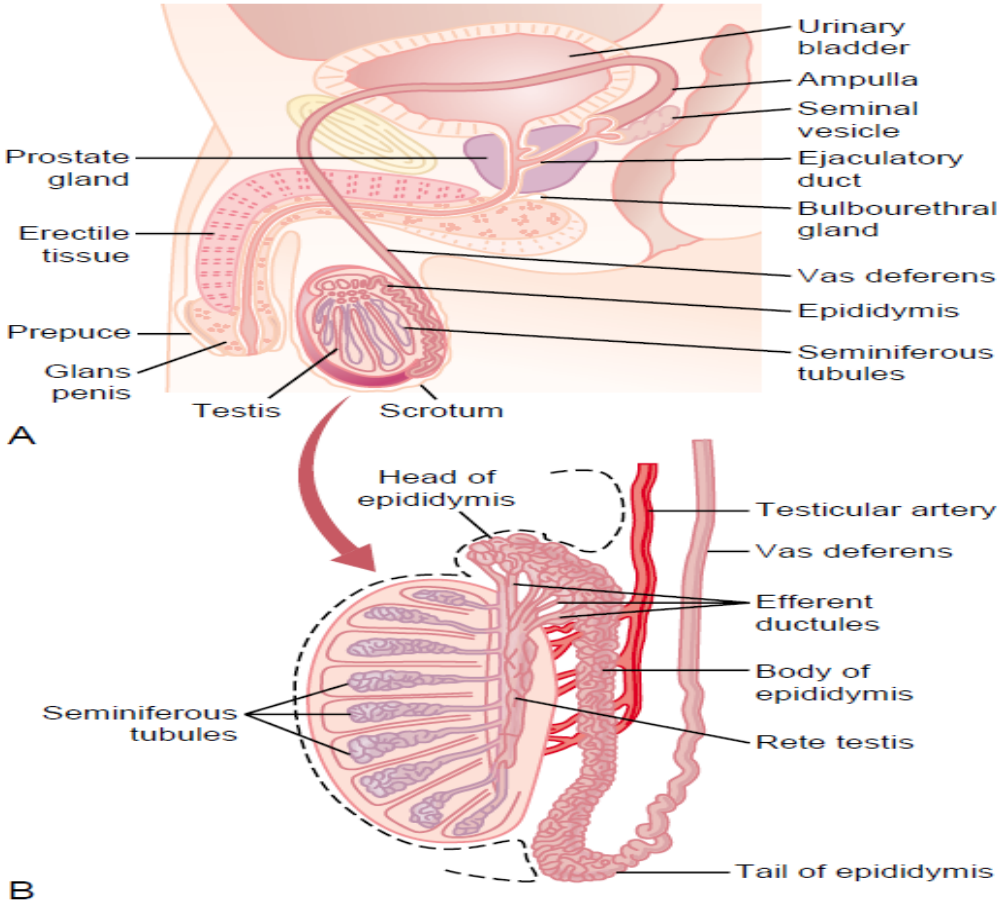
Lecture No.8

Reproductive and Hormonal Functions of the Male



The reproductive functions of the male can be divided into three major subdivisions: (1) spermatogenesis, which means simply the formation of sperm; (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.

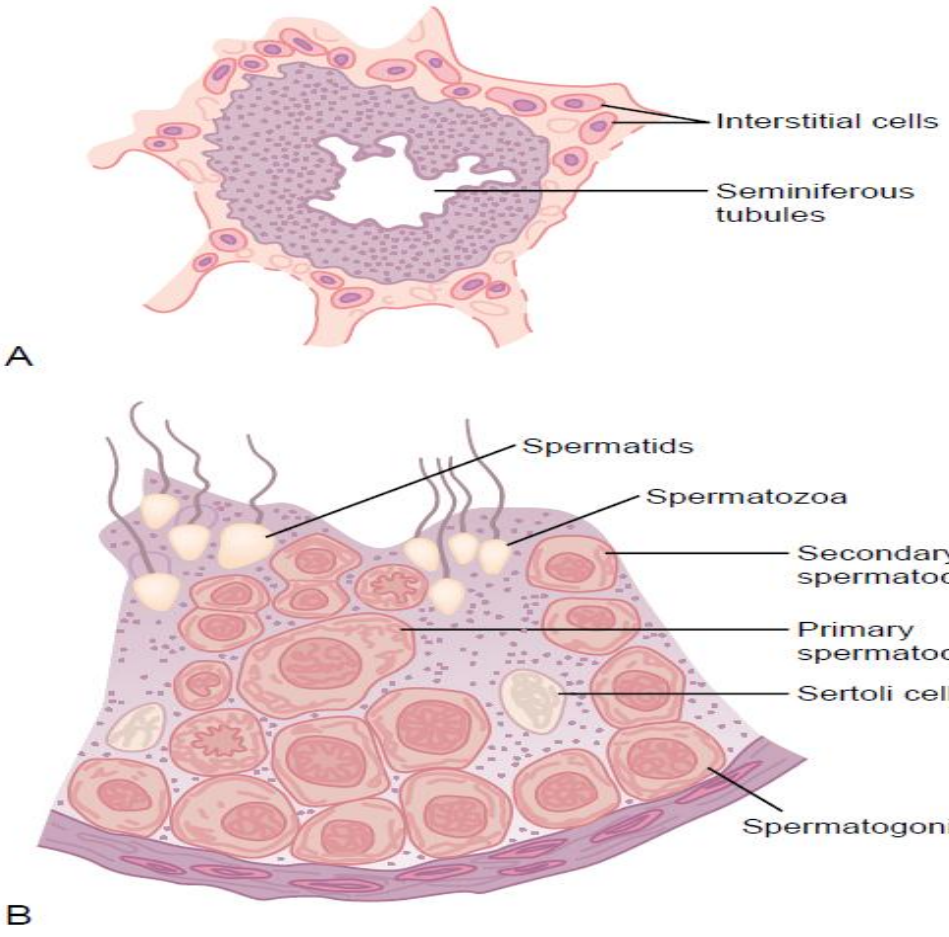
Physiologic Anatomy of the Male Sexual Organs

The figure above shows the various portions of the male reproductive system, and figure below 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*, 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*, too, 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's 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*. The spermatogonia begin to undergo mitotic division, beginning at

puberty, and continually proliferate and differentiate through definite stages of development to form sperm .

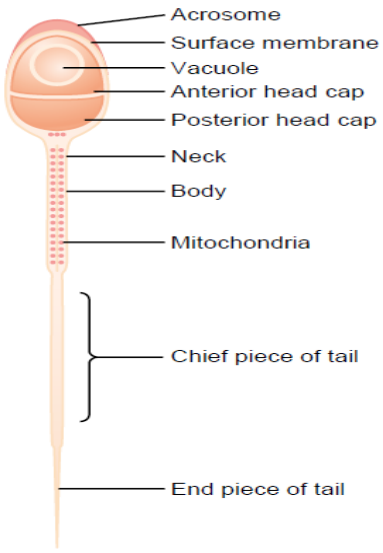
Steps of Spermatogenesis

Spermatogenesis occurs in the seminiferous tubules during active sexual life as the result of stimulation by anterior pituitary gonadotropic hormones, beginning at an average age of 13 years and continuing throughout most of the remainder of life but decreasing markedly in old age. In the first stage of spermatogenesis, the spermatogonia migrate among *Sertoli cells* toward the central lumen of the seminiferous tubule. The Sertoli cells are very large, with overflowing cytoplasmic envelopes that surround the developing spermatogonia all the way to the central lumen of the tubule.

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 the figure below, 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. This contains a number of 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 this is similar to that of cilia found on the surfaces of other types of cells (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 rhythmical 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 that 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. This allows them to move through the female genital tract in quest of the ovum.



Hormonal Factors That Stimulate Spermatogenesis

1. *Testosterone*, secreted by the *Leydig cells* located in the interstitium of the testis, 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, the 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 folliclestimulating 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 themselves; in its absence, as in pituitary dwarfs, spermatogenesis is severely deficient or absent, thus causing infertility.

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 significant testicular hormone, although as we shall see,much, if not most, of the testosterone is eventually converted into the more active hormone dihydrotestosterone in the target tissues. Testosterone is formed by the *interstitial cells of Leydig*, which lie in the interstices between the seminiferous tubules and constitute about 20 per cent of the mass of the adult testes. 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 any time 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. Finally, 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.

Metabolism of Testosterone

After secretion by the testes, about 97 per cent 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 either is transferred to the tissues or is 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 actions of testosterone are dependent on this conversion, whereas other actions are not.

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 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 recovered from a man’s urine.The exact source of estrogens in the male is unclear, but the following are 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 androstanediol in other tissues of the body, especially the liver, probably accounting for as much as 80 per cent 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. Then testosterone production 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, dwindling rapidly beyond age 50 to become 20 to 50 per cent of the peak value by age 80.

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 causes the newly developing genital ridge to secrete testosterone, whereas the female chromosome causes this ridge to 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, removal of the testes in the early male fetus causes development of female sexual organs. Thus, testosterone secreted first by the genital ridges and later by the fetal testes is responsible for the development of the male body characteristics, including the formation of a penis and a scrotum rather than formation of a clitoris and a vagina. Also, it causes formation of the prostate gland, seminal vesicles, and male genital ducts, while at the same time suppressing the 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, the administration of testosterone usually causes the testes 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, the 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 themselves, distinguish the male from the female as follows.

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 per cent increase in muscle mass over that in the female.This is associated with increased protein in the nonmuscle parts of the body as well. Many of the changes in the skin are due to deposition of proteins in the skin, and the changes in the voice also result partly from this protein anabolic function of testosterone.

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.

Effect on 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 per cent. Also, the average man has about 700,000 more red blood cells per cubic millimeter than the average woman. This difference may be due partly to the increased metabolic rate that occurs after testosterone administration rather than to a direct effect of testosterone on red blood cell production.

Effect on Electrolyte and Water Balance

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 per cent.

Gonadotropic Hormones: LH and FSH

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. 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.

Negative Feedback Control of Seminiferous Tubule Activity— Role of the Hormone Inhibin.

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 80–10). This hormone has a strong direct effect on the anterior pituitary gland to inhibit the secretion of FSH and possibly a slight effect on the hypothalamus to inhibit secretion of GnRH. Inhibin is a glycoprotein, like both LH and FSH, having a molecular weight between 10,000 and 30,000. It has been isolated from cultured Sertoli cells. Its potent inhibitory feedback 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.

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. But in the presence of testosterone, formation of female sexual organs is suppressed, and instead, male organs are induced. 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.