

Reproductive and Hormonal Functions of the Male (and Function of the Pineal Gland)

Male reproductive functions can be divided into three major subdivisions: (1) formation of sperm—spermatogenesis; (2) performance of the male sexual act; and (3) regulation of male reproductive functions by the various hormones. Associated with these reproductive functions are the effects of the male sex hormones on the accessory sexual organs, cellular metabolism, growth, and other functions of the body.

Physiological Anatomy of the Male Sexual Organs

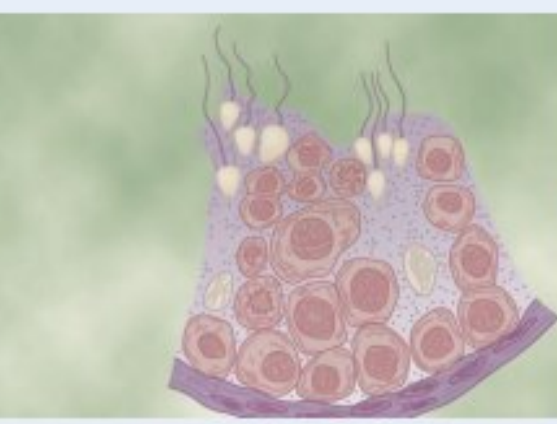
Figure 81-1A shows various portions of the male reproductive system, and **Figure 81-1B** gives a more detailed structure of the testis and epididymis. The testis is composed of up to 900 coiled *seminiferous tubules*, each averaging more than one-half meter long, in which the sperm are formed. The sperm then empty into the *epididymis*, which is another coiled tube about 6 meters long. The epididymis leads into the *vas deferens*, which enlarges into the *ampulla of the vas deferens* immediately before the vas enters the body of the *prostate gland*.

Two *seminal vesicles*, one located on each side of the prostate, empty into the prostatic end of the ampulla, and the contents from both the ampulla and the seminal vesicles pass into an *ejaculatory duct* leading through the body of the prostate gland and then emptying into the *internal urethra*. *Prostatic ducts* also empty from the prostate gland into the ejaculatory duct and from there into the prostatic urethra.

Finally, the *urethra* is the last connecting link from the testis to the exterior. The urethra is supplied with mucus derived from a large number of minute *urethral glands* located along its entire extent and even more so from bilateral *bulbourethral glands* (*Cowper glands*) located near the origin of the urethra.

SPERMATOGENESIS

During formation of the embryo, the *primordial germ cells* migrate into the testes and become immature germ cells called *spermatogonia*, which lie in two or three layers of the inner surfaces of the *seminiferous tubules* (a cross section of a tubule is shown in **Figure 81-2A**). At puberty the spermatogonia begin to undergo mitotic division and continually proliferate and differentiate through definite



stages of development to form sperm, as shown in **Figure 81-2B**.

STEPS OF SPERMATOGENESIS

Spermatogenesis occurs in the seminiferous tubules during active sexual life as the result of stimulation by anterior pituitary gonadotropic hormones. Spermatogenesis begins in the male at an average age of 13 years and continues throughout most of the remainder of life but decreases markedly in old age.

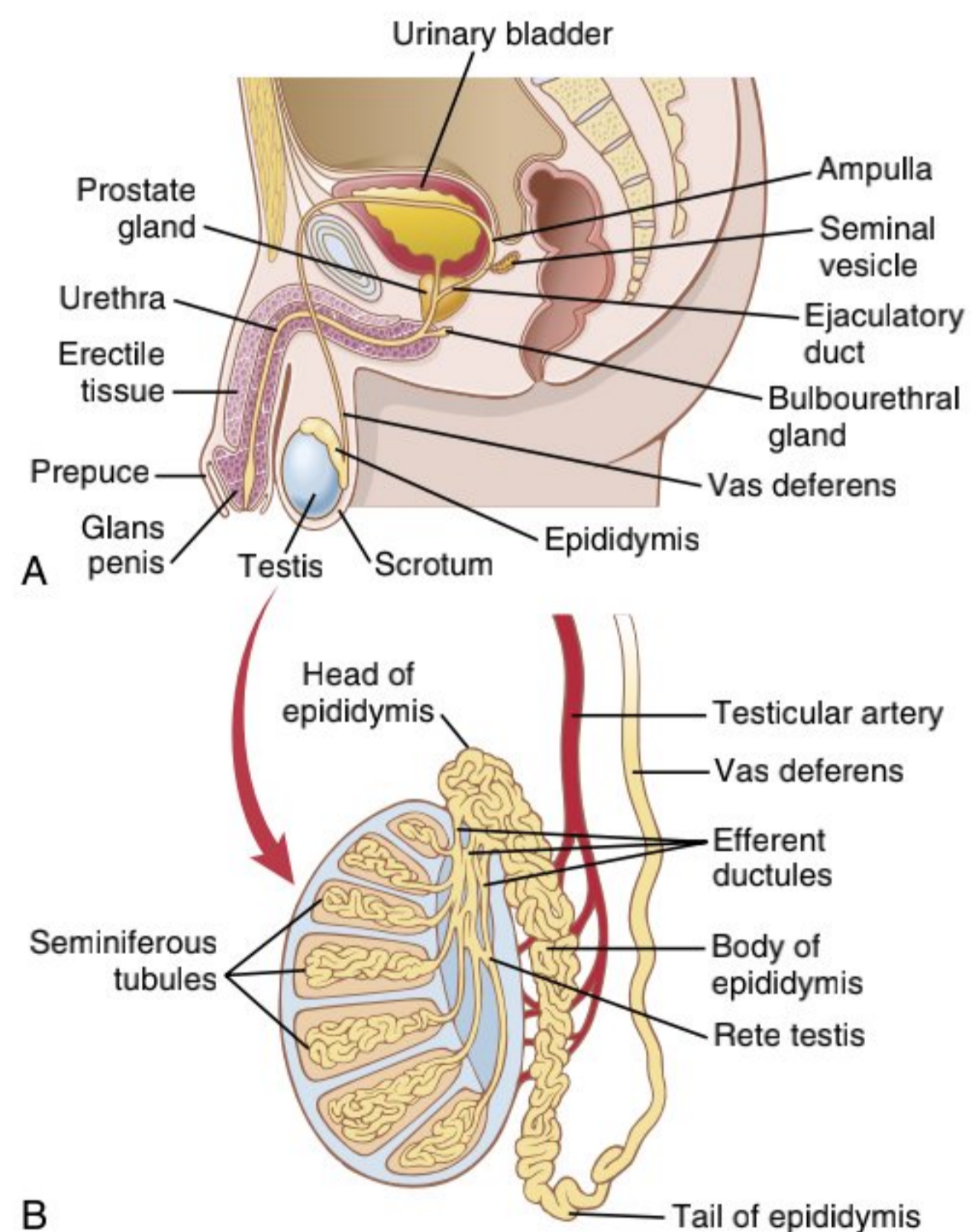


Figure 81-1 A, The male reproductive system. **B**, The internal structure of the testis and the relation of the testis to the epididymis. (**A**, Modified from Bloom V, Fawcett DW: *Textbook of Histology*, 10th ed. Philadelphia: WB Saunders, 1975. **B**, Modified from Guyton AC: *Anatomy and Physiology*. Philadelphia: Saunders College Publishing, 1985.)

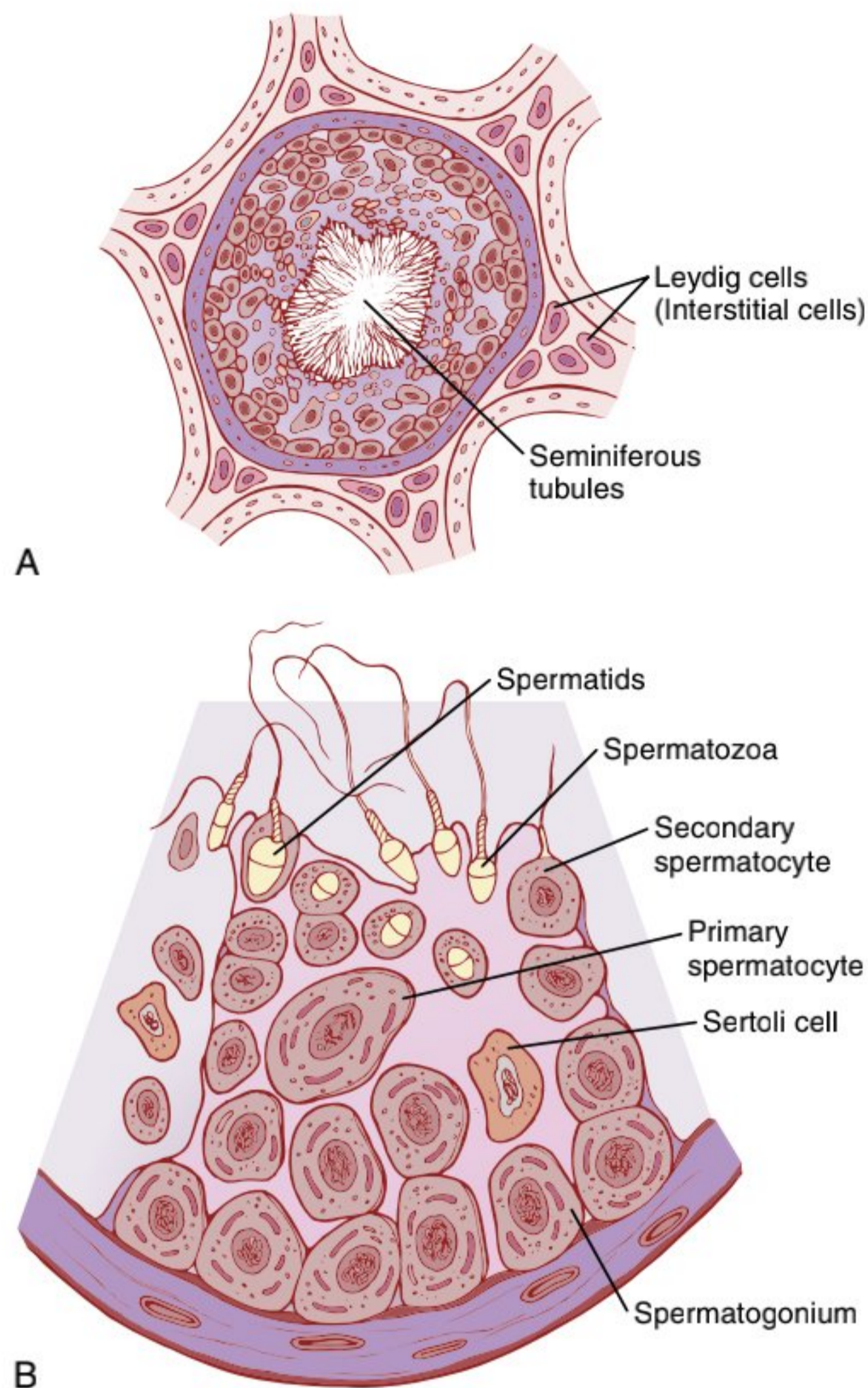


Figure 81-2 **A**, Cross section of a seminiferous tubule. **B**, Stages in the development of sperm from spermatogonia.

In the first stage of spermatogenesis, the spermatogonia migrate among *Sertoli cells* toward the central lumen of the seminiferous tubule. The Sertoli cells are large, with overflowing cytoplasmic envelopes that surround the developing spermatogonia all the way to the central lumen of the tubule.

Meiosis. Spermatogonia that cross the barrier into the Sertoli cell layer become progressively modified and enlarged to form large *primary spermatocytes* (Figure 81-3). Each of these primary spermatocytes, in turn, undergoes meiotic division to form two *secondary spermatocytes*. After another few days, these secondary spermatocytes also divide to form *spermatids* that are eventually modified to become *spermatozoa* (sperm).

During the change from the spermatocyte stage to the spermatid stage, the 46 chromosomes (23 pairs of chromosomes) of the spermatocyte are divided, and thus 23 chromosomes go to one spermatid and the other 23 go to the second spermatid. The chromosomal genes are also divided so that only one-half of the genetic characteristics of the eventual fetus are provided by the father, with the

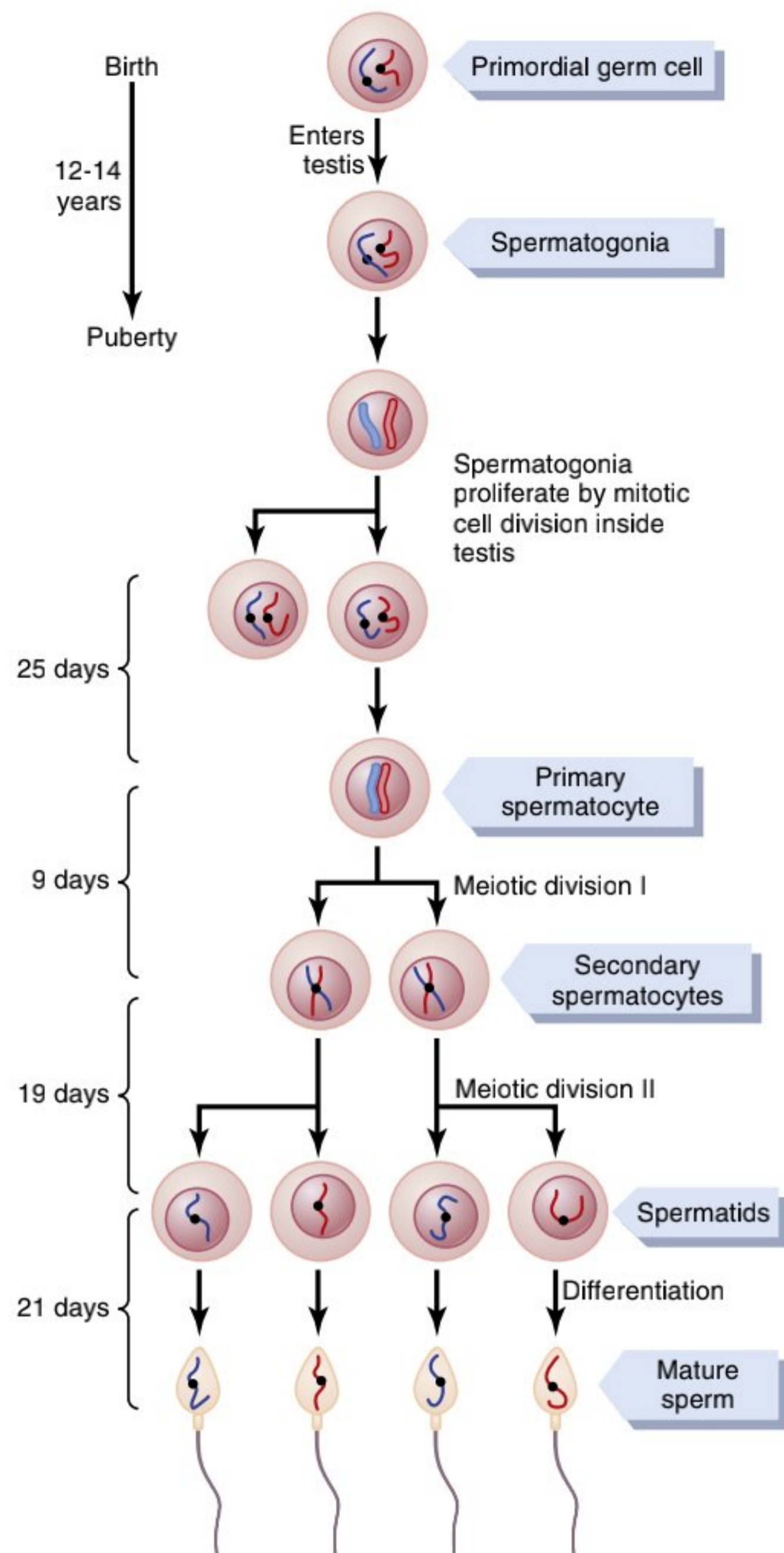


Figure 81-3 Cell divisions during spermatogenesis. During embryonic development, the primordial germ cells migrate to the testis, where they become spermatogonia. At puberty (usually 12 to 14 years after birth), the spermatogonia proliferate rapidly by mitosis. Some begin meiosis to become primary spermatocytes and continue through meiotic division I to become secondary spermatocytes. After completion of meiotic division II, the secondary spermatocytes produce spermatids, which differentiate to form spermatozoa.

other half being derived from the oocyte provided by the mother.

The entire period of spermatogenesis, from spermatogonia to spermatozoa, takes about 74 days.

Sex Chromosomes. In each spermatogonium, one of the 23 pairs of chromosomes carries the genetic information that determines the sex of each eventual offspring. This pair is composed of one X chromosome, which is

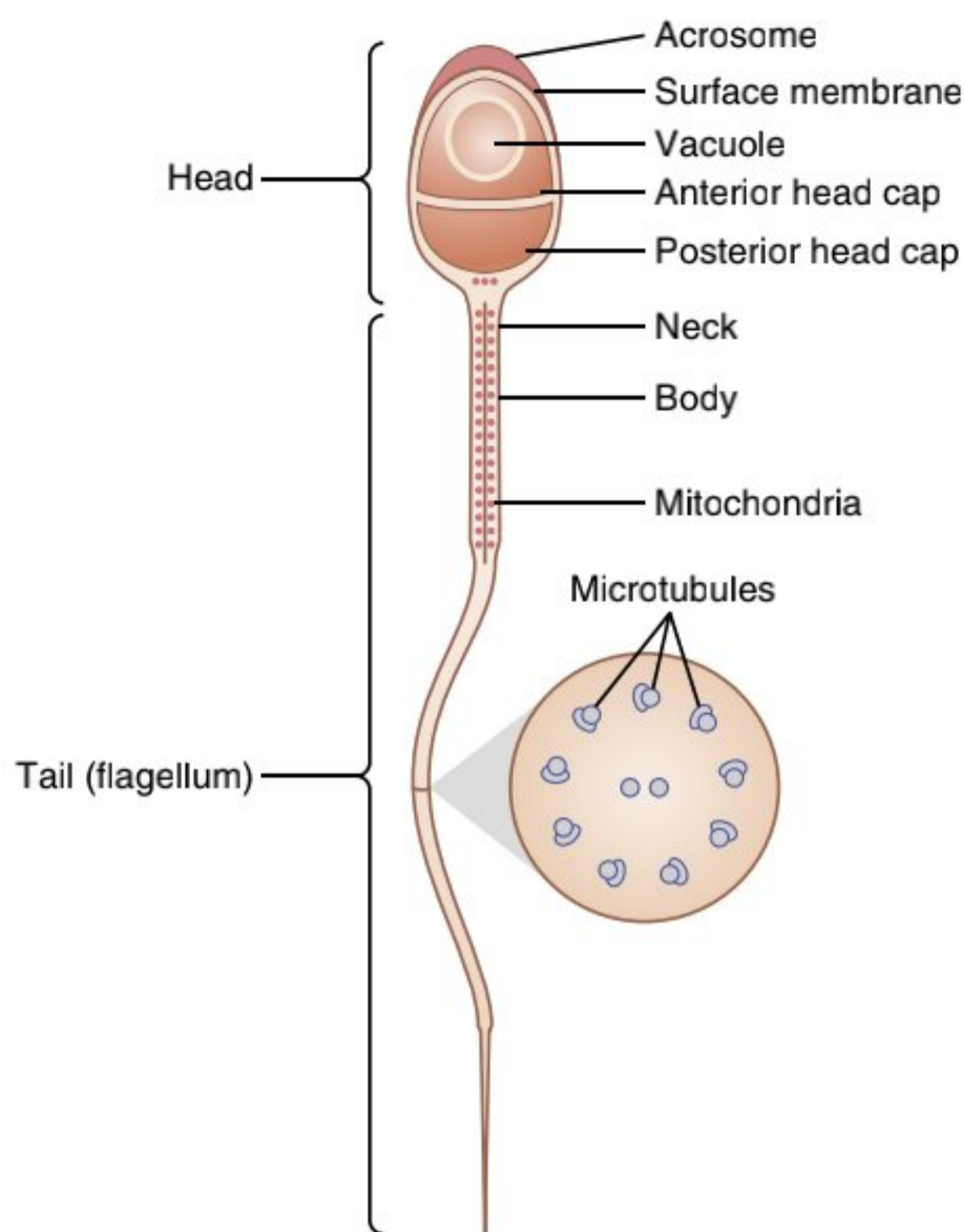


Figure 81-4 Structure of the human spermatozoon.

called the *female chromosome*, and one Y chromosome, the *male chromosome*. During meiotic division, the male Y chromosome goes to one spermatid that then becomes a *male sperm*, and the female X chromosome goes to another spermatid that becomes a *female sperm*. The sex of the eventual offspring is determined by which of these two types of sperm fertilizes the ovum. This process is discussed further in Chapter 83.

Formation of Sperm. When the spermatids are first formed, they still have the usual characteristics of epithelioid cells, but soon they begin to differentiate and elongate into spermatozoa. As shown in Figure 81-4, each spermatozoon is composed of a *head* and a *tail*. The head comprises the condensed nucleus of the cell, with only a thin cytoplasmic and cell membrane layer around its surface. On the outside of the anterior two-thirds of the head is a thick cap called the *acrosome* that is formed mainly from the Golgi apparatus. The acrosome contains several enzymes similar to those found in lysosomes of the typical cell, including *hyaluronidase* (which can digest proteoglycan filaments of tissues) and powerful *proteolytic enzymes* (which can digest proteins). These enzymes play important roles in allowing the sperm to enter the ovum and fertilize it.

The tail of the sperm, called the *flagellum*, has three major components: (1) a central skeleton constructed of 11 microtubules, collectively called the *axoneme*; the structure of the axoneme is similar to that of cilia found on the surfaces of other types of cells described in Chapter 2; (2) a thin cell membrane covering the axoneme;

and (3) a collection of mitochondria surrounding the axoneme in the proximal portion of the tail, called the *body of the tail*.

Back-and-forth movement of the tail (flagellar movement) provides motility for the sperm. This movement results from a rhythmic longitudinal sliding motion between the anterior and posterior tubules that make up the axoneme. The energy for this process is supplied in the form of adenosine triphosphate, which is synthesized by the mitochondria in the body of the tail.

Normal sperm move in a fluid medium at a velocity of 1 to 4 mm/min, which allows them to move through the female genital tract in quest of the ovum.

Hormonal Factors That Stimulate Spermatogenesis

The role of hormones in reproduction is discussed later in detail; for now, note that several hormones play essential roles in spermatogenesis. Some of these roles are as follows:

1. *Testosterone*, secreted by the *Leydig cells* located in the interstitium of the testis (see Figure 81-2), is essential for growth and division of the testicular germinal cells, which is the first stage in forming sperm.
2. *Luteinizing hormone*, secreted by the anterior pituitary gland, stimulates the Leydig cells to secrete testosterone.
3. *Follicle-stimulating hormone*, also secreted by the anterior pituitary gland, stimulates the *Sertoli cells*; without this stimulation, conversion of the spermatids to sperm (the process of spermiogenesis) will not occur.
4. *Estrogens*, formed from testosterone by the Sertoli cells when they are stimulated by follicle-stimulating hormone, are probably also essential for spermiogenesis.
5. *Growth hormone* (as well as most of the other body hormones) is necessary for controlling background metabolic functions of the testes. Growth hormone specifically promotes early division of the spermatogonia; in its absence, as in pituitary dwarfs, spermatogenesis is severely deficient or absent, thus causing infertility.

Maturation of Sperm in the Epididymis

After formation in the seminiferous tubules, the sperm require several days to pass through the 6-meter-long tubule of the *epididymis*. Sperm removed from the seminiferous tubules and from the early portions of the epididymis are nonmotile and cannot fertilize an ovum. However, after the sperm have been in the epididymis for 18 to 24 hours, they develop the *capability of motility*, even though several inhibitory proteins in the epididymal fluid still prevent final motility until after ejaculation.

Storage of Sperm in the Testes. The two testes of the human adult form up to 120 million sperm each day. Most

of these sperm are stored in the epididymis, although a small quantity is stored in the vas deferens. They can remain stored, while maintaining their fertility, for at least a month. During this time, they are kept in a deeply suppressed, inactive state by multiple inhibitory substances in the secretions of the ducts. Conversely, with a high level of sexual activity and ejaculations, they may be stored no longer than a few days.

After ejaculation, the sperm become motile and capable of fertilizing the ovum, a process called *maturation*. The Sertoli cells and the epithelium of the epididymis secrete a special nutrient fluid that is ejaculated along with the sperm. This fluid contains hormones (including both testosterone and estrogens), enzymes, and special nutrients that are essential for sperm maturation.

Physiology of the Mature Sperm. The normal motile, fertile sperm are capable of flagellated movement through the fluid medium at velocities of 1 to 4 mm/min. The activity of sperm is greatly enhanced in a neutral and slightly alkaline medium, as exists in the ejaculated semen, but it is greatly depressed in a mildly acidic medium. A strong acidic medium can cause the rapid death of sperm.

The activity of sperm increases markedly with increasing temperature, but so does the rate of metabolism, causing the life of the sperm to be considerably shortened. Although sperm can live for many weeks in the suppressed state in the genital ducts of the testes, the life expectancy of ejaculated sperm in the female genital tract is only 1 to 2 days.

FUNCTION OF THE SEMINAL VESICLES

Each seminal vesicle is a tortuous, loculated tube lined with a secretory epithelium that secretes a mucoid material containing an abundance of *fructose*, *citric acid*, and other nutrient substances, as well as large quantities of *prostaglandins* and *fibrinogen*. During the process of emission and ejaculation, each seminal vesicle empties its contents into the ejaculatory duct shortly after the vas deferens empties the sperm. This action adds greatly to the bulk of the ejaculated semen, and the fructose and other substances in the seminal fluid are of considerable nutrient value for the ejaculated sperm until one of the sperm fertilizes the ovum.

Prostaglandins are believed to aid fertilization in two ways: (1) by reacting with the female cervical mucus to make it more receptive to sperm movement and (2) by possibly causing backward, reverse peristaltic contractions in the uterus and fallopian tubes to move the ejaculated sperm toward the ovaries (a few sperm reach the upper ends of the fallopian tubes within 5 minutes).

FUNCTION OF THE PROSTATE GLAND

The prostate gland secretes a thin, milky fluid that contains calcium, citrate ion, phosphate ion, a clotting

enzyme, and a profibrinolysin. During emission, the capsule of the prostate gland contracts simultaneously with the contractions of the vas deferens so that the thin, milky fluid of the prostate gland adds further to the bulk of the semen. A slightly alkaline characteristic of the prostatic fluid may be quite important for successful fertilization of the ovum because the fluid of the vas deferens is relatively acidic owing to the presence of citric acid and metabolic end products of the sperm and, consequently, helps inhibit sperm fertility. Also, the vaginal secretions of the female are acidic (with a pH of 3.5–4.0). Sperm do not become optimally motile until the pH of the surrounding fluids rises to about 6.0 to 6.5. Consequently, it is probable that the slightly alkaline prostatic fluid helps neutralize the acidity of the other seminal fluids during ejaculation and thus enhances the motility and fertility of the sperm.

SEMEN

Semen, which is ejaculated during the male sexual act, is composed of the fluid and sperm from the vas deferens ($\approx 10\%$ of the total), fluid from the seminal vesicles (almost 60%), fluid from the prostate gland ($\approx 30\%$), and small amounts from the mucous glands, especially the bulbourethral glands. Thus, the bulk of the semen is seminal vesicle fluid, which is the last to be ejaculated and serves to wash the sperm through the ejaculatory duct and urethra.

The average pH of the combined semen is about 7.5, with the alkaline prostatic fluid having more than neutralized the mild acidity of the other portions of the semen. The prostatic fluid gives the semen a milky appearance, and fluid from the seminal vesicles and mucous glands gives the semen a mucoid consistency. Also, a clotting enzyme from the prostatic fluid causes the fibrinogen of the seminal vesicle fluid to form a weak fibrin coagulum that holds the semen in the deeper regions of the vagina where the uterine cervix lies. The coagulum then dissolves during the next 15 to 30 minutes because of lysis by fibrinolysin formed from the prostatic profibrinolysin. In the early minutes after ejaculation, the sperm remain relatively immobile, possibly because of the viscosity of the coagulum. As the coagulum dissolves, the sperm simultaneously become highly motile.

Although sperm can live for many weeks in the male genital ducts, once they are ejaculated in the semen, their maximal life span is only 24 to 48 hours at body temperature. At lowered temperatures, however, semen can be stored for several weeks, and when frozen at temperatures below -100°C , sperm have been preserved for years.

“Capacitation” of Spermatozoa Is Required for Fertilization of the Ovum

Although spermatozoa are said to be “mature” when they leave the epididymis, their activity is held in

check by multiple inhibitory factors secreted by the genital duct epithelia. Therefore, when they are first expelled in the semen, they are unable to fertilize the ovum. However, on coming in contact with the fluids of the female genital tract, multiple changes occur that activate the sperm for the final processes of fertilization. These collective changes are called *capacitation of the spermatozoa*, which normally requires from 1 to 10 hours. The following changes are believed to occur:

1. The uterine and fallopian tube fluids wash away the various inhibitory factors that suppress sperm activity in the male genital ducts.
2. While the spermatozoa remain in the fluid of the male genital ducts, they are continually exposed to many floating vesicles from the seminiferous tubules containing large amounts of cholesterol. This cholesterol is continually added to the cellular membrane covering the sperm acrosome, toughening this membrane and preventing release of its enzymes. After ejaculation, the sperm deposited in the vagina swim away from the cholesterol vesicles upward into the uterine cavity, and they gradually lose much of their other excess cholesterol during the next few hours. In so doing, the membrane at the head of the sperm (the acrosome) becomes much weaker.
3. The membrane of the sperm also becomes much more permeable to calcium ions, so calcium now enters the sperm in abundance and changes the activity of the flagellum, giving it a powerful whiplash motion in contrast to its previously weak undulating motion. In addition, the calcium ions cause changes in the cellular membrane that cover the leading edge of the acrosome, making it possible for the acrosome to release its enzymes rapidly and easily as the sperm penetrates the granulosa cell mass surrounding the ovum, and even more so as it attempts to penetrate the zona pellucida of the ovum.

Thus, multiple changes occur during the process of capacitation. Without these changes, the sperm cannot make its way to the interior of the ovum to cause fertilization.

Acrosome Enzymes, the "Acrosome Reaction," and Penetration of the Ovum

Stored in the acrosome of the sperm are large quantities of *hyaluronidase* and *proteolytic enzymes*. Hyaluronidase depolymerizes the hyaluronic acid polymers in the intercellular cement that holds the ovarian granulosa cells together. The proteolytic enzymes digest proteins in the structural elements of tissue cells that still adhere to the ovum.

When the ovum is expelled from the ovarian follicle into the fallopian tube, it still carries with it multiple layers of granulosa cells. Before a sperm can fertilize

the ovum, it must dissolve these granulosa cell layers, and then it must penetrate through the *zona pellucida*, the thick covering of the ovum. To achieve this penetration, the stored enzymes in the acrosome begin to be released. The hyaluronidase among these enzymes is especially important in opening pathways between the granulosa cells so that the sperm can reach the ovum.

When the sperm reaches the zona pellucida of the ovum, the anterior membrane of the sperm binds specifically with receptor proteins in the zona pellucida. Next, the entire acrosome rapidly dissolves, and all the acrosomal enzymes are released. Within minutes, these enzymes open a penetrating pathway for passage of the sperm head through the zona pellucida to the inside of the ovum. Within another 30 minutes, the cell membranes of the sperm head and of the oocyte fuse with each other to form a single cell. At the same time, the genetic material of the sperm and the oocyte combine to form a completely new cell genome, containing equal numbers of chromosomes and genes from mother and father. This is the process of *fertilization*; the embryo then begins to develop, as discussed in [Chapter 83](#).

Why Does Only One Sperm Enter the Oocyte? With as many sperm as there are, why does only one enter the oocyte? The reason is not entirely known, but within a few minutes after the first sperm penetrates the zona pellucida of the ovum, calcium ions diffuse inward through the oocyte membrane and cause multiple cortical granules to be released by exocytosis from the oocyte into the perivitelline space. These granules contain substances that permeate all portions of the zona pellucida and prevent binding of additional sperm, and they even cause any sperm that have already begun to bind to fall off. Thus, almost never does more than one sperm enter the oocyte during fertilization.

Abnormal Spermatogenesis and Male Fertility

The seminiferous tubular epithelium can be destroyed by several diseases. For example, bilateral *orchitis* (inflammation) of the testes resulting from *mumps* causes sterility in some affected males. Also, some male infants are born with degenerate tubular epithelia as a result of strictures in the genital ducts or other abnormalities. Finally, another cause of sterility, usually temporary, is *excessive temperature of the testes*.

Effect of Temperature on Spermatogenesis. Increasing the temperature of the testes can prevent spermatogenesis by causing degeneration of most cells of the seminiferous tubules besides the spermatogonia. It has often been stated that the reason the testes are located in the dangling scrotum is to maintain the temperature of these glands below the internal temperature of the body, although usually only about 2°C below the internal temperature. On cold days, scrotal reflexes cause the musculature of the scrotum to contract, pulling the testes close to the body to maintain this 2°C differential. Thus, the scrotum acts as a cooling

mechanism for the testes (but a *controlled* cooling), without which spermatogenesis might be deficient during hot weather.

Cryptorchidism. Cryptorchidism means failure of a testis to descend from the abdomen into the scrotum at or near the time of birth of a fetus. During development of the male fetus, the testes are derived from the genital ridges in the abdomen. However, at about 3 weeks to 1 month before birth of the baby, the testes normally descend through the inguinal canals into the scrotum. Occasionally this descent does not occur or occurs incompletely, and as a result one or both testes remain in the abdomen, in the inguinal canal, or elsewhere along the route of descent.

A testis that remains in the abdominal cavity throughout life is incapable of forming sperm. The tubular epithelium becomes degenerate, leaving only the interstitial structures of the testis. It has been claimed that even the few degrees higher temperature in the abdomen than in the scrotum is sufficient to cause this degeneration of the tubular epithelium and, consequently, to cause sterility, although this effect is not certain. Nevertheless, for this reason, operations to relocate the cryptorchid testes from the abdominal cavity into the scrotum before the beginning of adult sexual life can be performed on boys who have undescended testes.

Testosterone secretion by the fetal testes is the normal stimulus that causes the testes to descend into the scrotum from the abdomen. Therefore, many, if not most, cases of cryptorchidism are caused by abnormally formed testes that are unable to secrete enough testosterone. The surgical operation for cryptorchidism in these patients is unlikely to be successful.

Effect of Sperm Count on Fertility. The usual quantity of semen ejaculated during each coitus averages about 3.5 milliliters, and each milliliter of semen contains an average of about 120 million sperm, although even in “normal” males this quantity can vary from 35 million to 200 million. This means an average total of about 400 million sperm are usually present in the several milliliters of each ejaculate. When the number of sperm in each milliliter falls below about 20 million, the person is likely to be infertile. Thus, even though only a single sperm is necessary to fertilize the ovum, for reasons that are not understood, the ejaculate usually must contain a tremendous number of sperm for only one sperm to fertilize the ovum.

Effect of Sperm Morphology and Motility on Fertility. Occasionally, a man has a normal number of sperm but is still infertile. When this situation occurs, sometimes as many as one-half of the sperm are found to be abnormal physically, having two heads, abnormally shaped heads, or abnormal tails, as shown in **Figure 81-5**. At other times, the sperm appear to be structurally normal, but for reasons not understood, they are either entirely nonmotile or relatively nonmotile. Whenever most of the sperm are morphologically abnormal or are nonmotile, the person is likely to be infertile, even though the remainder of the sperm appear to be normal.



Figure 81-5 Abnormal infertile sperm, compared with a normal sperm on the *right*.

MALE SEXUAL ACT

NEURONAL STIMULUS FOR PERFORMANCE OF THE MALE SEXUAL ACT

The most important source of sensory nerve signals for initiating the male sexual act is the *glans penis*. The glans contains an especially sensitive sensory end-organ system that transmits into the central nervous system that special modality of sensation called *sexual sensation*. The slippery massaging action of intercourse on the glans stimulates the sensory end organs, and the sexual signals in turn pass through the pudendal nerve, then through the sacral plexus into the sacral portion of the spinal cord, and finally up the cord to the brain.

Impulses may also enter the spinal cord from areas adjacent to the penis to aid in stimulating the sexual act. For example, stimulation of the anal epithelium, the scrotum, and perineal structures in general can send signals into the cord that add to the sexual sensation. Sexual sensations can even originate in internal structures, such as in areas of the urethra, bladder, prostate, seminal vesicles, testes, and vas deferens. Indeed, one of the causes of “sexual drive” is filling of the sexual organs with secretions. Mild infection and inflammation of these sexual organs may sometimes stimulate sexual desire, and some “aphrodisiac” drugs, such as cantharidin, irritate the bladder and urethral mucosa, inducing inflammation and vascular congestion.

Psychic Element of Male Sexual Stimulation. Appropriate psychic stimuli can greatly enhance the ability of a person to perform the sexual act. Simply thinking sexual thoughts or even dreaming that the act of intercourse is being performed can initiate the male act, culminating in ejaculation. Indeed, *nocturnal emissions* during dreams, often called “wet dreams,” occur in many males during some stages of sexual life, especially during the teens.

Integration of the Male Sexual Act in the Spinal Cord. Although psychic factors usually play an important part in the male sexual act and can initiate or inhibit it, brain function is probably not necessary for its performance

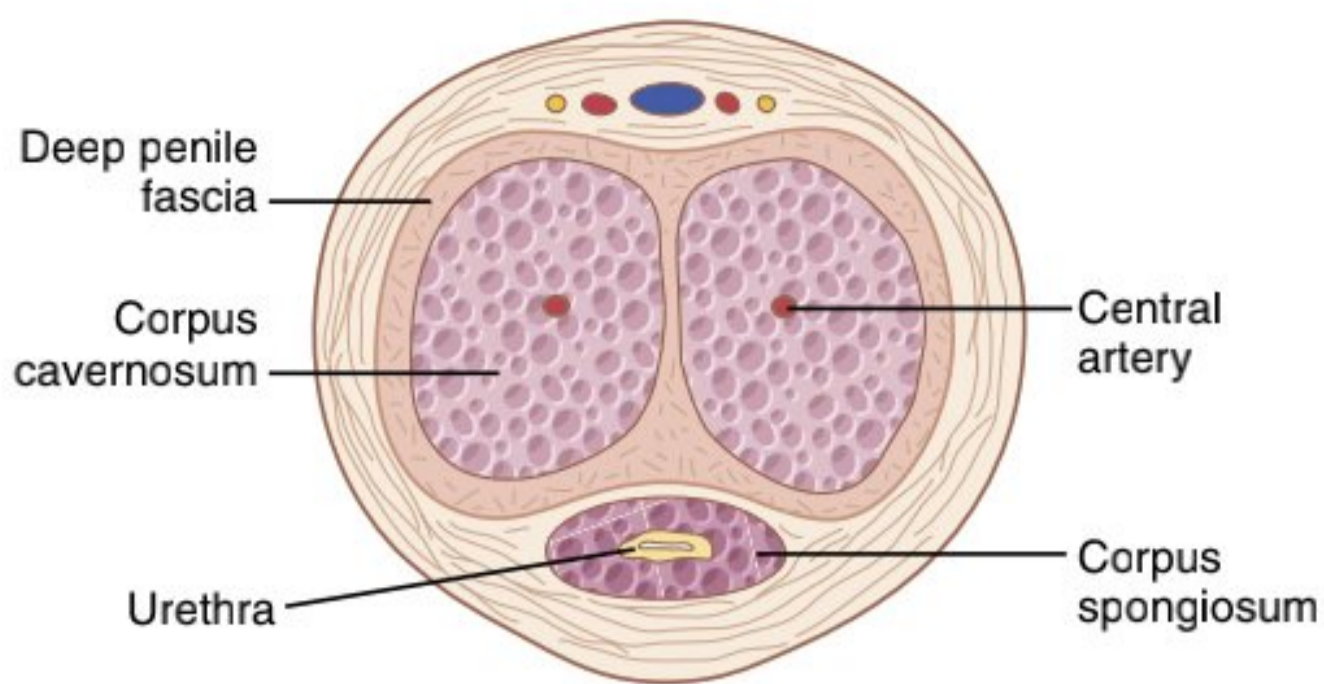


Figure 81-6 Erectile tissue of the penis.

because appropriate genital stimulation can cause ejaculation in some animals and occasionally in humans after their spinal cords have been cut above the lumbar region. The male sexual act results from inherent reflex mechanisms integrated in the sacral and lumbar spinal cord, and these mechanisms can be initiated by either psychic stimulation from the brain or actual sexual stimulation from the sex organs, but usually it is a combination of both.

STAGES OF THE MALE SEXUAL ACT

Penile Erection—Role of the Parasympathetic Nerves. Penile erection is the first effect of male sexual stimulation, and the degree of erection is proportional to the degree of stimulation, whether psychic or physical. Erection is caused by parasympathetic impulses that pass from the sacral portion of the spinal cord through the pelvic nerves to the penis. These parasympathetic nerve fibers, in contrast to most other parasympathetic fibers, are believed to release *nitric oxide* and/or *vasoactive intestinal peptide* in addition to acetylcholine. Nitric oxide activates the enzyme *guanylyl cyclase*, causing increased formation of *cyclic guanosine monophosphate* (GMP). The cyclic GMP especially relaxes the arteries of the penis and the trabecular meshwork of smooth muscle fibers in the *erectile tissue* of the *corpora cavernosa* and *corpus spongiosum* in the shaft of the penis, shown in **Figure 81-6**. As the vascular smooth muscles relax, blood flow into the penis increases, causing release of nitric oxide from the vascular endothelial cells and further vasodilation.

The erectile tissue of the penis consists of large cavernous sinusoids that are normally relatively empty of blood but become dilated tremendously when arterial blood flows rapidly into them under pressure while the venous outflow is partially occluded. Also, the erectile bodies, especially the two *corpora cavernosa*, are surrounded by strong fibrous coats; therefore, high pressure within the sinusoids causes ballooning of the erectile tissue to such an extent that the penis becomes hard and elongated, which is the phenomenon of *erection*.

Lubrication Is a Parasympathetic Function. During sexual stimulation, the parasympathetic impulses, in addition to promoting erection, cause the urethral glands and the bulbourethral glands to secrete mucus. This mucus flows through the urethra during intercourse to aid in lubrication during coitus. However, most of the lubrication of coitus is provided by the female sexual organs rather than by the male organs. Without satisfactory lubrication, the male sexual act is seldom successful because unlubricated intercourse causes grating, painful sensations that inhibit rather than excite sexual sensations.

Emission and Ejaculation Are Functions of the Sympathetic Nerves. Emission and ejaculation are the culmination of the male sexual act. When the sexual stimulus becomes extremely intense, the reflex centers of the spinal cord begin to emit *sympathetic impulses* that leave the cord at T12 to L2 and pass to the genital organs through the hypogastric and pelvic sympathetic nerve plexuses to initiate *emission*, the forerunner of ejaculation.

Emission begins with contraction of the vas deferens and the ampulla to cause expulsion of sperm into the internal urethra. Then, contractions of the muscular coat of the prostate gland followed by contraction of the seminal vesicles expel prostatic and seminal fluid also into the urethra, forcing the sperm forward. All these fluids mix in the internal urethra with mucus already secreted by the bulbourethral glands to form the semen. The process to this point is *emission*.

The filling of the internal urethra with semen elicits sensory signals that are transmitted through the pudendal nerves to the sacral regions of the cord, giving the feeling of sudden fullness in the internal genital organs. Also, these sensory signals further excite rhythmic contraction of the internal genital organs and cause contraction of the ischiocavernosus and bulbocavernosus muscles that compress the bases of the penile erectile tissue. These effects together cause rhythmic wavelike increases in pressure in the erectile tissue of the penis and the genital ducts and urethra, which “ejaculate” the semen from the urethra to the exterior. This final process is called *ejaculation*. At the same time, rhythmic contractions of the pelvic muscles and even of some of the muscles of the body trunk cause thrusting movements of the pelvis and penis, which also help propel the semen into the deepest recesses of the vagina and perhaps even slightly into the cervix of the uterus.

This entire period of emission and ejaculation is called the *male orgasm*. At its termination, the male sexual excitement disappears almost entirely within 1 to 2 minutes and erection ceases, a process called *resolution*.

TESTOSTERONE AND OTHER MALE SEX HORMONES

SECRETION, METABOLISM, AND CHEMISTRY OF THE MALE SEX HORMONES

Secretion of Testosterone by the Interstitial Cells of Leydig in the Testes. The testes secrete several male sex hormones, which are collectively called *androgens*, including *testosterone*, *dihydrotestosterone*, and *androstenedione*. Testosterone is so much more abundant than the others that one can consider it to be the primary testicular hormone, although much of the testosterone is eventually converted into the more active hormone dihydrotestosterone in target tissues.

Testosterone is formed by the *interstitial cells of Leydig*, which lie in the interstices between the seminiferous tubules and constitute about 20% of the mass of the adult testes, as shown in **Figure 81-7**. Leydig cells are almost nonexistent in the testes during childhood, when the testes secrete almost no testosterone, but they *are* numerous in the newborn male infant for the first few months of life and in the adult male after puberty; at both these times the testes secrete large quantities of testosterone. Furthermore, when tumors develop from the interstitial cells of Leydig, great quantities of testosterone are secreted. When the germinal epithelium of the testes is destroyed by x-ray treatment or excessive heat, the Leydig cells, which are less easily destroyed, often continue to produce testosterone.

Secretion of Androgens Elsewhere in the Body. The term "androgen" means any steroid hormone that has masculinizing effects, including testosterone; it also includes male sex hormones produced elsewhere in the body besides the testes. For example, the adrenal glands secrete at least five androgens, although the total masculinizing activity of all these androgens is normally so slight (<5%

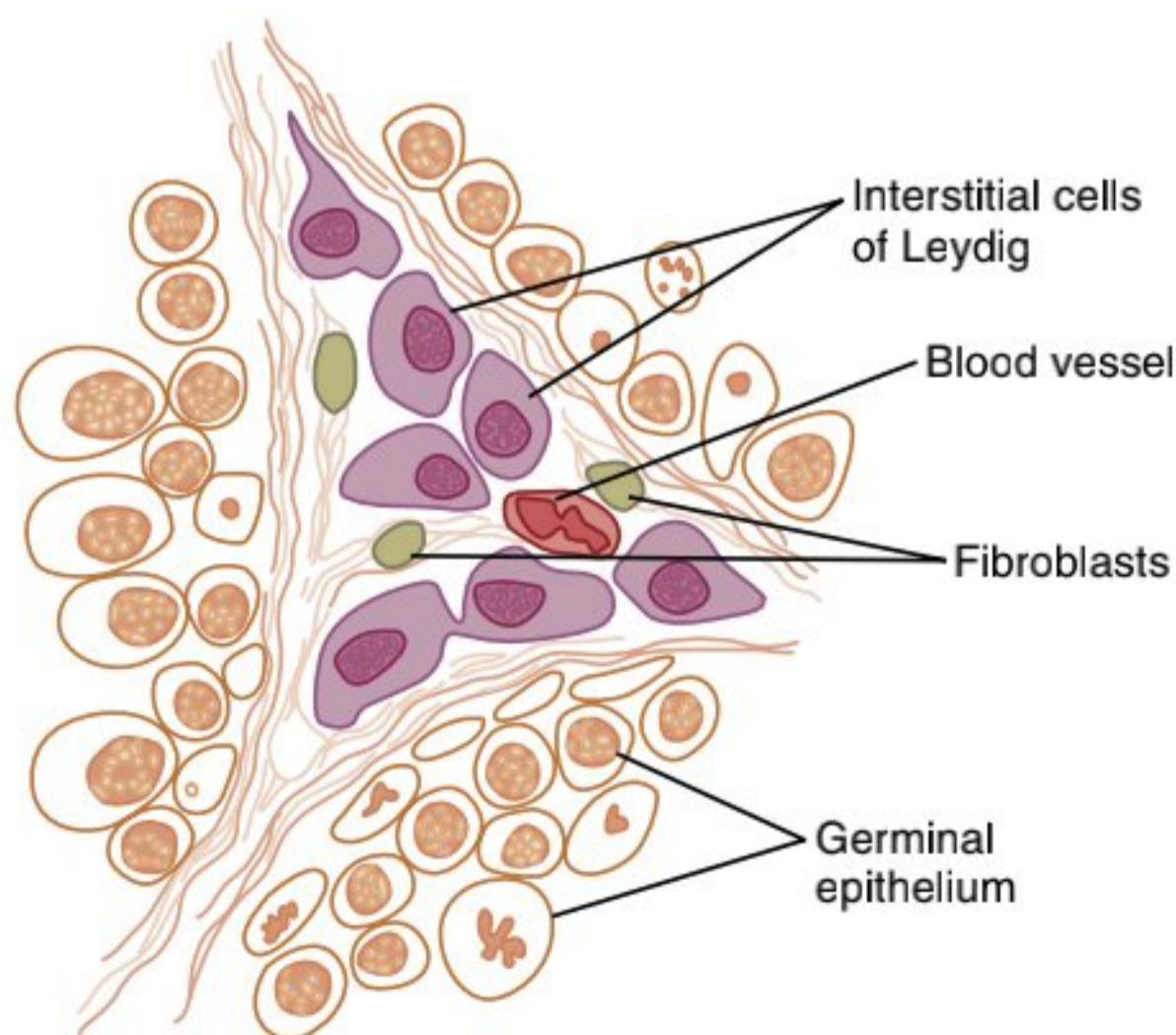


Figure 81-7 Interstitial cells of Leydig, the cells that secrete testosterone, located in the interstices between the seminiferous tubules.

of the total in the adult male) that even in women they do not cause significant masculine characteristics, except for causing growth of pubic and axillary hair. However, when a tumor of the adrenal androgen-producing cells occurs, the quantity of androgenic hormones may then become great enough to cause all the usual male secondary sexual characteristics to occur, even in females. These effects are described in connection with the adrenogenital syndrome in **Chapter 78**.

Rarely, embryonic crest cells in the ovary can develop into a tumor that produces excessive quantities of androgens in women; one such tumor is the *arrhenoblastoma*. The normal ovary also produces minute quantities of androgens, but they are not significant.

Androgens Are Steroids. All androgens are steroid compounds, as shown by the formulas in **Figure 81-8** for *testosterone* and *dihydrotestosterone*. Both in the testes and in the adrenals, the androgens can be synthesized either from cholesterol or directly from acetyl coenzyme A.

Metabolism of Testosterone. After secretion by the testes, about 97% of the testosterone becomes either loosely bound with plasma albumin or more tightly bound with a beta globulin called *sex hormone-binding globulin* and circulates in the blood in these states for 30 minutes to several hours. By that time, the testosterone is either transferred to the tissues or degraded into inactive products that are subsequently excreted.

Much of the testosterone that becomes fixed to the tissues is converted within the tissue cells to *dihydrotestosterone*, especially in certain target organs such as the prostate gland in the adult and the external genitalia of the male fetus. Some but not all actions of testosterone depend on this conversion. The intracellular functions are discussed later in this chapter.

Degradation and Excretion of Testosterone. The testosterone that does not become fixed to the tissues is rapidly converted, mainly by the liver, into *androsterone* and *dehydroepiandrosterone* and simultaneously conjugated as either glucuronides or sulfates (glucuronides, particularly). These substances are excreted either into the gut by way of the liver bile or into the urine through the kidneys.

Production of Estrogen in the Male. In addition to testosterone, small amounts of estrogens are formed in the male (about one fifth the amount in the nonpregnant female), and a reasonable quantity of estrogens can be recov-

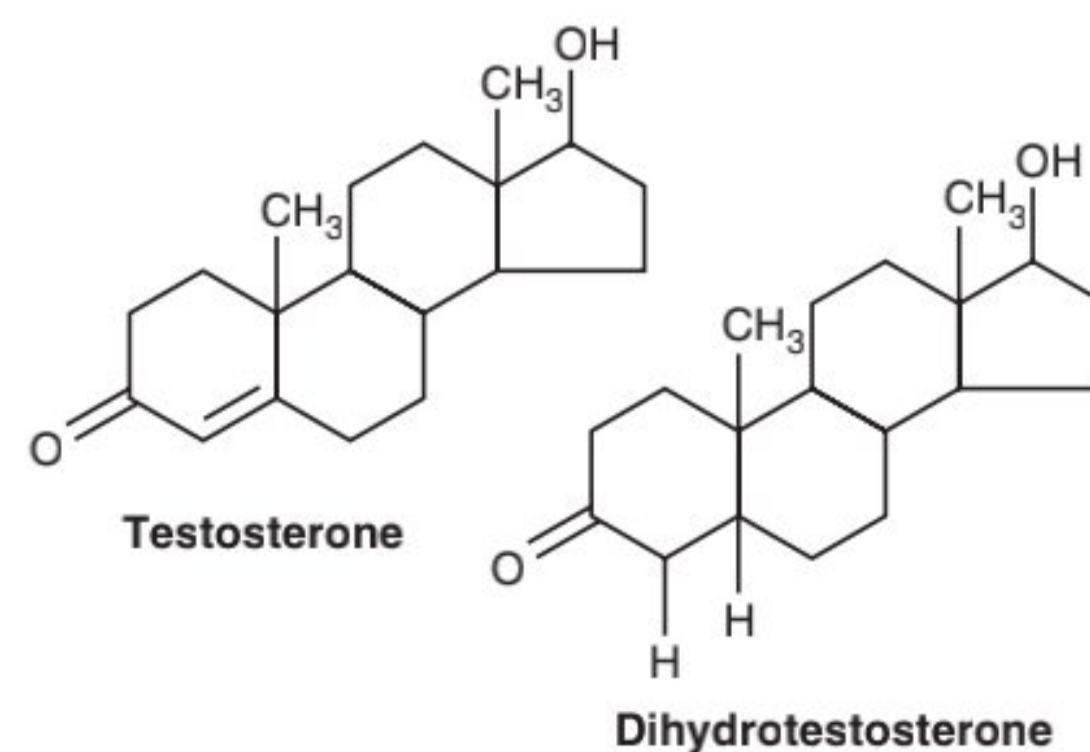


Figure 81-8 Testosterone and dihydrotestosterone.

ered from a man's urine. The exact source of estrogens in the male is unclear, but the following information is known:

1. The concentration of estrogens in the fluid of the seminiferous tubules is quite high and probably plays an important role in spermiogenesis. This estrogen is believed to be formed by the Sertoli cells by converting testosterone to estradiol.
2. Much larger amounts of estrogens are formed from testosterone and androstenediol in other tissues of the body, especially the liver, probably accounting for as much as 80% of the total male estrogen production.

FUNCTIONS OF TESTOSTERONE

In general, testosterone is responsible for the distinguishing characteristics of the masculine body. Even during fetal life, the testes are stimulated by chorionic gonadotropin from the placenta to produce moderate quantities of testosterone throughout the entire period of fetal development and for 10 or more weeks after birth; thereafter, essentially no testosterone is produced during childhood until about the ages of 10 to 13 years. Testosterone production then increases rapidly under the stimulus of anterior pituitary gonadotropic hormones at the onset of puberty and lasts throughout most of the remainder of life, as shown in **Figure 81-9**, dwindling somewhat beyond age 50 to 60 years. Some studies, however, suggest that plasma testosterone levels may remain in the normal range in most healthy males as they age; only about 10% to 20% of men over 60 years of age and 50% of men over 80 years of age have "low" testosterone levels below 3 ng/ml (usually expressed clinically as <300 ng/dl or <10.4 nmol/L). In recent years, it has become clear that there is a clear association between late onset reductions in testosterone and metabolic disorders such as obesity and type 2 diabetes mellitus.

Functions of Testosterone During Fetal Development

Testosterone begins to be elaborated by the male fetal testes at about the seventh week of embryonic life. Indeed, one of the major functional differences between the female and the male sex chromosome is that the male chromosome has the *sex-determining region Y (SRY) gene* that encodes a protein called the *testis determining factor* (also called the *SRY protein*). The SRY protein initiates a cascade of gene activations that cause the genital ridge cells to differentiate into cells that eventually become the testes and secrete testosterone, whereas the female chromosome causes this ridge to differentiate into cells that secrete estrogens.

Injection of large quantities of male sex hormone into pregnant animals causes development of male sexual organs, even though the fetus is female. Also, early removal of the testes in the male fetus causes development of female sexual organs.

Thus, testosterone secreted by the fetal testes is responsible for development of the male body characteristics, including the formation of a penis and a scrotum rather than formation of a clitoris and a vagina. It also causes formation of the prostate gland, seminal vesicles, and male genital ducts, while at the same time suppressing formation of female genital organs.

Effect of Testosterone to Cause Descent of the Testes. The testes usually descend into the scrotum during the last 2 to 3 months of gestation when the testes begin secreting reasonable quantities of testosterone. If a male child is born with undescended but otherwise normal testes, administration of testosterone usually causes the tes-

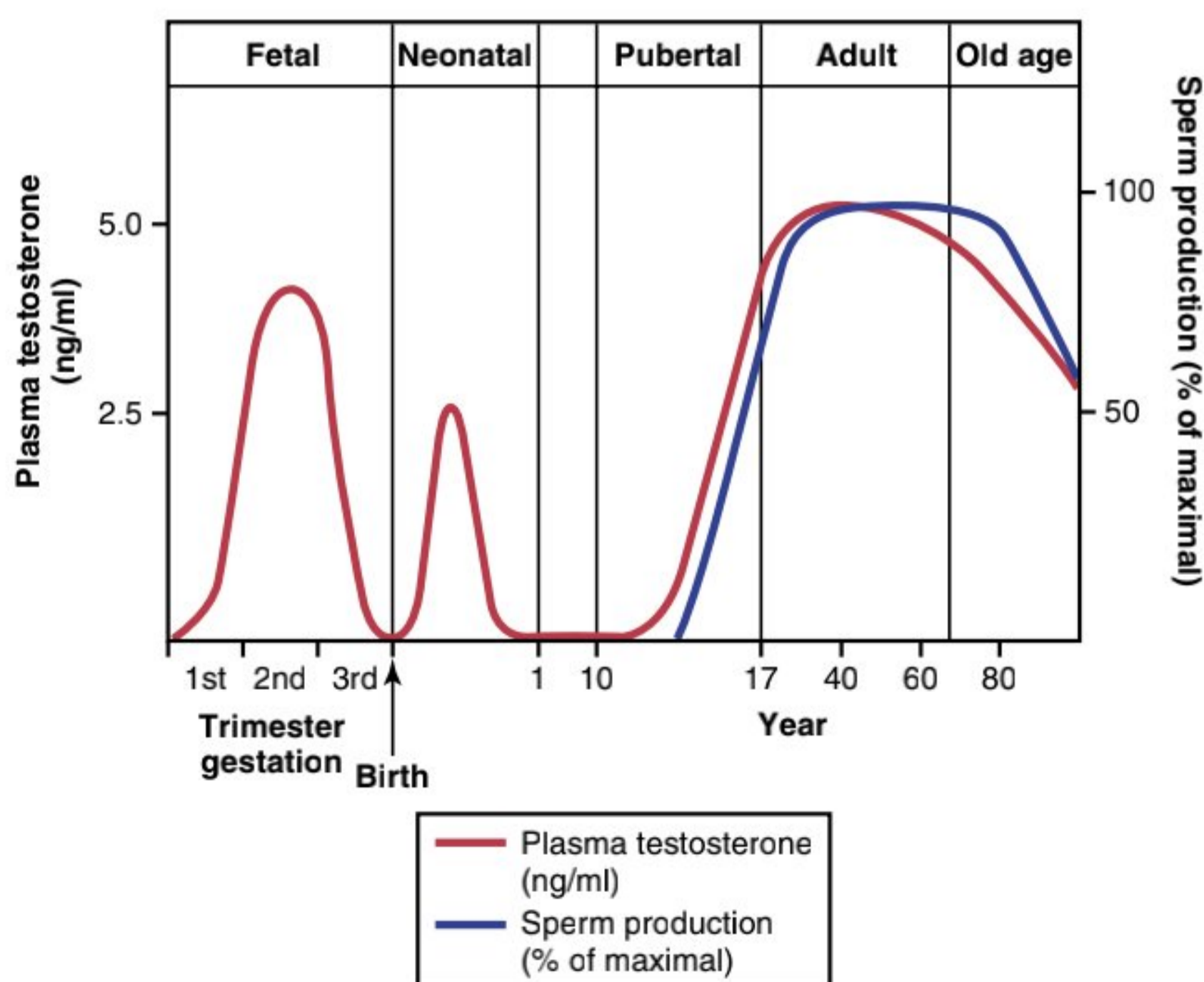


Figure 81-9 The different stages of male sexual function as reflected by average plasma testosterone concentrations (red line) and sperm production (blue line) at different ages. (Modified from Griffin JF, Wilson JD: *The testis*. In: Bondy PK, Rosenberg LE [eds]: *Metabolic Control and Disease*, 8th ed. Philadelphia: WB Saunders, 1980.)

tes to descend in the usual manner if the inguinal canals are large enough to allow the testes to pass.

Administration of gonadotropic hormones, which stimulate the Leydig cells of the newborn child's testes to produce testosterone, can also cause the testes to descend. Thus, the stimulus for descent of the testes is testosterone, indicating again that testosterone is an important hormone for male sexual development during fetal life.

Effect of Testosterone on Development of Adult Primary and Secondary Sexual Characteristics

After puberty, increasing amounts of testosterone secretion cause the penis, scrotum, and testes to enlarge about eightfold before the age of 20 years. In addition, testosterone causes the secondary sexual characteristics of the male to develop, beginning at puberty and ending at maturity. These secondary sexual characteristics, in addition to the sexual organs, distinguish the male from the female as follows.

Effect on the Distribution of Body Hair. Testosterone causes growth of hair (1) over the pubis, (2) upward along the linea alba of the abdomen sometimes to the umbilicus and above, (3) on the face, (4) usually on the chest, and (5) less often on other regions of the body, such as the back. It also causes the hair on most other portions of the body to become more prolific.

Male Pattern Baldness. Testosterone decreases the growth of hair on the top of the head; a man who does not have functional testes does not become bald. However, many virile men never become bald because baldness is a result of two factors: first, a *genetic background* for the development of baldness and, second, superimposed on this genetic background, *large quantities of androgenic hormones*. When a long-sustained androgenic tumor develops in a woman who has the appropriate genetic background, she becomes bald in the same manner as does a man.

Effect on the Voice. Testosterone secreted by the testes or injected into the body causes hypertrophy of the laryngeal mucosa and enlargement of the larynx. The effects at first cause a relatively discordant, "cracking" voice that gradually changes into the typical adult masculine voice.

Testosterone Increases Thickness of the Skin and Can Contribute to Development of Acne. Testosterone increases the thickness of the skin over the entire body and the ruggedness of the subcutaneous tissues. Testosterone also increases the rate of secretion by some or perhaps all of the body's sebaceous glands. Especially important is excessive secretion by the sebaceous glands of the face, which can result in *acne*. Therefore, acne is one of the most common features of male adolescence when the body is first becoming introduced to increased testosterone. After several years of testosterone secretion, the skin

normally adapts to the testosterone in a way that allows it to overcome the acne.

Testosterone Increases Protein Formation and Muscle Development. One of the most important male characteristics is development of increasing musculature after puberty, averaging about a 50% increase in muscle mass over that in the female. This increase in muscle mass is also associated with increased protein in the nonmuscle parts of the body. Many of the changes in the skin are due to deposition of proteins in the skin, and changes in the voice also result partly from this protein anabolic function of testosterone.

Because of the great effect that testosterone and other androgens have on the body's musculature, synthetic androgens are widely used by athletes to improve their muscular performance. This practice is to be severely deprecated because of prolonged harmful effects of excess androgens, as discussed in [Chapter 85](#) in relation to sports physiology. Testosterone or synthetic androgens are also occasionally used in old age as a "youth hormone" to improve muscle strength and vigor, but with questionable results. Some studies suggest that testosterone replacement therapy in elderly men may increase the risk of adverse cardiovascular events.

Testosterone Increases Bone Matrix and Causes Calcium Retention. After the great increase in circulating testosterone that occurs at puberty (or after prolonged injection of testosterone), the bones grow considerably thicker and deposit considerable additional calcium salts. Thus, testosterone increases the total quantity of bone matrix and causes calcium retention. The increase in bone matrix is believed to result from the general protein anabolic function of testosterone plus deposition of calcium salts in response to the increased protein.

Testosterone has a specific effect on the pelvis to (1) narrow the pelvic outlet, (2) lengthen it, (3) cause a funnel-like shape instead of the broad ovoid shape of the female pelvis, and (4) greatly increase the strength of the entire pelvis for load bearing. In the absence of testosterone, the male pelvis develops into a pelvis that is similar to that of the female.

Because of the ability of testosterone to increase the size and strength of bones, it is sometimes used in older men to treat osteoporosis.

When great quantities of testosterone (or any other androgen) are secreted abnormally in the still-growing child, the rate of bone growth increases markedly, causing a spurt in total body height. However, the testosterone also causes the epiphyses of the long bones to unite with the shafts of the bones at an early age. Therefore, despite the rapidity of growth, this early uniting of the epiphyses prevents the person from growing as tall as he would have grown had testosterone not been secreted at all. Even in normal men, the final adult height is slightly less than that which occurs in males castrated before puberty.

Testosterone Increases the Basal Metabolic Rate. Injection of large quantities of testosterone can increase the basal metabolic rate by as much as 15%. Also, even the usual quantity of testosterone secreted by the testes during adolescence and early adult life increases the rate of metabolism some 5% to 10% above the value that it would be were the testes not active. This increased metabolic rate is possibly an indirect result of the effect of testosterone on protein anabolism, with the increased quantity of proteins—the enzymes, especially—increasing activities of all cells.

Testosterone Increases Red Blood Cells. When normal quantities of testosterone are injected into a castrated adult, the number of red blood cells per cubic millimeter of blood increases 15% to 20%. Also, the average man has about 700,000 more red blood cells per cubic millimeter than the average woman. Despite the strong association of testosterone and increased hematocrit, testosterone does not appear to directly increase erythropoietin levels or have a direct effect on red blood cell production. The effect of testosterone to increase red blood cell production may be at least partly indirect because of the increased metabolic rate that occurs after testosterone administration.

Effect on Electrolyte and Water Balance. As pointed out in Chapter 78, many steroid hormones can increase the reabsorption of sodium in the distal tubules of the kidneys. Testosterone also has such an effect, but only to a minor degree in comparison with the adrenal mineralocorticoids. Nevertheless, after puberty, the blood and extracellular fluid volumes of the male in relation to body weight increase as much as 5% to 10%.

BASIC INTRACELLULAR MECHANISM OF ACTION OF TESTOSTERONE

Most of the effects of testosterone result basically from increased rate of protein formation in the target cells. In the prostate gland, for example, testosterone enters the prostatic cells within a few minutes after secretion. Then it is most often converted, under the influence of the intracellular enzyme 5α -reductase, to *dihydrotestosterone* which binds with a cytoplasmic “receptor protein.” This combination migrates to the cell nucleus where it binds with a nuclear protein and induces DNA-RNA transcription. Within 30 minutes, RNA polymerase has become activated, and the concentration of RNA begins to increase in the prostatic cells, which is followed by a progressive increase in cellular protein. After several days, the quantity of DNA in the prostate gland has also increased, and a simultaneous increase in the number of prostatic cells has occurred.

Testosterone stimulates production of proteins virtually everywhere in the body, although more specifically affecting the proteins in “target” organs or tissues responsible for the development of primary and secondary male sexual characteristics.

Some studies suggest that testosterone, like other steroid hormones, may also exert some rapid, *nongenomic effects* that do not require synthesis of new proteins. The physiological role of these nongenomic actions of testosterone, however, has yet to be determined.

CONTROL OF MALE SEXUAL FUNCTIONS BY HORMONES FROM THE HYPOTHALAMUS AND ANTERIOR PITUITARY GLAND

A major share of the control of sexual functions in both the male and the female begins with secretion of *gonadotropin-releasing hormone* (GnRH) by the hypothalamus (Figure 81-10). This hormone stimulates the anterior pituitary gland to secrete two other hormones called *gonadotropic hormones*: (1) *luteinizing hormone* (LH) and (2) *follicle-stimulating hormone* (FSH). In turn, LH is the primary stimulus for the secretion of testosterone by the testes, and FSH mainly stimulates spermatogenesis.

Gonadotropin-Releasing Hormone Increases Secretion of Luteinizing Hormone and Follicle-Stimulating Hormone

GnRH is a 10-amino acid peptide secreted by neurons whose cell bodies are located in the *arcuate nuclei of the hypothalamus*. The endings of these neurons terminate mainly in the median eminence of the hypothalamus, where they release GnRH into the hypothalamic-hypophysial portal vascular system. The GnRH is then transported to the anterior pituitary gland in the hypophysial portal blood and stimulates release of the two gonadotropins, LH and FSH.

GnRH is secreted intermittently a few minutes at a time once every 1 to 3 hours. The intensity of this hormone’s stimulus is determined in two ways: (1) by the frequency of these cycles of secretion and (2) by the quantity of GnRH released with each cycle.

Secretion of LH by the anterior pituitary gland is also cyclical, with LH following fairly faithfully the pulsatile release of GnRH. In contrast, FSH secretion increases and decreases only slightly with each fluctuation of GnRH secretion; instead, it changes more slowly over a period of many hours in response to longer-term changes in GnRH. Because of the much closer relation between GnRH secretion and LH secretion, GnRH is also widely known as *LH-releasing hormone*.

Gonadotropic Hormones: Luteinizing Hormone and Follicle-Stimulating Hormone

Both of the gonadotropic hormones, LH and FSH, are secreted by the same cells, called *gonadotropes*, in the anterior pituitary gland. In the absence of GnRH secretion from the hypothalamus, the gonadotropes in the pituitary gland secrete almost no LH or FSH.

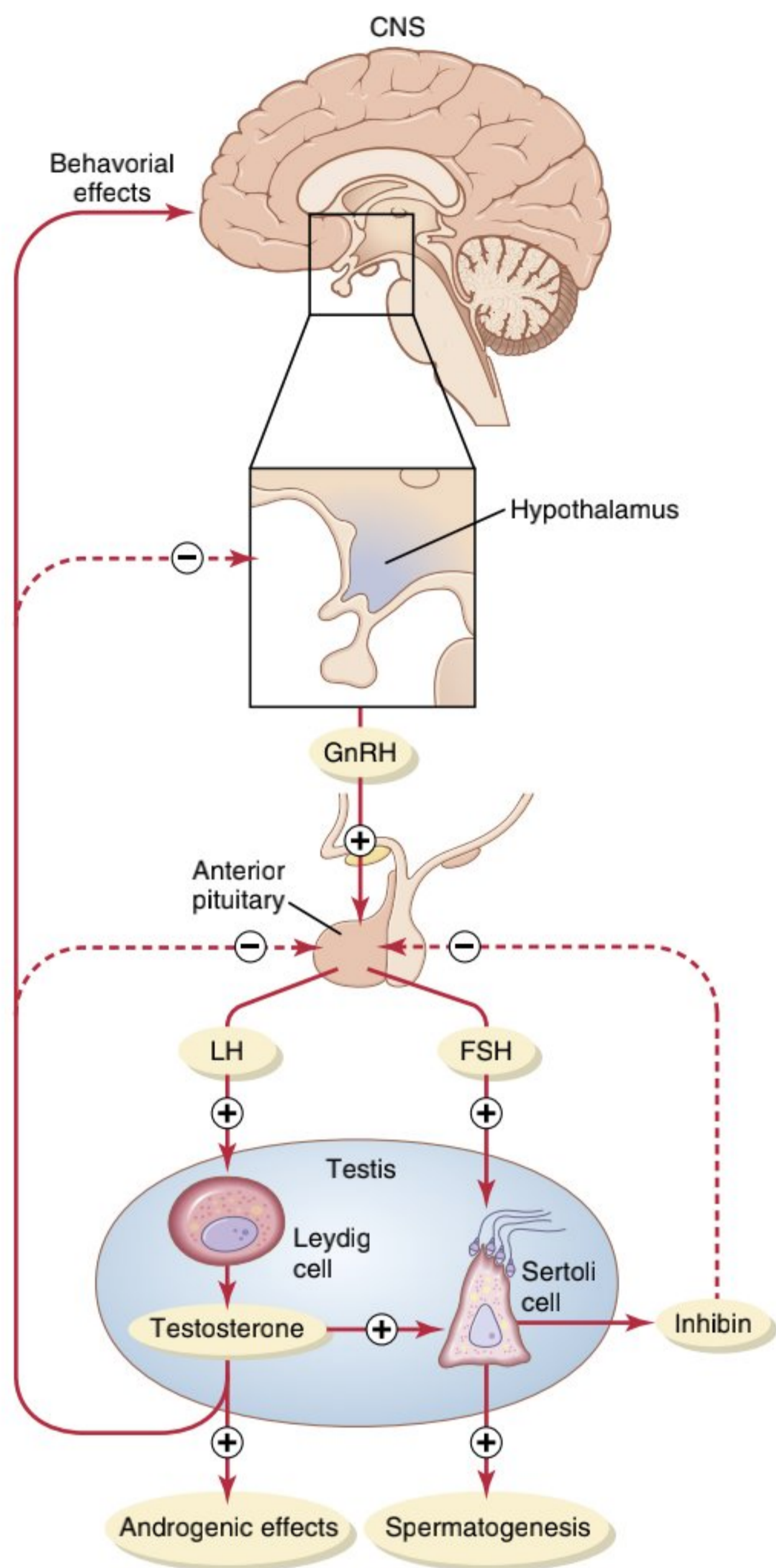


Figure 81-10 Feedback regulation of the hypothalamic-pituitary-testicular axis in males. Stimulatory effects are shown by *plus signs*, and negative feedback inhibitory effects are shown by *minus signs*. CNS, Central nervous system; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

LH and FSH are *glycoproteins*. They exert their effects on their target tissues in the testes mainly by *activating the cyclic adenosine monophosphate second messenger system*, which in turn activates specific enzyme systems in the respective target cells.

Regulation of Testosterone Production by Luteinizing Hormone. *Testosterone* is secreted by the *interstitial cells of Leydig* in the testes, but only when they are stimulated by LH from the anterior pituitary gland. Furthermore, the quantity of testosterone that is secreted increases ap-

proximately in direct proportion to the amount of LH that is available.

Mature Leydig cells are normally found in a child's testes for a few weeks after birth but then disappear until after the age of about 10 years. However, injection of purified LH into a child at any age or secretion of LH at puberty causes testicular interstitial cells that look like fibroblasts to evolve into functioning Leydig cells.

Inhibition of Anterior Pituitary Secretion of Luteinizing and Follicle-Stimulating Hormones by Testosterone—Negative Feedback Control of Testosterone Secretion. Testosterone secreted by the testes in response to LH has the reciprocal effect of inhibiting anterior pituitary secretion of LH (see **Figure 81-10**). Most of this inhibition probably results from a direct effect of testosterone on the hypothalamus to decrease secretion of GnRH. This effect in turn causes a corresponding decrease in secretion of LH and FSH by the anterior pituitary, and the decrease in LH reduces secretion of testosterone by the testes. Thus, whenever testosterone secretion becomes too great, this automatic negative feedback effect, operating through the hypothalamus and anterior pituitary gland, reduces testosterone secretion back toward the desired operating level. Conversely, too little testosterone allows the hypothalamus to secrete large amounts of GnRH, with a corresponding increase in anterior pituitary LH and FSH secretion and consequent increase in testicular testosterone secretion.

Regulation of Spermatogenesis by Follicle-Stimulating Hormone and Testosterone

FSH binds with specific FSH receptors attached to the Sertoli cells in the seminiferous tubules, which causes the Sertoli cells to grow and secrete various spermatogenic substances. Simultaneously, testosterone (and dihydrotestosterone) diffusing into the seminiferous tubules from the Leydig cells in the interstitial spaces also has a strong tropic effect on spermatogenesis. Thus, both FSH and testosterone are necessary to initiate spermatogenesis.

Role of Inhibin in Negative Feedback Control of Seminiferous Tubule Activity. When the seminiferous tubules fail to produce sperm, secretion of FSH by the anterior pituitary gland increases markedly. Conversely, when spermatogenesis proceeds too rapidly, pituitary secretion of FSH diminishes. The cause of this negative feedback effect on the anterior pituitary is believed to be secretion by the Sertoli cells of still another hormone called *inhibin* (see **Figure 81-10**). This hormone has a strong direct effect on the anterior pituitary gland to inhibit FSH secretion.

Inhibin is a glycoprotein, like LH and FSH, with a molecular weight between 10,000 and 30,000. It has been isolated from cultured Sertoli cells. Its potent inhibitory effect on

the anterior pituitary gland provides an important negative feedback mechanism for control of spermatogenesis, operating simultaneously with and in parallel to the negative feedback mechanism for control of testosterone secretion.

Human Chorionic Gonadotropin Secreted by the Placenta During Pregnancy Stimulates Testosterone Secretion by the Fetal Testes

During pregnancy, the hormone *human chorionic gonadotropin* (hCG) is secreted by the placenta and circulates in the mother and in the fetus. This hormone has almost the same effects on the sexual organs as LH.

During pregnancy, if the fetus is a male, hCG from the placenta causes the testes of the fetus to secrete testosterone. This testosterone is critical for promoting formation of the male sexual organs, as pointed out earlier. We discuss hCG and its functions during pregnancy in greater detail in [Chapter 83](#).

Puberty and Regulation of Its Onset

Initiation of the onset of puberty has long been a mystery, but it has now been determined that *during childhood the hypothalamus does not secrete significant amounts of GnRH*. One of the reasons for this is that, during childhood, the slightest secretion of any sex steroid hormones exerts a strong inhibitory effect on hypothalamic secretion of GnRH. Yet, for reasons still not fully understood, at the time of puberty, the secretion of hypothalamic GnRH breaks through the childhood inhibition and adult sexual life begins.

Male Adult Sexual Life and Male Climacteric. After puberty, gonadotropic hormones are produced by the male pituitary gland for the remainder of life, and at least some spermatogenesis usually continues until death. Many men, however, begin to exhibit slowly decreasing sexual functions in their late 50s or 60s, especially if they smoke or are obese and have associated cardiovascular and metabolic disorders, such as hypertension, atherosclerosis, and type 2 diabetes mellitus. There is considerable variation in the decline of sexual function, with healthy men continuing to be virile until their 80s and 90s.

The slow, gradual decline in sexual function is also related, in part, to a decrease in testosterone secretion, as shown in [Figure 81-9](#). The decrease in male sexual function is called the *male climacteric*.

Abnormalities of Male Sexual Function

The Prostate Gland and Its Abnormalities

The prostate gland remains relatively small throughout childhood and begins to grow at puberty under the stimulus of testosterone. This gland reaches an almost stationary size by the age of 20 years and remains at this size up to the age of about 50 years. At that time, in some men it begins to involute, along with decreased production of testosterone by the testes.

A benign prostatic fibroadenoma frequently develops in the prostate in many older men and can cause urinary obstruction. This hypertrophy is caused not by testosterone but instead by abnormal overgrowth of prostate tissue.

Cancer of the prostate gland is a different problem that accounts for about 2% to 3% of all male deaths. Once cancer of the prostate gland occurs, the cancerous cells are usually stimulated to more rapid growth by testosterone and are inhibited by removal of both testes so that testosterone cannot be formed. Prostatic cancer usually can be inhibited by administration of estrogens. Even some patients who have prostatic cancer that has already metastasized to almost all the bones of the body can be successfully treated for a few months to years by removal of the testes, estrogen therapy, or both; after initiation of this therapy, the metastases usually diminish in size, and the bones partially heal. This treatment does not stop the cancer but slows it and sometimes greatly diminishes the severe bone pain.

Hypogonadism in the Male

When the testes of a male fetus are nonfunctional during fetal life, none of the male sexual characteristics develop in the fetus. Instead, female organs are formed. The reason for this is that the basic genetic characteristic of the fetus, whether male or female, is to form female sexual organs if there are no sex hormones. However, in the presence of testosterone, formation of female sexual organs is suppressed and male organs are induced instead.

When a boy loses his testes before puberty, a state of eunuchism ensues in which he continues to have infantile sex organs and other infantile sexual characteristics throughout life. The height of an adult eunuch is slightly greater than that of a normal man because the bone epiphyses are slow to unite, although the bones are quite thin and the muscles are considerably weaker than those of a normal man. The voice is childlike, there is no loss of hair on the head, and the normal adult masculine hair distribution on the face and elsewhere does not occur.

When a man is castrated after puberty, some of his male secondary sexual characteristics revert to those of a child, and others remain of adult masculine character. The sexual organs regress slightly in size but not to a childlike state, and the voice regresses from the bass quality only slightly. However, there is loss of masculine hair production, loss of the thick masculine bones, and loss of the musculature of the virile male.

Also in a castrated adult male, sexual desires are decreased but not lost, provided sexual activities have been practiced previously. Erection can still occur as before, although with less ease, but it is rare that ejaculation can take place, primarily because the semen-forming organs degenerate and there has been a loss of the testosterone-driven psychic desire.

Some cases of hypogonadism are caused by a genetic inability of the hypothalamus to secrete normal amounts of GnRH. This condition is often associated with a simultaneous abnormality of the feeding center of the hypothalamus, causing the person to greatly overeat. Consequently, obesity occurs along with eunuchism. A patient with this condition is shown in [Figure 81-11](#); the condition is called *adiposogenital syndrome*, *Fröhlich's syndrome*, or *hypothalamic eunuchism*.

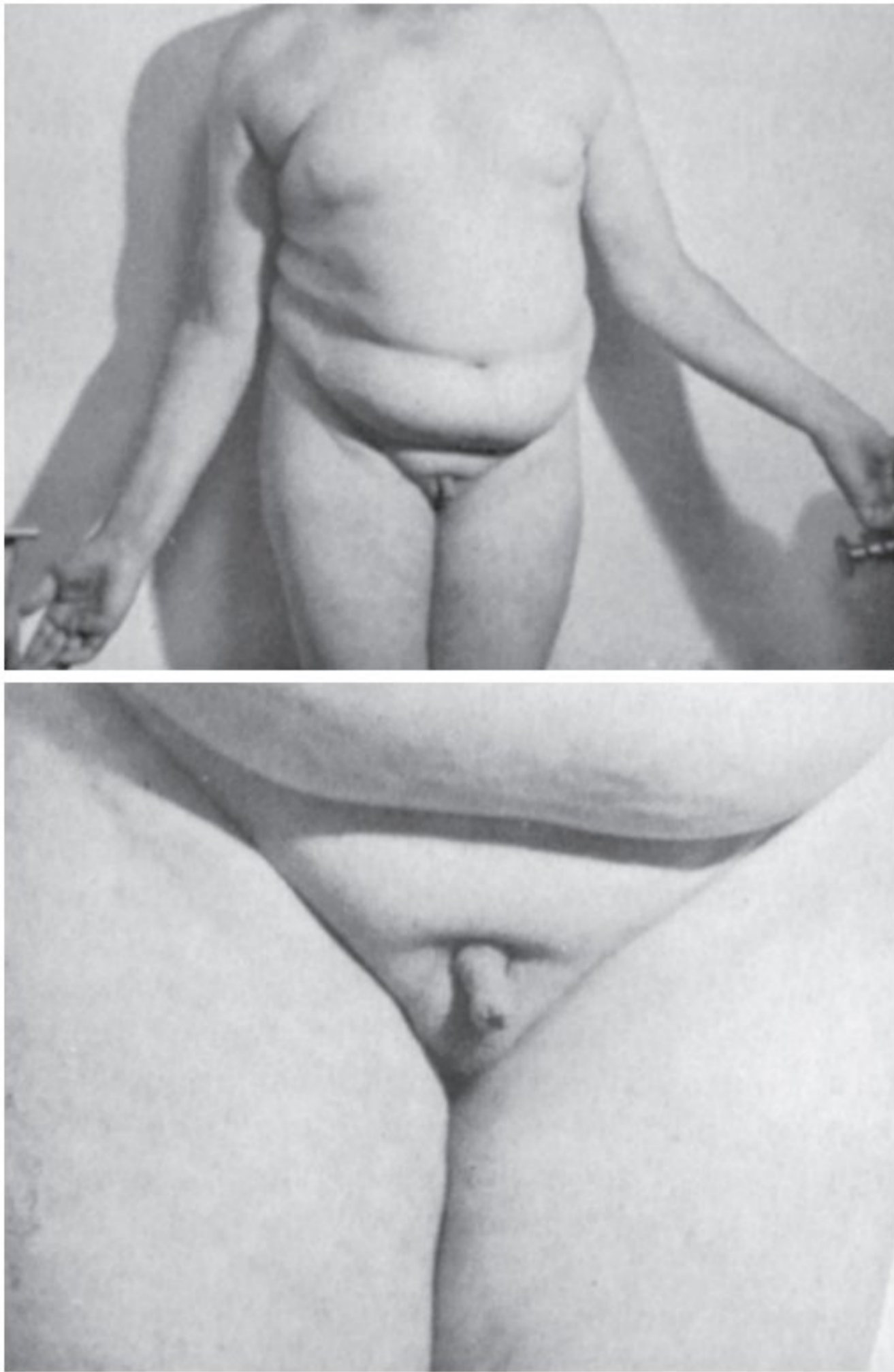


Figure 81-11 Adiposogenital syndrome in an adolescent male. Note the obesity and childlike sexual organs. (Courtesy Dr. Leonard Posey.)

Testicular Tumors and Hypergonadism in the Male

Interstitial Leydig cell tumors develop in rare cases in the testes. These tumors sometimes produce as much as 100 times the normal quantities of testosterone. When such tumors develop in young children, they cause rapid growth of the musculature and bones but also early uniting of the epiphyses, so that the eventual adult height is actually considerably less than that which would have been achieved otherwise. Such interstitial cell tumors also cause excessive development of the male sexual organs, all skeletal muscles, and other male sexual characteristics. In the adult male, small interstitial cell tumors are difficult to diagnose because masculine features are already present.

Much more common than interstitial Leydig cell tumors are *tumors of the germinal epithelium*. Because germinal cells are capable of differentiating into almost any type of cell, many of these tumors contain multiple tissues, such as placental tissue, hair, teeth, bone, skin, and so forth, all found together in the same tumorous mass called a *teratoma*. These tumors often secrete few hormones, but if a significant quantity of placental tissue develops in the tumor, it may secrete large quantities of hCG with functions similar to those of LH. Also, estrogenic hormones are sometimes secreted by these tumors and cause the condition called *gynecomastia* (overgrowth of the breasts).

Erectile Dysfunction in the Male

Erectile dysfunction, also called “impotence,” is characterized by an inability of the man to develop or maintain an erection of sufficient rigidity for satisfactory sexual intercourse. Neurological problems, such as trauma to the parasympathetic nerves from prostate surgery, deficient levels of testosterone, and some *drugs* (e.g., *nicotine*, *alcohol*, and *antidepressants*) can also contribute to erectile dysfunction.

In men older than 40 years, erectile dysfunction is most often caused by underlying vascular disease. As discussed previously, adequate blood flow and nitric oxide formation are essential for penile erection. Vascular disease, which can occur as a result of uncontrolled *hypertension*, *diabetes*, and *atherosclerosis*, reduces the ability of the body’s blood vessels, including those in the penis, to dilate. Part of this impaired vasodilation is due to decreased release of nitric oxide.

Erectile dysfunction caused by vascular disease can often be successfully treated with *phosphodiesterase-5 (PDE-5) inhibitors* such as sildenafil (Viagra), vardenafil (Levitra), or tadalafil (Cialis). These drugs increase cyclic GMP levels in the erectile tissue by inhibiting the enzyme *phosphodiesterase-5*, which rapidly degrades cyclic GMP. Thus, by inhibiting the degradation of cyclic GMP, the PDE-5 inhibitors enhance and prolong the effect of cyclic GMP to cause erection.

Function of the Pineal Gland in Controlling Seasonal Fertility in Some Animals

For as long as the pineal gland has been known to exist, myriad functions have been ascribed to it, including (1) enhancing sex, (2) staving off infection, (3) promoting sleep, (4) enhancing mood, and (5) increasing longevity (as much as 10% to 25%). It is known from comparative anatomy that the pineal gland is a vestigial remnant of what was a third eye located high in the back of the head in some lower animals. Many physiologists have been content with the idea that this gland is a nonfunctional remnant, but others have claimed for many years that it plays important roles in the control of sexual activities and reproduction.

Now, after years of research, it appears that the pineal gland does indeed play a regulatory role in sexual and reproductive function. In animals that bear their young at certain seasons of the year and in which the pineal gland has been removed or the nervous circuits to the pineal gland have been sectioned, the normal periods of seasonal fertility are lost. To these animals, such seasonal fertility is important because it allows birth of the offspring at the time of year, usually springtime or early summer, when survival is most likely. The mechanism of this effect is not entirely clear, but it seems to be the following.

First, the pineal gland is controlled by the amount of light or “time pattern” of light seen by the eyes each day. For example, in the hamster, more than 13 hours of *darkness* each day activates the pineal gland, whereas less than that amount of darkness fails to activate it, with a critical balance between activation and nonactivation. The nervous pathway involves the passage of light signals from the eyes to the suprachiasmatic nucleus of the hypothalamus and then to the pineal gland, activating pineal secretion.

Second, the pineal gland secretes *melatonin* and several other similar substances. Either melatonin or one of the other substances is believed to pass either by way of the blood or through the fluid of the third ventricle to the anterior pituitary gland to *decrease* gonadotropic hormone secretion.

Thus, in the presence of pineal gland secretion, gonadotropic hormone secretion is suppressed in some species of animals, and the gonads become inhibited and even partly involuted, which is what presumably occurs during the early winter months when there is increasing darkness. However, after about 4 months of dysfunction, gonadotropic hormone secretion breaks through the inhibitory effect of the pineal gland and the gonads become functional once more, ready for a full springtime of activity.

Does the pineal gland have a similar function for control of reproduction in humans? The answer to this question is unknown. However, tumors sometimes occur in the region of the pineal gland. Some of these tumors secrete excessive quantities of pineal hormones, whereas others are tumors of surrounding tissue and press on the pineal gland to destroy it. Both types of tumors are often associated with hypogonadal or hypergonadal function, so perhaps the pineal gland does play at least some role in controlling sexual drive and reproduction in humans.

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