRH). GnRH moves down the hypothalamic-pituitary portal system and stimulates the secretion of LH and FSH by the gonadotrophs of the anterior pituitary. LH binds to receptors on the Leydig cells and FSH binds to receptors on the Sertoli cells. Leydig cells reside in the interstitium of the testes, between seminiferous tubules, and produce testosterone. Sertoli cells are located within the seminiferous tubules, support spermatogenesis, contain FSH and testosterone receptors, and produce estradiol, albeit at low levels.

Testosterone belongs to a class of steroid hormones, the androgens, which promote "maleness." It carries out multiple functions, including feedback on the hypothalamus and anterior pituitary; the support of spermatogenesis; the regulation of behavior, including sexual behavior; and the development and maintenance of secondary sex characteristics. Sertoli cells also produce glycoprotein hormones— nhibin, activin, and follistatin—that regulate the secretion of FSH.

The duct system that transports sperm from the testis to the outside through the penis includes the epididymis, vas deferens, and urethra. The sperm acquire motility and the capability to fertilize in the epididymis; they are stored in the epididymis and in the vas deferens. They are transported via the urethra through the penis and are ultimately expelled by ejaculation. The accessory structures of the male reproductive tract include the prostate gland, seminal vesicles, and bulbourethral glands. These glands contribute several constituents to the seminal fluid that are necessary for maintaining functional sperm.

## REGULATION OF TESTICULAR FUNCTION

Testicular function is regulated by LH and FSH. LH regulates the secretion of testosterone by the Leydig cells and FSH, in synergy with testosterone, regulates the production of spermatozoa.

### Hypothalamic Neurons Produce Gonadotropin-Releasing Hormone

Hypothalamic neurons produce **gonadotropin-releasing hormone** (GnRH), a decapeptide, which regulates the secretion of **luteinizing hormone** (LH) and **follicle-stimulating hormone** (FSH). Although neurons that produce GnRH can be located in various areas of the brain, their highest concentration is in the medial basal hypothalamus, in the region of the infundibulum and arcuate nucleus. GnRH enters the hypothalamic-pituitary portal system and binds to receptors on the plasma membranes of pituitary cells, resulting in the synthesis and release of LH and FSH.

A variety of external cues and internal signals influence the secretion of GnRH, LH, and FSH. For example, the amount of GnRH, FSH, and LH secreted changes with age, stress levels, and hormonal state. In addition, various disease states lead to hyposecretion of GnRH. Little, if any, secretion of hypothalamic GnRH occurs in patients with prepubertal **hypopituitarism**, resulting in a failure of the development of the testes, primarily a result of a lack of LH, FSH, and testosterone.

Male patients with **Kallmann's syndrome** are hypogonadal from a deficiency in LH and FSH secretion because of a failure of GnRH neurons to migrate from the olfactory bulbs, their embryological site of origin. These patients do not have a sufficient hypothalamic source of GnRH to maintain secretion of LH and FSH, and the testes fail to undergo significant development.

GnRH originates from a large precursor molecule called preproGnRH (Fig. 37.2). PreproGnRH consists of a signal peptide, native GnRH, and a GnRH-associated peptide (GAP). The signal peptide (or leader sequence) allows the protein to cross the membrane of the rough ER. However, both the signal peptide and GAP are enzymatically cleaved at the rough ER prior to GnRH secretion.

### Distinct Gonadotrophs Produce LH and FSH

Three distinct pituitary LH- and FSH-secreting cells have been identified. Gonadotrophs contain either LH or FSH, and some cells contain both LH and FSH. GnRH can induce the secretion of both hormones simultaneously because GnRH receptors are present on all of these cell types.

LH and FSH each contain two polypeptide subunits, referred to as alpha and beta chains, that are about 15 kDa in

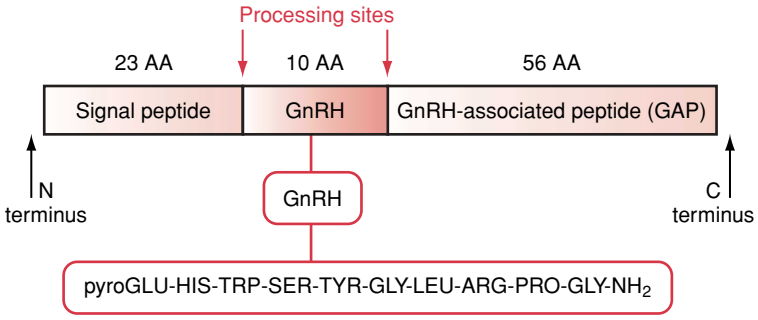


**FIGURE 37.2** **The precursor molecule, pre-proGnRH, that contains GnRH.** The amino acid sequence of GnRH, a decapeptide is indicated at the bottom.

size. Both hormones contain the same α subunit but different β subunits. Each hormone is glycosylated prior to release into the general circulation. Glycosylation regulates the half-life, protein folding for receptor recognition, and biological activity of the hormone.

LH and FSH bind membrane receptors on Leydig and Sertoli cells, respectively. The activation of LH and FSH receptors on these cells increases the intracellular second messenger cAMP. The two gonadotropin receptors are linked to G proteins and adenylyl cyclase for the production of cAMP from ATP. For the most part, cAMP can account for all of the actions of LH and FSH on testicular cells. cAMP binds to protein kinase A, which activates transcription factors such as **steroidogenic factor-1** (SF-1) and **cAMP response element binding protein** (CREB). These factors activate the promoter region of the genes of steroidogenic enzymes that control testosterone production by Leydig cells. Similar signal-transducing events occur in Sertoli cells that regulate the production of estradiol. The testis converts testosterone and some other androgens to estradiol by the process of aromatization, although estradiol production is low in males.

Another major function of the testis is the production of mature sperm, inhibin (a protein produced by Sertoli cells that suppresses FSH secretion), and androgen-binding protein. Activin and follistatin production by testicular cells in humans is currently being investigated.

## GnRH Is Secreted in a Pulsatile Manner

GnRH in the hypothalamus is secreted in a pulsatile manner into the hypothalamic-hypophyseal portal blood. GnRH pulsatility is ultimately necessary for proper functioning of the testes because it regulates the secretion of FSH and LH, which are also released in a pulsatile fashion (Fig. 37.3). Continuous exposure of gonadotrophs to GnRH results in desensitization of GnRH receptors, leading to a decrease in LH and FSH release. Therefore, the pulsatile pattern of GnRH release serves an important physiological function. The administration of GnRH at an improper frequency results in a decrease in circulating concentrations of LH and FSH.

Most evidence for GnRH pulses has come from animal studies because GnRH must be measured in hypothalamic-hypophyseal portal blood, an extremely difficult area to obtain blood samples in humans. Since discrete pulses of GnRH are followed by distinct pulses of FSH and LH, measurements of the pulses of LH and FSH in serum indirectly indicate that GnRH pulses have occurred. Numerous human studies measuring pulsatile secretion of LH and FSH in peripheral blood at various times have provided much of the information regarding the role of LH and FSH in regulating testicular development and function. However, the exact relationship between endogenous GnRH pulses and LH and FSH secretion in humans is unknown.

Hypogonadal eunuchoid men exhibit low levels of LH in serum and do not exhibit pulsatile secretion of LH. Pulsatile injections of GnRH restore LH and FSH secretion and increase sperm counts. FSH pulses tend to be smaller in amplitude than LH pulses, mostly because FSH has a longer half-life than LH in the circulation.

Although the exact identity of the cells responsible for generating GnRH pulsatility is unknown, the presence of a **pulse generator** in the hypothalamus has been postulated. The putative pulse generator resides in the medial basal hypothalamus and is responsible for the synchronized and rhythmic firing of a population of neurons. The activity of the pulse generator is modified by several factors. For example, castration causes a large increase in basal LH levels in serum, as evidenced by an increase in frequency and amplitude of LH pulses. Therefore, the pulse generator may be tonically inhibited by testosterone. However, GnRH neurons lack receptors for gonadal steroids, suggesting that

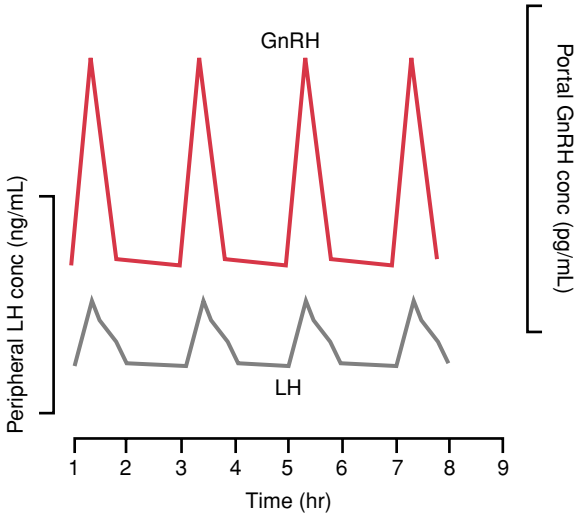


**FIGURE 37.3** **A diagram of the pulsatile release of GnRH in portal blood and LH in peripheral blood.**

steroidal effects are mediated by other neurons whose neuropeptides, neurohormones, or vasoactive agents regulate the activity of the GnRH-producing neurons.

### Steroids and Polypeptides From the Testis Regulate LH and FSH Secretion

Testosterone, estradiol, inhibin, activin, and follistatin are major testicular hormones that regulate the release of the gonadotropins LH and FSH. Generally, testosterone, estradiol, and inhibin reduce the secretion of LH and FSH in the male. Activin stimulates the secretion of FSH, whereas follistatin inhibits FSH secretion.

Testosterone inhibits LH release by decreasing the secretion of GnRH and, to a lesser extent, by reducing gonadotroph sensitivity to GnRH. Estradiol formed from testosterone by aromatase also has an inhibitory effect on GnRH secretion. Acute testosterone treatment does not alter pituitary responsiveness to GnRH, but prolonged exposure significantly reduces the secretory response to GnRH.

Removal of the testes results in increased circulating levels of LH and FSH. Replacement therapy with physiological doses of testosterone restores LH to precastration levels but does not completely correct FSH levels. This observation led to a search for a gonadal factor that specifically inhibits FSH release. The polypeptide hormone **inhibin** was eventually isolated from seminal fluid. Inhibin is produced by Sertoli cells, and has a molecular weight of 32 to 120 kDa, the 32-kDa form being the most prominent. Inhibin is composed of two dissimilar subunits, α and β, which are held together by disulfide bonds. There are two β subunit forms, called A and B. Inhibin B consists of the α subunit bound by a disulfide bridge to the βB subunit and is the physiologically important form of inhibin in the human male. Inhibin acts directly on the anterior pituitary and inhibits the secretion of FSH but not LH.

**Activin** is produced by Sertoli cells, stimulates the secretion of FSH, has an approximate molecular weight of 30 kDa and has multiple forms based on the βA and βB subunits of inhibin. The multiple forms of activin are called activin A (two βA subunits linked by a disulfide bridge), activin B (two βB subunits), and activin AB (one βA and one βB subunit). The major form of activin in the male is currently unknown although both Sertoli and Leydig cells have been implicated in its secretion.

**Follistatin** is a 31 to 45 kDa single-chain protein hormone, with several isoforms, that binds and deactivates activin. Thus, the deactivation of activin by binding to follistatin reduces FSH secretion. Follistatin is apparently produced by Sertoli cells and acts as a paracrine factor on the developing spermatogenic cells.

## THE MALE REPRODUCTIVE ORGANS

The testes produce spermatozoa and transport them through a series of ducts in preparation for fertilization. The testes also produce testosterone that regulates development of the male gametes, male sex characteristics, and male behavior.

### The Testis Is the Site of Sperm Formation

During embryonic stages of development, the testes lie attached to the posterior abdominal wall. As the embryo elongates, the testes move to the inguinal ring. Between the seventh month of pregnancy and birth, the testes descend through the inguinal canal into the scrotum. The location of the testes in the scrotum is important for sperm production, which is optimal at 2 to 3°C lower than core body temperature. Two systems help maintain the testes at a cooler temperature. One is the **pampiniform plexus** of blood vessels, which serves as a countercurrent heat exchanger between warm arterial blood reaching the testes and cooler venous blood leaving the testes. The second is the **cremasteric muscle**, which responds to changes in temperature by moving the testes closer or farther away from the body. Prolonged exposure of the testes to elevated temperature, fever, or thermoregulatory dysfunction can lead to temporary or permanent sterility as a result of a failure of spermatogenesis, whereas steroidogenesis is unaltered.

The testes are encapsulated by a thick fibrous connective tissue layer, the tunica albuginea. Each human testis contains hundreds of tightly packed **seminiferous tubules**, ranging from 150 to 250 μm in diameter and from 30 to 70 cm long. The tubules are arranged in lobules, separated by extensions of the tunica albuginea, and open on both ends into the rete testis. Examination of a cross section of a testis reveals distinct morphological compartmentalization. Sperm production is carried out in the avascular seminiferous tubules, whereas testosterone is produced by the **Leydig cells**, which are scattered in a vascular, loose connective tissue between the seminiferous tubules in the interstitial compartment.

Each seminiferous tubule is composed of two somatic cell types (myoid cells and Sertoli cells) and germ cells. The seminiferous tubule is surrounded by a basement membrane (basal lamina) with myoid cells on its perimeter, which define its outer limit. On the inside of the basement membrane are large, irregularly shaped **Sertoli cells**, which extend from the basement membrane to the lumen (Fig. 37.4). Sertoli cells are attached to one another near their base by tight junctions (Fig. 37.5). The tight junctions divide each tubule into a **basal compartment**, whose constituents are exposed to circulating agents, and an **adluminal compartment**, which is isolated from bloodborne elements. The tight junctions limit the transport of fluid and macromolecules from the interstitial space into the tubular lumen, forming the **blood-testis barrier**.

Located between the nonproliferating Sertoli cells are germ cells at various stages of division and differentiation. Mitosis of the **spermatogonia** (diploid progenitors of spermatozoa) occurs in the basal compartment of the seminiferous tubule (see Fig. 37.5). The early meiotic cells (primary spermatocytes) move across the junctional complexes into the adluminal compartment, where they mature into **spermatozoa** or **gametes** after meiosis. The adluminal compartment is an immunologically privileged site. Spermatozoa that develop in the adluminal compartment are not recognized as "self" by the immune system. Consequently, males can develop antibodies against their own sperm, resulting in infertility. Sperm antibodies neutralize the ability of sperm to function. Sperm antibodies are often present after vasec-

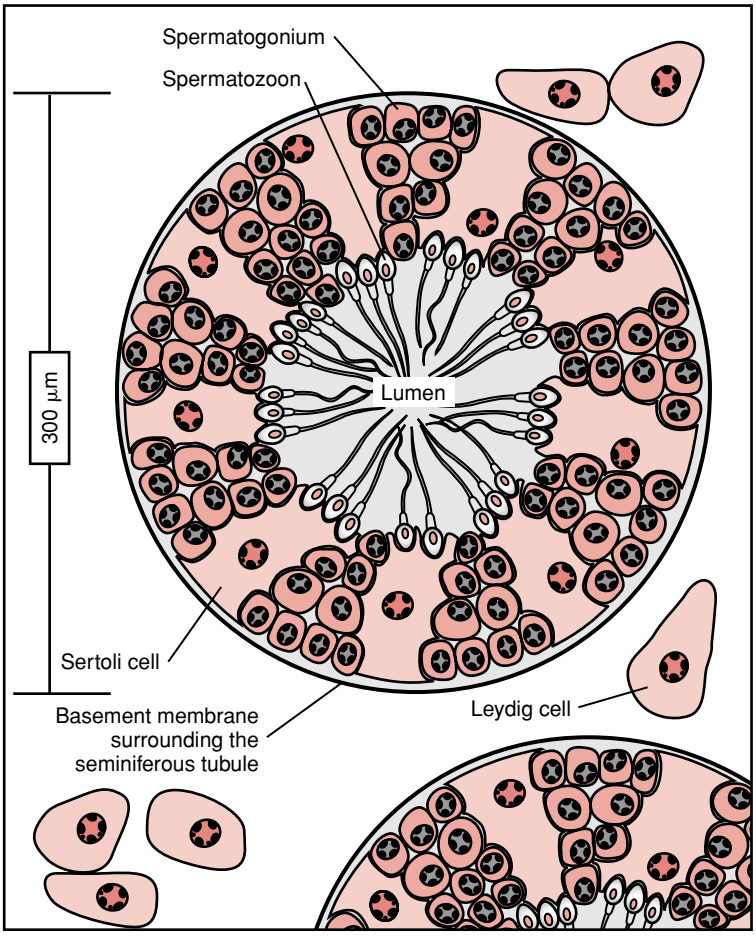


**FIGURE 37.4** **The testis.** This cross-sectional view shows the anatomic relationship of the Leydig cells, basement membrane, seminiferous tubules, Sertoli cells, spermatogonia, and spermatozoa. (Modified from Alberts B, Bray D, Lewis M, et al. Molecular Biology of the Cell. 3rd Ed. New York: Garland, 1994.)

tomy or testicular injury and in some autoimmune diseases where the adluminal compartment is ruptured, allowing sperm to mingle with immune cells from the circulation.

## Sertoli Cells Have Multiple Functions

Sertoli cells are critical to germ cell development, as indicated by their close contact. As many as 6 to 12 spermatids may be attached to a Sertoli cell. Sertoli cells phagocytose residual bodies (excess cytoplasm resulting from the transformation of spermatids to spermatozoa) and damaged germ cells, provide structural support and nutrition for germ cells, secrete fluids, and assist in **spermiation**, the final detachment of mature spermatozoa from the Sertoli cell into the lumen. Spermiation may involve **plasminogen activator**, which converts plasminogen to plasmin, a proteolytic enzyme that assists in the release of the mature sperm into the lumen. Sertoli cells also synthesize large amounts of transferrin, an iron-transport protein important for sperm development.

During the fetal period, Sertoli cells and gonocytes form the seminiferous tubules as Sertoli cells undergo numerous rounds of cell divisions. Shortly after birth, Sertoli cells cease proliferating, and throughout life, the number of sperm produced is directly related to the number of Sertoli cells. At puberty, the capacity of Sertoli cells to bind FSH and testosterone increases. Receptors for FSH, present only on the plasma membranes of Sertoli cells, are glycoproteins linked to adenylyl cyclase via G proteins. FSH exerts multiple effects on the Sertoli cell, most of which are mediated by cAMP and protein kinase A (Fig. 37.6). FSH stimulates the production of androgen-binding protein and plasminogen activator, increases secretion of inhibin, and induces aromatase activity for the conversion of androgens to estrogens. The testosterone receptor is within the nucleus of the Sertoli cell.

**Androgen-binding protein** (ABP) is a 90-kDa protein, made of a heavy and a light chain, that has a high binding affinity for dihydrotestosterone and testosterone. It is similar in function, with some homology in structure, to another binding protein, sex hormone-binding globulin (SHBG), synthesized in the liver. ABP is found at high concentrations in the human testes and epididymis. It serves as a carrier of testosterone in Sertoli cells, as a storage protein for androgens in the seminiferous tubules, and as a carrier of testosterone from the testes to the epididymis.

Other products of the Sertoli cell are inhibin, follistatin, and activin. Inhibin suppresses FSH release from the pituitary gonadotrophs. The pituitary gonadotrophs and testicular Sertoli cells form a classical negative-feedback loop in which FSH stimulates inhibin secretion and inhibin suppresses FSH release. Inhibin also functions as a paracrine

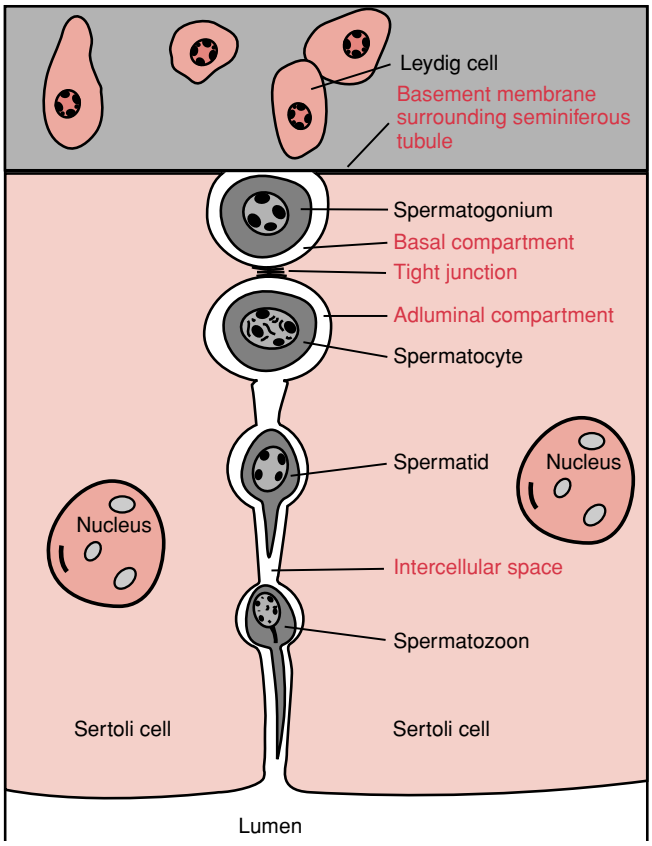


**FIGURE 37.5 Sertoli cells. Sertoli cells are connected by tight junctions, which divide the intercellular space into a basal compartment and an adluminal compartment.** Spermatogonia are located in the basal compartment and maturing sperm in the adluminal compartment. Spermatocytes are formed from the spermatogonia and cross the tight junctions into the adluminal compartment, where they mature into spermatozoa. (Modified from Alberts B, Bray D, Lewis M, et al. Molecular Biology of the Cell. 3rd Ed. New York: Garland, 1994.)

agent in the testes. Activin stimulates the release of FSH. Follistatin, an activin-binding protein, reduces FSH secretion induced by activin.

## Leydig Cells Produce Testosterone

Leydig cells are large polyhedral cells that are often found in clusters near blood vessels in the interstitium between seminiferous tubules. They are equipped to produce steroids because they have numerous mitochondria, a prominent smooth ER, and conspicuous lipid droplets.

Leydig cells undergo significant changes in quantity and activity throughout life. This mechanism may depend on a nuclear transcription factor, steroidogenic factor-1 (SF-1), that recognizes a sequence in the promoter of all genes encoding CYP enzymes. In the human fetus, the period from weeks 8 to 18 is marked by active steroidogenesis, which is obligatory for differentiation of the male genital ducts. Leydig cells at this time are prominent and very active, reaching their maximal steroidogenic activity at about 14 weeks, when they constitute more than 50% of the testicular volume. Because the fetal hypothalamic-pituitary axis is still underdeveloped, steroidogenesis is controlled by **human chorionic gonadotropin (hCG)** from the placenta, rather than by LH from the fetal pituitary (see Chapter 39); LH and hCG bind the same receptor. After this period, Leydig cells slowly regress. At about 2 to 3 months of postnatal life, male infants have a significant rise in testosterone production (infantile testosterone surge), the regulation and function of which are unknown. Leydig cells remain quiescent throughout childhood but increase in number and activity at the onset of puberty.

Leydig cells do not have FSH receptors, but FSH can increase the number of developing Leydig cells by stimulating the production of growth stimulators from Sertoli cells that subsequently enhance the growth of the Leydig cells. In addition, androgens stimulate the proliferation of developing Leydig cells. Estrogen receptors are present on Leydig cells, and they reduce the proliferation and activity of these cells.

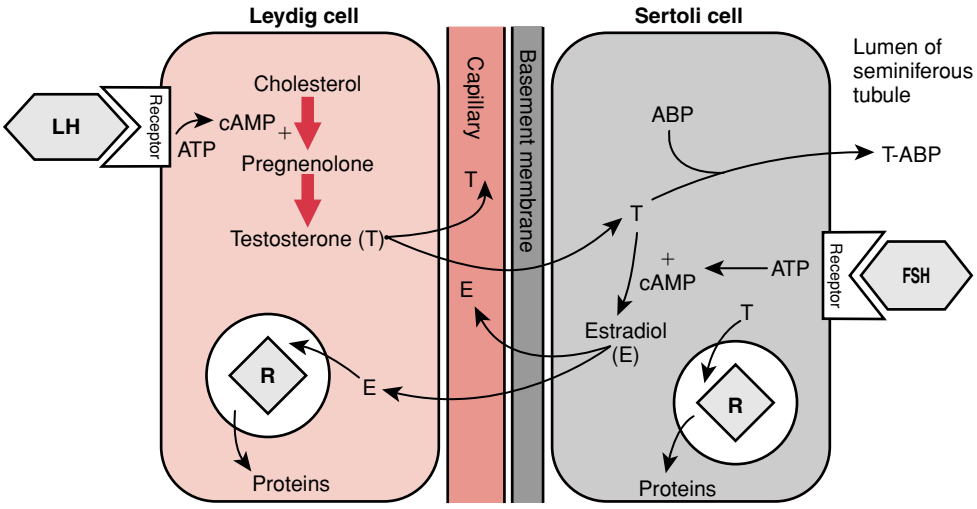


**FIGURE 37.6 Regulation, hormonal products, and interactions between Leydig and Sertoli cells.** ABP, androgen-binding protein; E, estradiol; T, testosterone; R, receptor.

Leydig cells have LH receptors, and the major effect of LH is to stimulate androgen secretion via a cAMP-dependent mechanism (see Fig. 37.6). The main product of Leydig cells is testosterone, but two other androgens of less biological activity, dehydroepiandrosterone (DHEA) and androstenedione, are also produced.

There are bidirectional interactions between Sertoli and Leydig cells (see Fig. 37.6). The Sertoli cell is incapable of producing testosterone but contains testosterone receptors as well as FSH-dependent aromatase. The Leydig cell does not produce estradiol but contains receptors for it, and estradiol can suppress the response of the Leydig cell to LH. Testosterone diffuses from the Leydig cells, crosses the basement membrane, enters the Sertoli cell, and binds to ABP. As a result, androgen levels can reach high local concentrations in the seminiferous tubules. Testosterone is obligatory for spermatogenesis and the proper functioning of Sertoli cells. In Sertoli cells, testosterone also serves as a precursor for estradiol production. The daily role of estradiol in the functioning of Leydig cells is unclear, but it may modulate responses to LH.

### The Duct System Functions in Sperm Maturation, Storage, and Transport

After formation in the seminiferous tubules, spermatozoa are transported to the rete testes and from there through the efferent ductules to the **epididymis**. This movement of sperm is accomplished by ciliary movement in the efferent ductules, by muscle contraction, and by the flow of fluid.

The epididymis is a single, tightly coiled duct, 4 to 5 m long. It is composed of a head (caput), a body (corpus), and a tail (cauda) (Fig. 37.7). The functions of the epididymis are storage, protection, transport, and maturation of sperm cells. Maturation at this point includes a change in functional capacity as sperm make their way through the epididymis. The sperm become capable of forward mobility during migration through the body of the epididymis. A significant portion of sperm maturation is carried out in the caput, whereas sperm are stored in the cauda.

Frequent ejaculation results in reduced sperm numbers and increased numbers of immotile sperm in the ejaculate. The cauda connects to the vas deferens, which forms a dilated tube, the ampulla, prior to entering the prostate. The ampulla also serves as a storage site for sperm. Cutting and ligation of the vas deferens or vasectomy is an effective method of male contraception. Because sperm are stored in the ampulla, men remain fertile for 4 to 5 weeks after vasectomy.

### Erection and Ejaculation Are Neurally Regulated

Erection is associated with sexual arousal emanating from sexually related psychic and/or physical stimuli. During sexual arousal, impulses from the genitalia, together with nerve signals originating in the limbic system, elicit motor impulses in the spinal cord. These neuronal impulses are carried by the parasympathetic nerves in the sacral region of the spinal cord via the cavernous nerve branches of the prostatic plexus that enter the penis. Those signals cause vasodilation of the arterioles and corpora cavernosa. The smooth muscles in those structures relax, and the blood vessels dilate and begin to engorge with blood. The thin-walled veins become compressed by the swelling of the blood-filled arterioles and cavernosa, restricting blood flow. The result is a reduction in the outflow of blood from the penis, and blood is trapped in the surrounding erectile tissue, leading to engorgement, rigidity, and elongation of the penis in an erect position.

**Semen**, consisting of sperm and the associated fluids, is expelled by a neuromuscular reflex that is divided into two sequential phases: emission and ejaculation. **Emission** moves sperm and associated fluids from the cauda epididymis and vas deferens into the urethra. The latter process involves efferent stimuli originating in the lumbar areas (L1 and L2) of the spinal cord and is mediated by adrenergic sympathetic (hypogastric) nerves that induce contraction of smooth muscles of the epididymis and vas deferens. This action propels sperm through the ejaculatory ducts and into the urethra. Sympathetic discharge also closes the internal urethral sphincter, which prevents retrograde ejaculation into the urinary bladder. **Ejaculation** is the expulsion of the semen from the penile urethra; it is initiated after emission. The filling of the urethra with sperm initiates sensory signals via the pudendal nerves that travel to the sacrospinal region of the cord. A spinal reflex mechanism that induces rhythmic contractions of the striated bulbospongiosus muscles surrounding the penile urethra results in propelling the semen out of the tip of the penis.

The secretions of the accessory glands promote sperm survival and fertility. The accessory glands that contribute to the secretions are the seminal vesicles, prostate gland, and bulbourethral glands. The semen contains only 10% sperm by volume, with the remainder consisting of the combined secretions of the accessory glands. The normal volume of semen is 3 mL with 20 to 50 million sperm per milliliter; normal is considered more than 20 million sperm per milliliter. The **seminal vesicles** contribute about 75% of the semen volume. Their secretion contains fructose (the principal substrate for glycolysis of ejaculated sperm), ascorbic acid, and prostaglandins. In fact, prostaglandin concentrations are high and were first discovered in semen but were mistakenly considered the product of the prostate. Seminal vesicle secretions are also responsible for coagulation of the semen seconds after ejaculation. Prostate gland secretions (~0.5 mL) include fibrinolysin, which is responsible for liquefaction of the coagulated semen 15 to 30 minutes after ejaculation, releasing sperm.

## SPERMATOGENESIS

Spermatogenesis is a continual process involving mitosis of the male germ cells that undergo extensive morphological changes in cell shape and, ultimately, meiosis to produce the haploid spermatozoa. Sperm are produced throughout life beginning with puberty. Sperm production declines in the elderly.

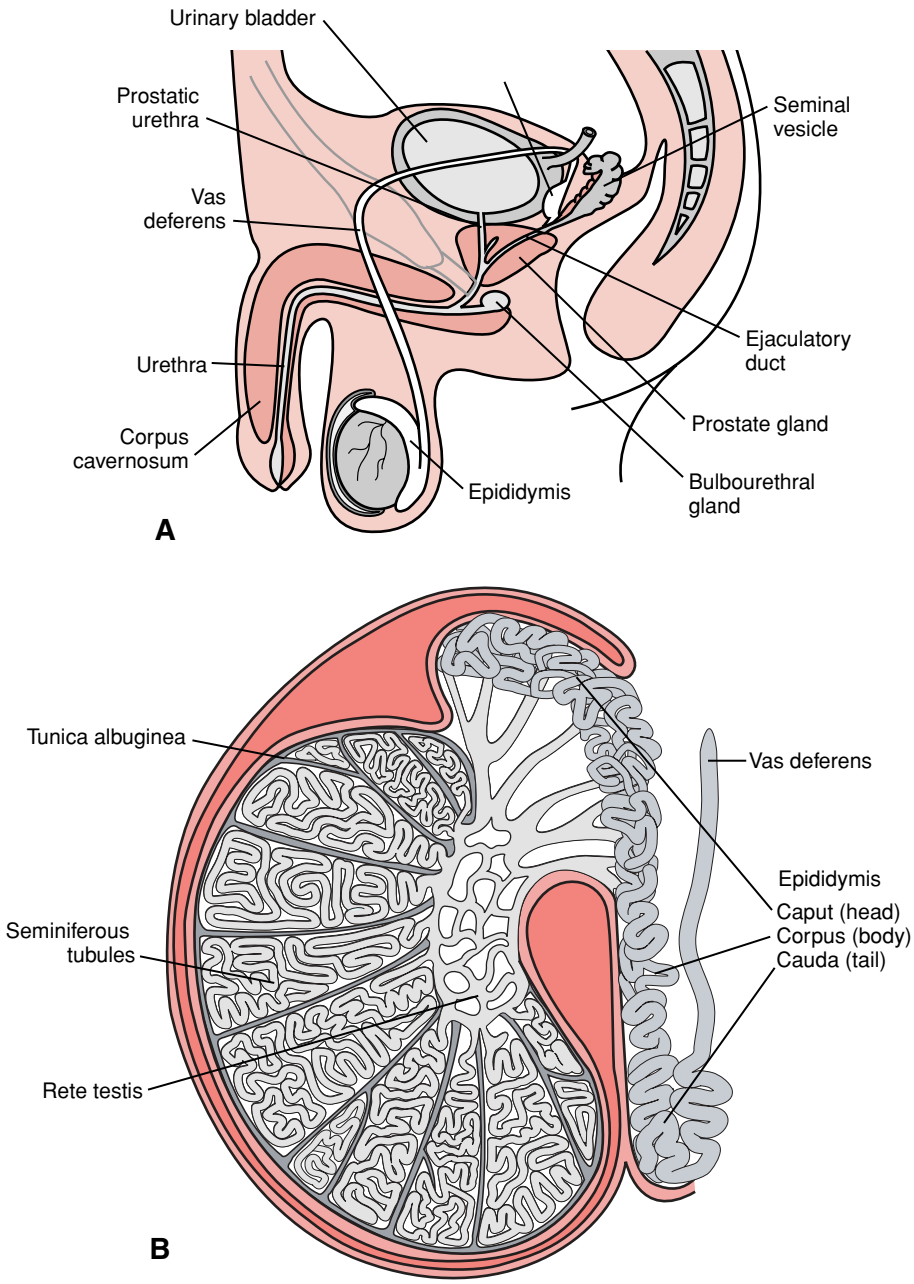


**FIGURE 37.7 The male reproductive organs.** The top drawing is a general side view. The bottom enlargement shows a sagittal section of the testis, epididymis, and vas deferens.

## Spermatogenesis Is an Ongoing Process From Puberty to Senescence

**Spermatogenesis** is the process of transformation of male germ cells into spermatozoa. This process can be divided into three distinct phases. The phases include cellular proliferation by **mitosis**, two reduction divisions by **meiosis** to produce haploid spermatids, and cell differentiation by a process called **spermiogenesis**, in which the spermatids differentiate into spermatozoa (Fig. 37.8). Spermatogenesis begins at puberty, so the seminiferous tubules are quiescent throughout childhood. Spermatogenesis is initiated shortly before puberty, under the influence of the rising levels of gonadotropins and testosterone, and continues throughout life, with a slight decline during old age.

The time required to produce mature spermatozoa from the earliest stage of spermatogonia is 65 to 70 days. Because several developmental stages of spermatogenic cells occur during this time frame, the stages are collectively known as the **spermatogenic cycle**. There is synchronized development of spermatozoa within the seminiferous tubules, and each stage is morphologically distinct. A spermatogonium becomes a mature spermatozoon after going through several rounds of mitotic divisions, a couple of meiotic divisions, and a few weeks of differentiation. Hormones can alter the number of spermatozoa, but they generally do not affect the duration of the cycle. Spermatogenesis occurs along the length of each seminiferous tubule in successive cycles. New cycles are initiated at regular time intervals (every 2 to 3 weeks) before the previous ones are com-

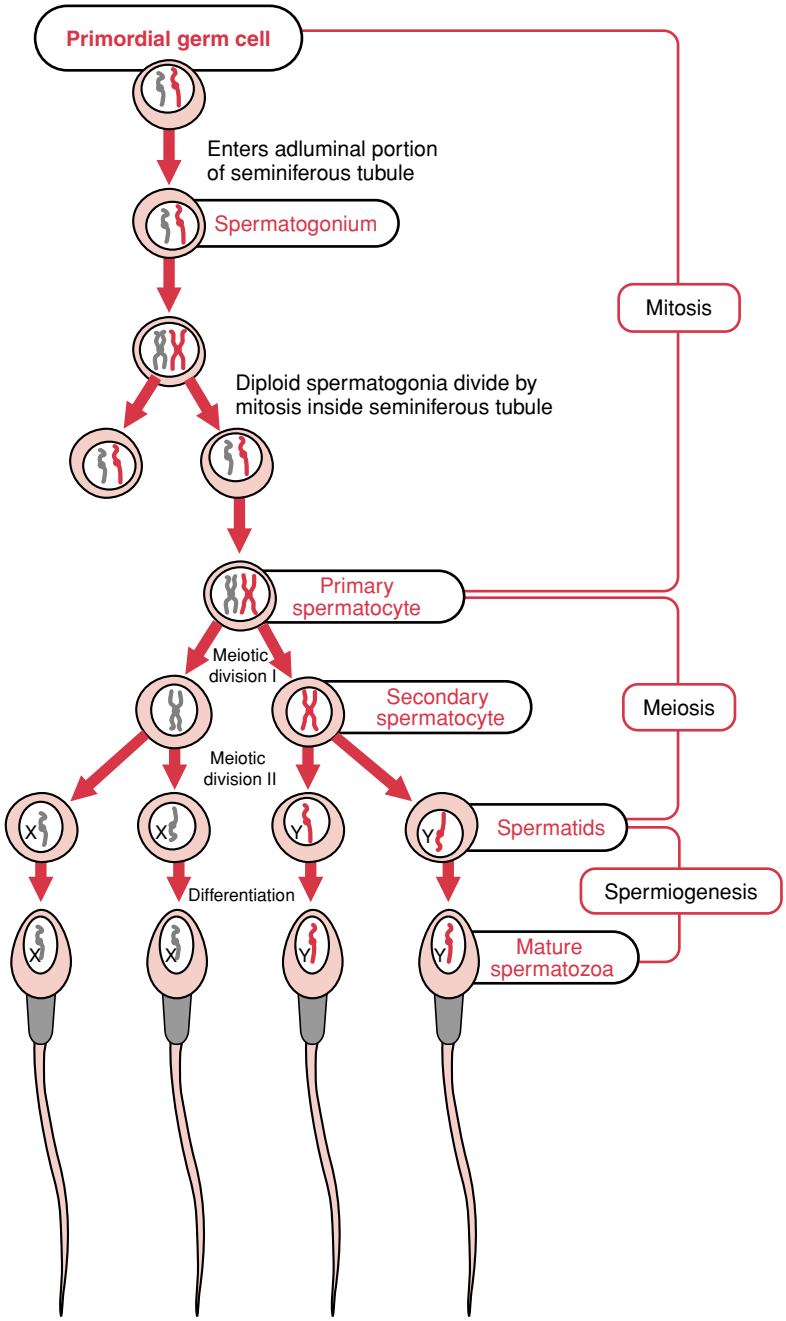


**FIGURE 37.8 The process of spermatogenesis, showing successive cell divisions and remodeling leading to the formation of haploid spermatozoa.** (Modified from Alberts B, Bray D, Lewis M, et al. Molecular Biology of the Cell. 3rd Ed. New York: Garland, 1994.)

pleted. Consequently, cells at different stages of development are spaced along each tubule in a "spermatogenic wave." Such a succession ensures the continuous production of fresh spermatozoa. Approximately 200 million spermatozoa are produced daily in the adult human testes, which is about the same number of sperm present in a normal ejaculate.

Since sperm cells are rapidly dividing and undergoing meiosis, they are sensitive to external agents that alter cell division. Chemical carcinogens, chemotherapeutic agents, certain drugs, environmental toxins, irradiation, and extreme temperatures are factors that can reduce the number of replicating germ cells or cause chromosomal abnormalities in individual cells. While defective somatic cells are normally detected and destroyed by the immune system, the blood-testis barrier isolates advanced germ cells from immune surveillance.

If the blood-testis barrier is ruptured by physical injury or infection and sperm cells within the barrier are exposed to circulating immune cells, it is possible that antibodies will develop to the sperm cells. In the past, it was thought that the development of antisperm antibodies could lead to male infertility. It appears that men with high levels of antisperm antibodies may exhibit some infertility problems. However, studies of men who have developed low or moderate levels of antisperm antibodies after vasectomy and who have had their vasa deferens reconnected have normal fertility if the vasectomy was for a relatively short time. Vasectomy does not ap-

pear to change hormone or sperm production by the testes. Nevertheless, in some cases, a high level of antisperm antibodies in men and women leads to infertility.

## Spermatogonia Undergo Mitotic and Meiotic Divisions and Become Spermatids

Spermatogonia undergo several rounds of mitotic division prior to entering the meiotic phase (see Fig. 37.8). The spermatogonia remain in contact with the Sertoli cells, migrate away from the basal compartment near the walls of the seminiferous tubules and cross into the adluminal compartment of the tubule (see Fig. 37.5). After crossing into the adluminal compartment, the cells differentiate into spermatocytes prior to undergoing meiosis I. The first meiotic division of **primary spermatocytes** gives rise to diploid (2n chromosomes) **secondary spermatocytes**.

The second meiotic division produces haploid (1 set of chromosomes) cells called **spermatids**. Of every four spermatids emanating from a primary spermatocyte, two contain X chromosomes and two have Y chromosomes (see Fig. 37.8). Because of the numerous mitotic divisions and two rounds of meiosis, each spermatogonium committed to meiosis should have yielded 256 spermatids, if all cells survive.

There are numerous developmental disorders of spermatogenesis. The most frequent is **Klinefelter's syndrome**, which causes hypogonadism and infertility in men. Patients with this disorder have an accessory X chromosome caused by meiotic nondisjunction. The typical karyotype is 47 XXY, but there are other chromosomal mosaics. Testicular volume is reduced more than 75% and ejaculates contain few, if any, spermatozoa. Spermatogonic cell differentiation beyond the primary spermatocyte stage is rare.

## The Formation of a Mature Spermatozoon Requires Extensive Cell Remodeling

Spermatids are small, round, and nondistinctive cells. During the second half of the spermatogenic cycle they undergo considerable restructuring to form mature spermatozoa. Notable changes include alterations in the nucleus, the formation of a tail, and a massive loss of cytoplasm. The nucleus becomes eccentric and decreases in size, and the chromatin becomes condensed. The **acrosome**, a lysosome-like structure unique to spermatozoa, buds from the Golgi apparatus, flattens, and covers most of the nucleus. The centrioles, located near the Golgi apparatus, migrate to the caudal pole and form a long axial filament made of nine peripheral doublet microtubules surrounding a central pair (9 + 2 arrangement). This becomes the **axoneme** or major portion of the tail. Throughout this reshaping process, the cytoplasmic content is redistributed and discarded. During spermiation, most of the remaining cytoplasm is shed in the form of residual bodies.

The reasons for this lengthy and metabolically costly process become apparent when the unique functions of this cell are considered. Unlike other cells, the spermatozoon serves no apparent purpose in the organism. Its only function is to reach, recognize, and fertilize an egg; hence, it must fulfill several prerequisites: It should possess an energy supply and means of locomotion, it should be able to withstand a foreign and even hostile environment, it should be able to recognize and penetrate an egg, and it must carry all the genetic information necessary to create a new individual.

The mature spermatozoon exhibits a remarkable degree of structural and functional specialization well adapted to carry out these functions. The cell is small, compact, and streamlined; it is about 1 to 2 μm in diameter and can exceed 50 μm in length in humans. It is packed with specialized organelles and long axial fibers but contains only a few of the normal cytoplasmic constituents, such as ribosomes, ER, and Golgi apparatus. It has a very prominent nucleus, a flexible tail, numerous mitochondria, and an assortment of proteolytic enzymes.

The spermatozoon consists of three main parts: a head, a middle piece, and a tail. The two major components in the head are the condensed chromatin and the acrosome. The haploid chromatin is transcriptionally inactive throughout the life of the sperm until fertilization, when the nucleus decondenses and becomes a pronucleus. The acrosome contains proteolytic enzymes, such as hyaluronidase, acrosin, neuraminidase, phospholipase A, and esterases. They are inactive until the **acrosome reaction** occurs upon contact of the sperm head with the egg (see Chapter 39). Their proteolytic action enables sperm to penetrate through the egg membranes. The middle piece contains spiral sheaths of mitochondria that supply energy for sperm metabolism and locomotion. The tail is composed of a 9 + 2 arrangement of microtubules, which is typical of cilia and flagella, and is surrounded by a fibrous sheath that provides some rigidity. The tail propels the sperm by a twisting motion, involving interactions between tubulin fibers and dynein side arms and requiring ATP and magnesium.

## Testosterone Is Essential for Sperm Production and Maturation

Spermatogenesis requires high intratesticular levels of testosterone, secreted from the LH-stimulated Leydig cells. The testosterone diffuses across the basement membrane of the seminiferous tubule, crosses the blood-testis barrier, and complexes with ABP. Sertoli cells, but not spermatogenic cells, contain receptors for testosterone. Sertoli cells also contain FSH receptors. However, recent studies using mice, in which the β subunit of FSH has been mutated to an inactive form, reveal that the testes are small but do produce sperm. The absolute requirement for FSH in sperm production remains unknown. From these data, it appears that testosterone may be sufficient for spermatogenesis.

The actions of FSH and testosterone at each point of sperm cell production are unknown. Upon entering meiosis, spermatogenesis appears to depend on the availability of FSH and testosterone. In human males, FSH is thought to be required for the initiation of spermatogenesis before puberty. When adequate sperm production has been achieved, LH alone (through stimulation of testosterone production) or testosterone alone is sufficient to maintain spermatogenesis.

## TESTICULAR STEROIDOGENESIS

Following spermatogenesis, the second primary function of the testes is steroidogenesis. **Steroidogenesis** is the production of the steroid hormones, mainly testosterone. Testosterone is then converted to dihydrotesterone (DHT), the most biologically active androgen, and to estradiol, the most biologically estrogen.

### Testosterone Production Requires Two Intracellular Compartments and Several Enzymes

Steroid hormones are produced from cholesterol by the adrenal cortex, ovaries, testes, and placenta. Cholesterol, a 27-carbon (C27) steroid, can be obtained from the diet or synthesized within the body from acetate. Each organ uses a similar steroid biosynthetic pathway, but the relative amount of the final products depends on the particular subset of enzymes expressed in that tissue and the trophic hormones (LH, FSH, ACTH) stimulating specific cells within the organ. The major steroid produced by the testis is **testosterone**, but other androgens, such as androstenediol, androstenedione, and dehydroepiandrosterone (DHEA), as well as a small amount of estradiol, are also produced.

Cholesterol from low-density lipoprotein (LDL) and high-density lipoprotein (HDL) is released in the Leydig cell and transported from the outer mitochondrial membrane to the inner mitochondrial membrane, a process regulated by **steroidogenic acute regulatory protein** (StAR). Under the influence of LH, with cAMP as a second messenger, cholesterol is converted to pregnenolone (C21) by cholesterol side-chain cleavage enzyme (CYP11A1), which removes 6 carbons attached to the 21 position. Pregnenolone is a key intermediate for all steroid hormones in various steroidogenic organs (Fig. 37.9; see also Fig. 34.5). Pregnenolone is transported out of mitochondria by specific transport proteins. The pregnenolone then moves by diffusion to the smooth ER, where the remainder of sex hormone biosynthesis takes place.

Pregnenolone can be converted to testosterone via two pathways, the **delta 5 pathway** and the **delta 4 pathway**. In the delta 5 pathway, the double bond is in ring B; in the delta 4 pathway the double bond is in ring A (see Fig. 37.9). The delta 5 intermediates include 17α-hydroxypregnenolone, DHEA, and androstenediol, while the delta 4 intermediates are progesterone, 17α-hydroxyprogesterone, and androstenedione.

The conversion of C21 steroids (the progestins) to androgens (C19 steroids) proceeds in two steps: first, 17α-hydroxylation of pregnenolone (to form 17α-hydroxypregnenolone) and second, C17,20 cleavage; thus, two carbons are removed to form DHEA. This hydroxylation and cleavage is accomplished by a single enzyme, 17α-hydroxylase or 17,20-lyase (CYP17). DHEA is converted to androstenedione by another two-step enzymatic reaction: dehydrogenation in position 3 (catalyzed by 3β-hydroxysteroid dehydrogenase [3β-HSD]) and shifting of the double bond from ring B to ring A (catalyzed by delta 4,5-ketosteroid isomerase); these two may be the same enzyme. The final reaction yielding testosterone is carried out by 17-ketosteroid reductase (17β-hydroxysteroid dehydrogenase), which substitutes the keto group in position 17 with a hydroxyl group. Unlike all the preceding enzymatic reactions, this is a reversible step but tends to favor testosterone.

Although estrogens are only minor products of testicular steroidogenesis, they are normally found in low concentrations in men. Androgens (C19) are converted to estrogens (C18) by the action of the enzyme complex aromatase (CYP19). Aromatization involves the removal of the methyl group in position 19 and the rearrangement of ring A into an unsaturated aromatic ring. The products of aromatization of testosterone and androstenedione are estradiol and estrone, respectively (see Fig. 37.9). In the testis, the Sertoli cell is the main site of aromatization, which is stimulated by FSH; however, aromatization may also occur in peripheral tissues that lack FSH receptors (e.g., adipose tissue).

### The Effects of LH on Leydig Cells Are Primarily Mediated by cAMP

The action of LH on Leydig cells is mediated through specific LH receptors on the plasma membrane. A Leydig cell has about 15,000 LH receptors, and occupancy of less than 5% of these is sufficient for maximal steroidogenesis. This is an example of "spare receptors" (see Chapter 31). Excess receptors increase target cell sensitivity to low circulating levels of hormones by increasing the probability that sufficient receptors will be occupied to induce a response. After exposure to a high LH concentration, the number of LH receptors and testosterone production decrease. However, in response to the initial high concentration of LH, testosterone production will increase and then decrease. Thereafter, subsequent challenges with LH lead to no response or decreased responses. This so-called desensitization involves a loss of surface LH receptors as a result of internalization and receptor modification by phosphorylation.

The LH receptor is a single 93-kDa glycoprotein composed of three functional domains: a glycosylated extracellular hormone-binding domain, a transmembrane spanning domain that contains seven noncontiguous segments, and an intracellular domain. The receptor is coupled to a stimulatory G protein ($G_s$) via a loop of one of the LH receptor transmembrane segments. The activation of $G_s$ results in increased adenylyl cyclase activity, the production of cAMP, and the activation of protein kinase A (Fig. 37.10).

Low doses of LH can stimulate testosterone production without detectable changes in total cell cAMP concentration. However, the amount of cAMP bound to the regulatory subunit of protein kinase A (PKA) increases in response to such low doses of LH. This response emphasizes the importance of compartmentalization for both enzymes and substrates in mediating hormonal action. Other intracellular mediators, such as the phosphatidylinositol system or calcium, have roles in regulating Leydig cell steroidogenesis, but it appears that the PKA pathway may predominate.

The proteins phosphorylated by PKA are specific for each cell type. Some of these, such as cAMP response element binding protein (CREB), which functions as a DNA-binding protein, regulate the transcription of cholesterol

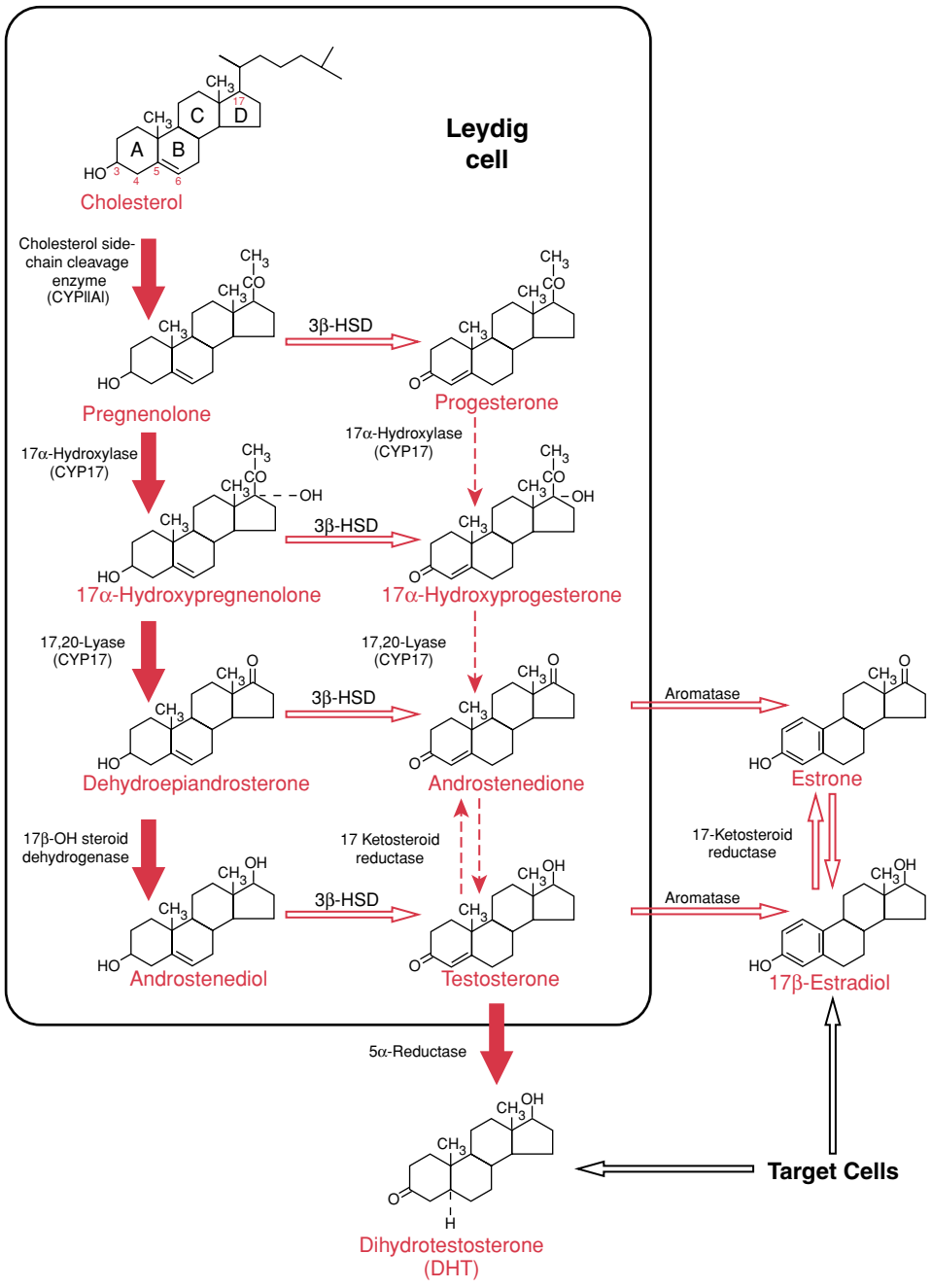


**FIGURE 37.9 Steroidogenesis in Leydig cells and further modifications of androgens in target cells.** Solid arrows represent the delta 5 pathway. Dashed arrows represent the delta 4 pathway.

side-chain cleavage enzyme (CYP11A1), the rate-limiting enzyme in the conversion of cholesterol to pregnenolone. cAMP is inactivated by **phosphodiesterase** to AMP. This enzyme plays a major role in regulating LH (and, possibly, FSH) responses because phosphodiesterase is activated by gonadotropin stimulation. The increase in phosphodiesterase reduces the response to LH (and FSH). Certain drugs can inhibit phosphodiesterase; gonadotropin hormone responses will increase dramatically in the presence of those drugs. Numerous isoforms of phosphodiesterase and adenylyl cyclase exist; specific types of each in the testis have not yet been revealed.

LH stimulates steroidogenesis by two principal activations. One is the phosphorylation of cholesterol esterase, which releases cholesterol from its intracellular stores. The other is the activation of CYP11A1.

Leydig cells also contain receptors for **prolactin** (PRL). Hyperprolactinemia in men with pituitary tumors, usually microadenomas, is associated with decreased testosterone levels. This condition is due to a direct effect of elevated circulating levels of PRL on Leydig cells, reducing the number of LH receptors or inhibiting downstream signaling events. In addition, hyperprolactinemia may decrease LH secretion by reducing the pulsatile nature of its release. Under nonpathological conditions, however, PRL may synergize with LH to stimulate testosterone production by increasing the number of LH receptors.

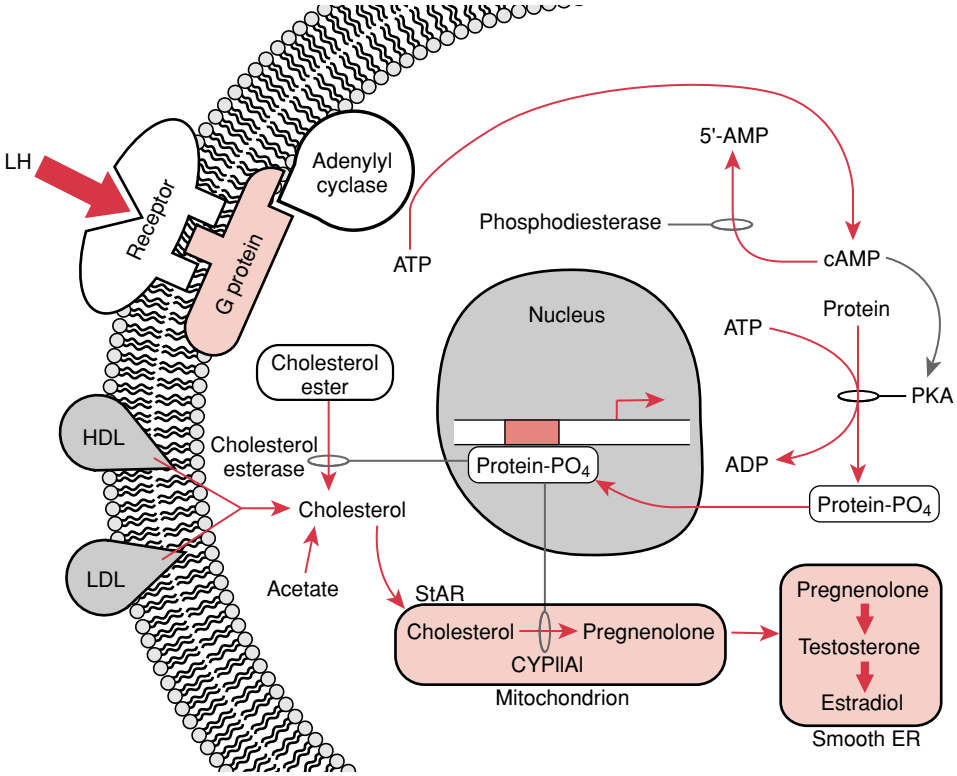


**FIGURE 37.10** **A proposed intracellular mechanism by which LH stimulates testosterone synthesis.**

## THE ACTIONS OF ANDROGENS

DHT enhances development of the male reproductive tract, accompanying accessory ducts and glands, and male sex characteristics, including behavior. A lack of androgen secretion or action causes feminization.

### Peripheral Tissues Process and Metabolize Testosterone

Testosterone is not stored in Leydig cells but diffuses into the blood immediately after being synthesized. An adult man produces 6 to 7 mg testosterone per day. This amount slowly declines after age 50 and reaches about 4 mg/day in the seventh decade of life. Therefore, men do not undergo a sudden cessation of sex steroid production upon aging, as women do during their postmenopausal period, when the ova are completely depleted.

Testosterone circulates bound to plasma proteins, with only 2 to 3% present as the free hormone. About 30 to 40% is bound to albumin and the remainder to **sex hormone-binding globulin** (SHBG), a 94-kDa glycoprotein produced by the liver. SHBG binds both estradiol and testosterone, with a higher binding affinity for testosterone. Because its production is increased by estrogens and decreased by androgens, plasma SHBG concentration is higher in women than in men. SHBG serves as a reservoir for testosterone, and therefore, a sudden decline in newly formed testosterone may not be evident because of the large pool bound to proteins. SHBG, in effect, deactivates testosterone because only the unbound hormone can enter the cell. SHBG also prolongs the half-life of circulating testosterone because testosterone is cleared from the circulation much more slowly if bound to a protein. Any type of liver damage or disease will generally reduce SHBG production. The latter can upset the hormonal balance between LH and testosterone. For example, if SHBG declines acutely, then free testosterone may increase while the total amount of circulating testosterone would decrease. In response to the increase in free testosterone, LH levels would decline in a homeostatic attempt to reduce testosterone production.

Once testosterone is released into the circulation, its fate is variable. In most target tissues, testosterone functions as a prohormone and is converted to the biologically active derivatives DHT by **5α-reductase** or estradiol by aromatase (Fig. 37.11). Skin, hair follicles, and most of the male reproductive tract contain an active 5α-reductase. The enzyme irreversibly catalyzes the reduction of the double bond in ring A and generates DHT (see Fig. 37.9). DHT has a high binding affinity for the androgen receptor and is 2 to 3 times more potent than testosterone.

Congenital deficiency of 5α-reductase in males results in ambiguous genitalia containing female and male characteristics because DHT is critical for directing the normal development of male external genitalia during embryonic life (see Chapter 39). Without DHT, the female pathway may predominate, even though the genetic sex is male and small, undescended testes are present in the inguinal region. DHT is nonaromatizable and cannot be converted to estrogens.

Drugs that inhibit 5α-reductase are currently used to reduce prostatic hypertrophy because DHT induces hyperplasia of prostatic epithelial cells. In addition, analogs of GnRH, as either agonists or antagonists, can be given to patients to reduce the secretion of androgen in androgen-dependent

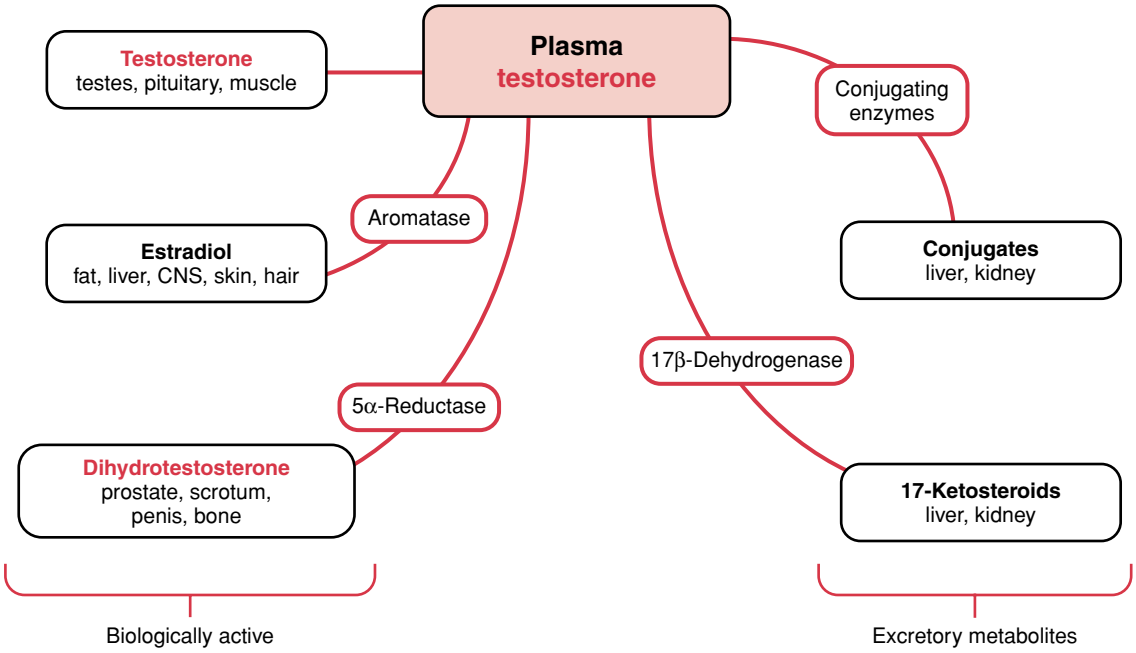


**FIGURE 37.11** **Conversion of testosterone to different products in extratesticular sites.**

neoplasia or cancer (see Clinical Focus Box 37.1). In the case of the GnRH antagonist, this analog blocks the secretion of LH. In contrast, GnRH agonists given in large quantities initially induce the secretion of LH (and androgen). However, this response is followed by down-regulation of GnRH receptors on the pituitary gonadotrophs and, ultimately, a dramatic decline in circulating LH and androgen.

Aromatization of some androgens to estrogens occurs in fat, liver, skin, and brain cells. Circulating levels of total estrogens (estradiol plus estrone) in men can approach those of women in their early follicular phase. Men are protected from feminization as long as production of and tissue responsiveness to androgens are normal. The treatment of hypogonadal male patients with high doses of aromatizable testosterone analogs (or testosterone), the use of anabolic steroids by athletes, abnormal reductions in testosterone secretion, estrogen-producing testicular tumors, and tissue insensitivity to androgens can lead to **gynecomastia** or breast enlargement. All of these conditions are characterized by a decrease in the testosterone-to-estradiol ratio.

Androgens are metabolized in the liver to biologically inactive water-soluble derivatives suitable for excretion by the kidneys. The major products of testosterone metabolism are two 17-ketosteroids, androsterone and etiocholanolone. These, as well as native testosterone, are conjugated in position 3 to form sulfates and glucuronides, which are water-soluble and excreted into the urine (see Fig. 37.11).

## Androgens Have Effects on Reproductive and Nonreproductive Tissues

An **androgen** is a substance that stimulates the growth of the male reproductive tract and the development of secondary sex characteristics. Androgens have effects on almost every tissue, including alteration of the primary sex structures (i.e., the testes and genital tract) and stimulation of the secondary sex structures (i.e., accessory glands) and development of secondary sex characteristics responsible for masculine phenotypic expression. Androgens also affect both sexual and nonsexual behavior. The relative potency ranking of androgens is DHT > testosterone > androstenedione > DHEA. The action of sex steroid hormones on somatic tissue, such as muscle, is referred to as "anabolic" because the end result is increased muscle size. This action is mediated by the same molecular mechanisms that result in virilization.

Between 8 and 18 weeks of fetal life, androgens mediate differentiation of the male genitalia. The organogenesis of the wolffian (mesonephric) ducts into the epididymis, vas deferens, and seminal vesicles is directly influenced by testosterone, which reaches these target tissues by diffusion rather than by a systemic route. The differentiation of the urogenital sinus and the genital tubercle into the penis, scrotum, and prostate gland depends on testosterone being converted to DHT. Toward the end of fetal life, the descent of the testes into the scrotum is promoted by testosterone and insulin-like hormones from Leydig cells (see Chapter 39).

The onset of puberty is marked by enhanced androgenic activity. Androgens promote the growth of the penis and scrotum, stimulate the growth and secretory activity of the epididymis and accessory glands, and increase the pigmentation of the genitalia. Enlargement of the testes occurs under the influence of the gonadotropins (LH and FSH). Spermatogenesis, which is initiated during puberty, depends on adequate amounts of testosterone. Throughout adulthood, androgens are responsible for maintaining the structural and functional integrity of all reproductive tissues. Castration of adult men results in regression of the reproductive tract and involution of the accessory glands.

**CLINICAL FOCUS BOX 37.1**

**Prostate Cancer**

Some prostate cancers are highly dependent upon androgens for cellular proliferation; therefore, physicians attempt to totally ablate the secretion of androgens by the testes. Generally, two options for those patients are surgical castration and chemical castration. Surgical castration is irreversible and requires the removal of the testes, while chemical castration is reversible.

One option for chemical treatment of these patients is the use of analogs of GnRH, the hormone that regulates the secretion of LH and FSH. Long-acting GnRH agonists or antagonists reduce LH and FSH secretion by different mechanisms. GnRH agonists reduce gonadotropin secretion by desensitization of the pituitary gonadotrophs to GnRH, leading to a reduction of LH and FSH secretion. GnRH agonists initially stimulate GnRH receptors on pituitary cells and ultimately reduce their numbers. GnRH antagonists bind to GnRH receptors on the pituitary cells, prevent endogenous GnRH from binding to those receptors, and subsequently reduce LH and FSH secretion. Shortly after treatment, testicular concentrations of androgens decline because of the low levels of circulating LH and FSH. The expectation is that androgen-dependent cancer cells will cease or slow proliferation and, ultimately, die.

GnRH agonists (leuprolide acetate [trade name Lupron]) are usually used in combination with other drugs in order to block most effectively androgenic activity. For example, one of the androgen-blocking drugs includes 5α-reductase inhibitors that prevent the conversion of testosterone to the highly active androgen dihydrotestosterone (DHT). In addition,

antiandrogens, such as flutamide, bind to the androgen receptor and prevent binding of endogenous androgen. Some prostate cancers are androgen-independent, and the treatment requires nonhormonal therapies, including chemotherapy and radiation.

## Androgens Are Responsible for Secondary Sex Characteristics and the Masculine Phenotype

Androgens effect changes in hair distribution, skin texture, pitch of the voice, bone growth, and muscle development. Hair is classified by its sensitivity to androgens into nonsexual (eyebrows and extremities); ambisexual (axilla), which is responsive to low levels of androgens; and sexual (face, chest, upper pubic triangle), which is responsive only to high androgen levels. Hair follicles metabolize testosterone to DHT or androstenedione. Androgens stimulate the growth of facial, chest, and axillary hair; however, along with genetic factors, they also promote temporal hair recession and loss. Normal axillary and pubic hair growth in women is also under androgenic control, whereas excess androgen production in women causes the excessive growth of sexual hair (**hirsutism**).

The growth and secretory activity of the sebaceous glands on the face, upper back, and chest are stimulated by androgens, primarily DHT, and inhibited by estrogens. Increased sensitivity of target cells to androgenic action, especially during puberty, is the cause of **acne vulgaris** in both males and females. Skin derived from the urogenital ridge (e.g., the prepuce, scrotum, clitoris, and labia majora) remains sensitive to androgens throughout life and contains an active 5α-reductase. Growth of the larynx and thickening of the vocal cords are also androgen-dependent. Eunuchs maintain the high-pitched voice typical of prepubertal boys because they were castrated prior to puberty.

The growth spurt of adolescent males is influenced by a complex interplay between androgens, growth hormone (GH), nutrition, and genetic factors. The growth spurt includes growth of the vertebrae, long bones, and shoulders. The mechanism by which androgens (likely DHT) alter bone metabolism is unclear. Androgens accelerate closure of the epiphyses in the long bones, eventually limiting further growth. Because of the latter, precocious puberty is associated with a final short adult stature, whereas delayed puberty or eunuchoidism usually results in tall stature. Androgens have multiple effects on skeletal and cardiac muscle. Because 5α-reductase activity in muscle cells is low, the androgenic action is due to testosterone. Testosterone stimulates muscle hypertrophy, increasing muscle mass; however, it has minimal or no effect on muscle hyperplasia. Testosterone, in synergy with GH, causes a net increase in muscle protein.

Other nonreproductive organs and systems are affected, directly or indirectly, by androgens, including the liver, kidneys, adipose tissue, and hematopoietic and immune systems. The kidneys are larger in males, and some renal enzymes (e.g., β-glucuronidase and ornithine decarboxylase) are induced by androgens. HDL levels are lower and triglyceride concentrations higher in men, compared to premenopausal women, a fact that may explain the higher prevalence of atherosclerosis in men. Androgens increase red blood cell mass (and, hence, hemoglobin levels) by stimulating erythropoietin production and by increasing stem cell proliferation in the bone marrow.

## The Brain Is a Target Site for Androgen Action

Many sites in the brain contain androgen receptors, with the highest density in the hypothalamus, preoptic area, septum, and amygdala. Most of those areas also contain aromatase and many of the androgenic actions in the brain result from the aromatization of androgens to estrogens. The pituitary also has abundant androgen receptors, but no aromatase. The enzyme 5α-reductase is widely distributed in the brain, but its activity is generally higher during the prenatal period than in adults. Sexual dimorphism in the size, number, and arborization of neurons in the preoptic area, amygdala, and superior cervical ganglia has been recently recognized in humans.

Unlike most species, which mate only to produce offspring, in humans, sexual activity and procreation are not tightly linked. Superimposed on the basic reproductive mechanisms dictated by hormones are numerous psycho-

logical and societal factors. In normal men, no correlation is found between circulating testosterone levels and sexual drive, frequency of intercourse, or sexual fantasies. Similarly, there is no correlation between testosterone levels and impotence or homosexuality. Castration of adult men results in a slow decline in, but not a complete elimination of, sexual interest and activity. See Clinical Focus Box 37.2 for a discussion of the effects of testosterone administration.

## REPRODUCTIVE DYSFUNCTIONS

Male reproductive dysfunctions may by caused by endocrine disruption, morphological alterations in the reproductive tract, neuropathology, and genetic mutations. Several medical tests, including serum hormone levels, physical examination of the reproductive organs, and sperm count are important in ascertaining causes of reproductive dysfunctions.

### Hypogonadism Can Result From Defects at Several Levels

Male **hypogonadism** may result from defects in spermatogenesis, steroidogenesis, or both. It may be a primary defect in the testes or secondary to hypothalamic-pituitary dysfunction, and determining whether the onset of gonadal failure occurred before or after puberty is important in establishing the cause. However, several factors must be considered. First, normal spermatogenesis almost never occurs with defective steroidogenesis, but normal steroidogenesis can be present with defective spermatogenesis. Second, primary testicular failure removes feedback inhibition from the hypothalamic-pituitary axis, resulting in elevated plasma gonadotropins. In contrast, hypothalamic and/or pituitary failure is almost always accompanied by decreased gonadotropin and steroid levels and reduced testicular size. Third, gonadal failure before puberty results in the absence of secondary sex characteristics, creating a distinctive clinical presentation called **eunuchoidism**. In contrast, men with a postpubertal testicular failure retain masculine features but exhibit low sperm counts or a reduced ability to produce functional sperm.

To establish the cause(s) of reproductive dysfunction, physical examination and medical history, semen analysis, hormone determinations, hormone stimulation tests, and genetic analysis are performed. Physical examination should establish whether eunuchoidal features (i.e., infantile appearance of external genitalia and poor or absent development of secondary sex characteristics) are present. In men with adult-onset reproductive dysfunction, physical examination can uncover problems such as cryptorchidism (nondescendent testes), testicular injury, varicocele (an abnormality of the spermatic vasculature), testicular tumors, prostatic inflammation, or gynecomastia. Medical and family history help determine delayed puberty, anosmia (an inability to smell, often associated with GnRH dysfunction), previous fertility, changes in sexual performance, ejaculatory disturbances, or impotence (an inability to achieve or maintain erection).

One step in the evaluation of fertility is semen analysis. Semen are analyzed on specimens collected after 3 to 5 days of sexual abstinence, as the number of sperm ejaculated remains low for a couple of days after ejaculation. Initial examination includes determination of viscosity, liquefaction, and semen volume. The sperm are then counted and the percentage of sperm showing forward motility is scored. The spermatozoa are evaluated morphologically, with attention to abnormal head configuration and defective tails. Chemical analysis can provide information on the secretory activity of the accessory glands, which is considered abnormal if semen volume is too low or sperm motility is impaired. Fructose and prostaglandin levels are determined to assess the function of the seminal vesicles and levels of zinc, magnesium, and acid phosphatase to evaluate the prostate. Terms used in evaluating fertility include aspermia (no semen), hypospermia and hyperspermia (too small or too large semen volume), azoospermia (no spermatozoa), and oligozoospermia (reduced number of spermatozoa).

Serum testosterone, estradiol, LH, and FSH analyses are performed using radioimmunoassays. Free and total testosterone levels should be measured; because of the pulsatile nature of LH release, several consecutive blood samples are needed. Dynamic hormone stimulation tests are most valuable for establishing the site of abnormality. A failure to increase LH release upon treatment with **clomiphene**, an

**CLINICAL FOCUS BOX 37.2**

**Effects of Testosterone Administration**

Although testosterone has a role in stimulating spermatogenesis, infertile men with a low sperm count do not benefit from testosterone treatment. Unless given at supraphysiological doses, exogenous testosterone cannot achieve the required local high concentration in the testis. One function of androgen-binding protein in the testis is to sequester testosterone, which significantly increases its local concentration.

Exogenous testosterone given to men would normally inhibit endogenous LH release through a negative-feedback effect on the hypothalamic-pituitary axis, and lead to a suppression of testosterone production by the Leydig cells and a further decrease in testicular testosterone concentrations. Ultimately, because LH levels decrease when exogenous testosterone is administered, testicular size decreases, as has been reported for men who abuse androgens.

High levels of androgens have an anabolic effect on muscle tissue, leading to increased muscle mass, strength, and performance, a desired result for body builders and athletes. Androgen abuse has been associated with abnormally aggressive behavior and the potential for increased incidence of liver and brain tumors.

antiestrogen, likely indicates a hypothalamic abnormality. Clomiphene blocks the inhibitory effects of estrogen and testosterone on endogenous GnRH release. An absence of or blunted testosterone rise after hCG injection suggests a primary testicular defect. Genetic analysis is used when congenital defects are suspected. The presence of the Y chromosome can be revealed by karyotyping of cultured peripheral lymphocytes or direct detection of specific Y antigens on cell surfaces.

## Reproductive Disorders Are Associated With Hypogonadotropic or Hypergonadotropic States

Endocrine factors are responsible for approximately 50% of hypogonadal or infertility cases. The remainder is of unknown etiology or the result of injury, deformities, and environmental factors. Endocrine-related hypogonadism can be classified as hypothalamic-pituitary defects (hypogonadotropic because of the lack of LH and/or FSH), primary gonadal defects (hypergonadotropic because gonadotropins are high as a result of a lack of negative feedback from the testes), and defective androgen action (usually the result of absence of androgen receptor or 5α-reductase). Each of these is further subdivided into several categories, but only a few examples are discussed here.

**Hypogonadotropic hypogonadism** can be congenital, idiopathic, or acquired. The most common congenital form is Kallmann's syndrome, which results from decreased or absent GnRH secretion, as mentioned earlier. It is often associated with anosmia or hyposmia and is transmitted as an autosomal dominant trait. Patients do not undergo pubertal development and have eunuchoidal features. Plasma LH, FSH, and testosterone levels are low, and the testes are immature and have no sperm. There is no response to clomiphene, but intermittent treatment with GnRH can produce sexual maturation and full spermatogenesis.

Another category of hypogonadotropic hypogonadism, **panhypopituitarism** or **pituitary failure**, can occur before or after puberty and is usually accompanied by a deficiency of other pituitary hormones. **Hyperprolactinemia**, whether from hypothalamic disturbance or pituitary adenoma, often results in decreased GnRH production, hypogonadotropic state, impotence, and decreased libido. It can be treated with dopaminergic agonists (e.g., bromocryptine), which suppress PRL release (see Chapter 38). Excess androgens can also result in suppression of the hypothalamic-pituitary axis, resulting in lower LH levels and impaired testicular function. This condition often results from **congenital adrenal hyperplasia** and increased adrenal androgen production from 21-hydroxylase (CYP21A2) deficiency (see Chapter 34).

**Hypergonadotropic hypogonadism** usually results from impaired testosterone production, which can be congenital or acquired. The most common disorder is Klinefelter's syndrome discussed earlier.

## Male Pseudohermaphroditism Often Results From Resistance to Androgens

A **pseudohermaphrodite** is an individual with the gonads of one sex and the genitalia of the other. One of the most interesting causes of male reproductive abnormalities is an end organ insensitivity to androgens. The best characterized syndrome is **testicular feminization**, an X-linked recessive disorder caused by a defect in the testosterone receptor. In the classical form, patients are male pseudohermaphrodites with a female phenotype and an XY male genotype. They have abdominal testes that secrete testosterone but no other internal genitalia of either sex (see Chapter 39). They commonly have female external genitalia, but with a short vagina ending in a blind pouch. Breast development is typical of a female (as a result of peripheral aromatization of testosterone), but axillary and pubic hair, which are androgen-dependent, are scarce or absent. Testosterone levels are normal or elevated, estradiol levels are above the normal male range, and circulating gonadotropin levels are high. The inguinally located testes usually have to be removed because of an increased risk of cancer. After orchiectomy, patients are treated with estradiol to maintain a female phenotype.

## REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A major causal factor in some cases of hypogonadism is
   (A) Reduced secretion of gonadotropin-releasing hormone (GnRH)
   (B) Hypersecretion of pituitary LH and FSH as the result of increased GnRH
   (C) Excess secretion of testicular activin by Sertoli cells
   (D) Failure of the hypothalamus to respond to testosterone
   (E) Increased number of FSH receptors in the testis
2. The major function of follistatin is
   (A) Bind FSH and increase FSH secretion
   (B) Inhibit the production of seminal fluid
   (C) Reduce testosterone secretion by Leydig cells
   (D) Stimulate the production of spermatogonia
   (E) Bind activin and thus decrease FSH secretion
3. A major function of the epididymis is
   (A) Storage and transport of mature sperm
   (B) Initiating the development of spermatozoa
   (C) Secretion of estrogens
   (D) Production of inhibin
   (E) Secretion of fluids that contribute to semen
4. The production of mature spermatozoa from spermatogonia
   (A) Takes 32 days
   (B) Takes 70 days
   (C) Takes 150 days
   (D) Is unaffected by Kallmann's syndrome
   (E) Is independent of testicular temperature

*(continued)*

5. The first enzymatic reaction, which is the rate-limiting step, in the production of testosterone
   (A) Occurs in the mitochondria
   (B) Occurs in the ribosomes
   (C) Involves aromatization
   (D) Generates progesterone as the immediate derivative
   (E) Is stimulated by FSH
6. Testosterone is
   (A) Bound to high-density lipoprotein (HDL)
   (B) Bound to activin
   (C) Converted to dihydrotestosterone in the prostate
   (D) Converted to 17-hydroxyprogesterone in the liver
   (E) Metabolized by cholesterol side-chain cleavage enzyme
7. Sex hormone-binding globulin (SHBG)
   (A) Binds testosterone with a higher affinity than estradiol
   (B) Reduces the total amount of circulating testosterone
   (C) Decreases the half-life of testosterone
   (D) Stimulates the secretion of inhibin
   (E) Blocks the synthesis of androgen-binding protein
8. The production of estradiol by the testes requires
   (A) Sertoli cell follistatin
   (B) LH and Leydig cells
   (C) Activin but not LH
   (D) Leydig cell, Sertoli cells, LH, and FSH
   (E) Leydig cells and FSH
9. Eunuchs are tall because
   (A) Estrogens stimulate the growth of long bones
   (B) Excess LH delays epiphyseal closure of the long bones
   (C) Reduced androgen and estrogen delays epiphyseal closure in long bones
   (D) The lack of testes stimulates closure of the epiphyses
   (E) They secrete excess androgen

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