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 one is shown in Figure 80–2*A*). The spermatogonia begin to undergo mitotic division, beginning at puberty, and continually proliferate and differentiate through definite stages of development to form sperm, as shown in Figure 80–2*B*.

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

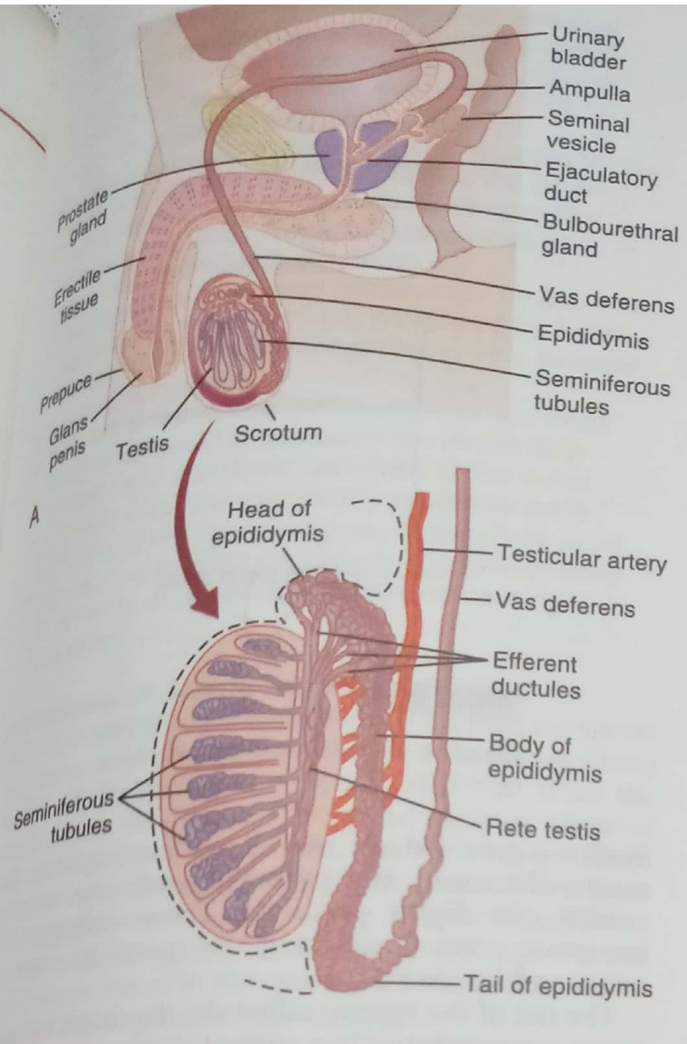

Figure 80–1

A, Male reproduction system. (Modified from Bloom V, Fawcett DW: Textbook of Histology, 10th ed. Philadelphia: WB Saunders Co, 1975.) *B*, Internal structure of the testis and relation of the testis to the epididymis. (Redrawn from Guyton AC: Anatomy and Physiology. Philadelphia: Saunders College Publishing, 1985.)

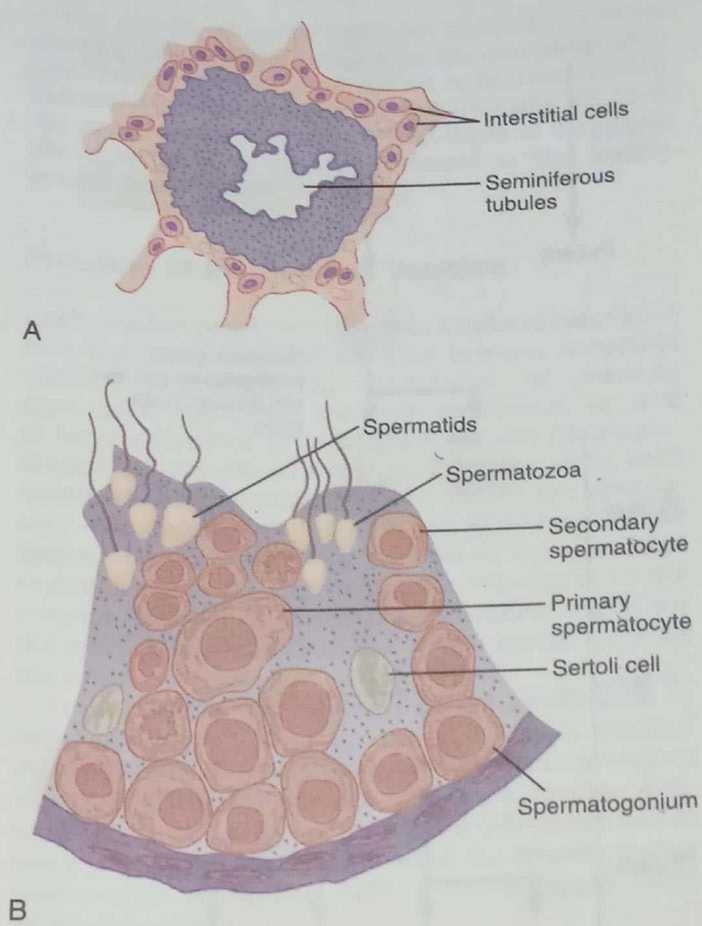

Figure 80–2

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

cells are very 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 80–3). Each of these, in turn, undergoes meiotic division to form two *secondary spermatocytes*. After another few days, these too 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, so that 23 chromosomes go to one spermatid and the other 23 to the second spermatid. This also divides the chromosomal genes so that only one half of the genetic characteristics of the eventual fetus are provided by the father, while the other half are 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 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 is discussed further in Chapter 82.

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 80–4, each spermatozoon is composed of a *head* and a

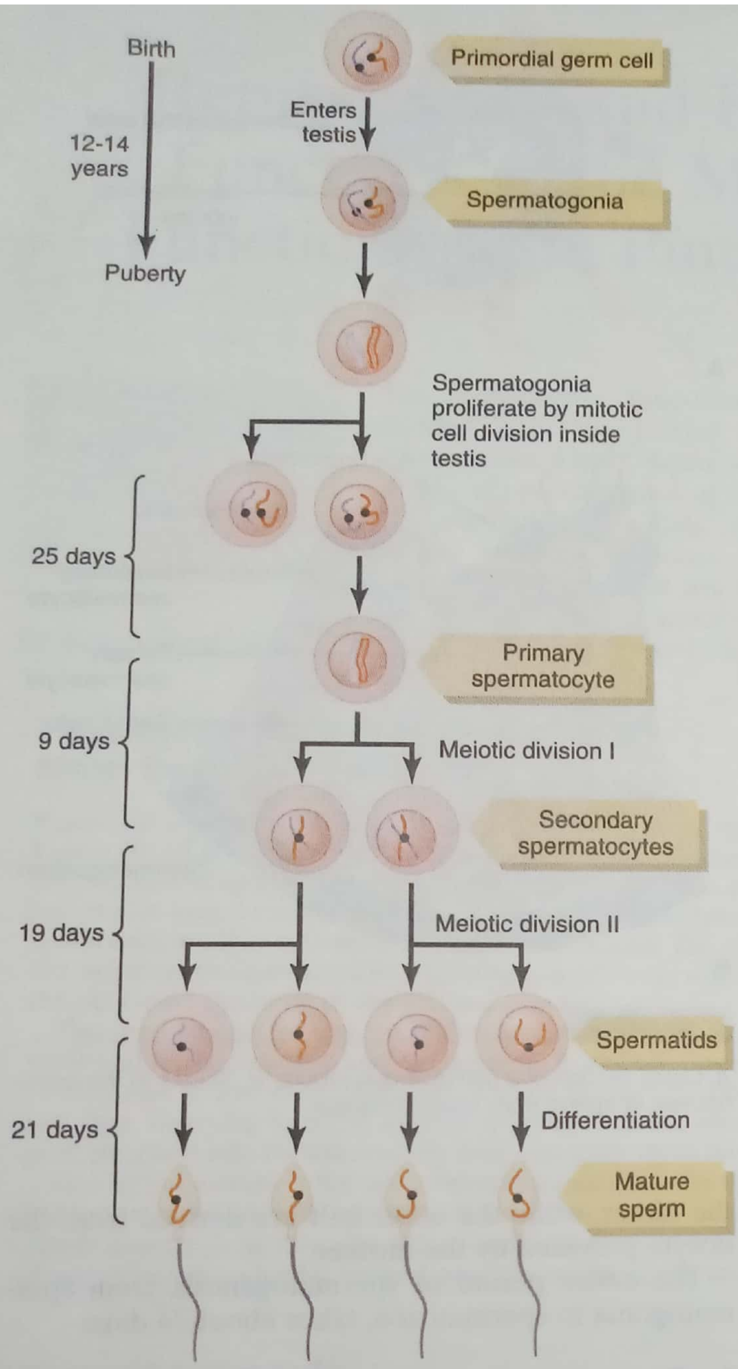

Figure 80–3

Cell divisions during spermatogenesis. During embryonic development the primordial germ cells migrate to the testis where they become spermatogonia. At puberty (usually 12 to14 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.

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

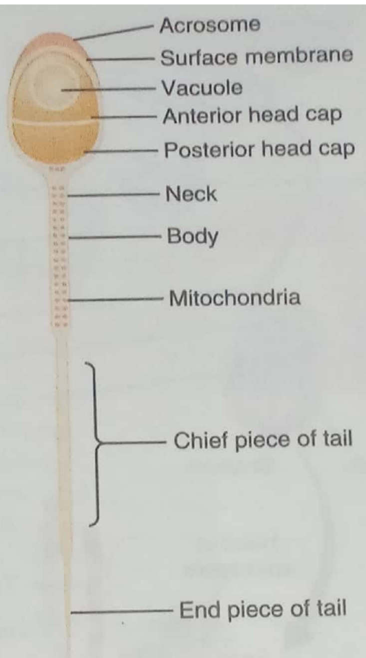

Figure 80–4

Structure of the human spermatozoon.

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 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 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

We shall discuss the role of hormones in reproduction later, but at this point, let us note that several hormones play essential roles in spermatogenesis. Some of these are as follows:

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 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 themselves; 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 they cannot fertilize an ovum. However, after the sperm have been in the epididymis for some 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. The two testes of the human adult form up to 120 million sperm each day. A small quantity of these can be stored in the epididymis, but most are stored in the vas deferens. They can remain stored, 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, storage may be no longer than a few days.

After ejaculation, the sperm become motile, and they also become 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 though 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 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, 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 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 to inhibit sperm fertility. Also, the vaginal secretions of the female are acidic (pH of 3.5 to 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 to 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 sexua[l] act, is composed of the fluid and sperm from the va[s] produced as the testes are outside the abdominal cavities within the scrotum and due to circulation of air around the scrotum. It is further maintained by the scrotal sac with the help of the dartos muscle. When scrotal temperature decreases, the testes are brought nearer to the body by the contraction of dartos and the distance from the body is increased due to relaxation of dartos in case when the scrotal temperature increases. It is also helped by the counter current exchange of heat in the spermatic vessels. Increased temperature as in cryptorchidism (see above), when the testes are in the abdominal cavity, leads to failure of spermatogenesis.

(6) Growth hormone and other hormones necessary for general metabolism and growth are also necessary in normal concentration for spermatogenesis. Oestrogen formed locally may also be useful.

(7) Seminal fluid with its fructose content helps in the maturation of sperms.

(8) Vitamin E, C and several members of the B complex are required for normal spermatogenesis.

SEMEN

It is the fluid that is ejaculated during orgasm from the male genital tract. It contains sperm, seminal fluid and secretion from prostate, etc. (the main bulk of the fluid part of the semen is contributed by these glands).

Ejaculation is the process of ejection of semen, which requires an intact autonomic nervous system. After sympathectomy, ejaculation fails to occur. For ejaculation, afferent impulses from penis and other places leads to reflex contraction of the smooth muscles in epididymis, vas, seminal vesicles and prostate. There is simultaneous discharge from the accessory glands into the urethra. Then by the contraction of bulbospongiosus and ischiocavernosus, the semen is ejected out. At the same time, there is contraction of the internal urethral sphincter to prevent entry of semen into the urinary bladder and this also prevents micturition during the process.

Composition and Character

1. Volume : About 2.5 ml to 3.5 ml per ejaculation after several days of abstinence.

2. Semen is a white opalescent fluid, which coagulates immediately by a factor from the seminal vesicles but liquifies later on (after 15 to 20 minutes) by prostatic specific antigen (PSA).

Note : PSA level in blood increases in various abnormalities in prostate.

3. It's pH is about 7.4 to 7.5. It is maintained by the buffers like phosphates and bicarbonates. It is more alkaline than the body fluids due to the alkaline prostatic fluid. This is necessary (as the vaginal fluid is acidic) to keep the spermatozoa alive and motile in the female genital tract.

4. Sperm count is 40 to 100 million/ml (of this 80% should be normal and motile). Sterility occurs if the sperm count is below 20 million/ml (but 50% of the males, those have sperm count of 20 to 40 million are sterile). If the abnormal sperms are more than 20%, then fertilisation is unlikely.

5. Semen contains fructose secreted from the seminal vesicles, which is very much important for nutrition of the sperms. Semen also contains prostaglandins in high amount together with, zinc, citric acid, phospholipids, spermin, etc.

The male reproductive system (Fig.10.1) is composed of the following :

1. Primary reproductive organs : A pair of testes (sing. testis). Testes are situated in the scrotal sac outside the abdominal cavity for maintenance of favourable temperature. Its function is gametogenesis and secretion of androgens.

2. Accessory reproductive organs : Vas deferens, seminal vesicles, ejaculatory ducts, prostate, bulbourethral glands (Cowper's glands) and penis. These constitute the seminal tracts from each testis, and also elaborate some secretions. Epididymis drains and opens into the prostatic urethra, where the prostatic glands and the Cowper's glands also open. The seminal vesicles open into the ejaculatory ducts.

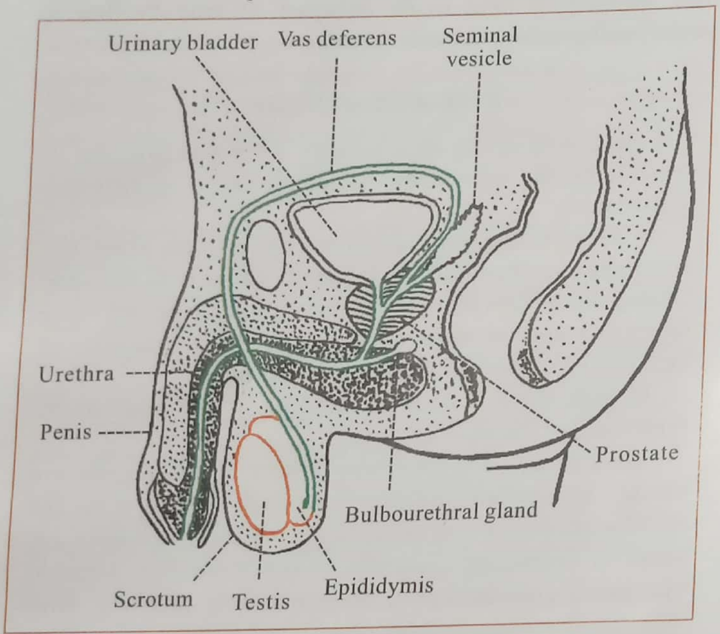

Fig. 10.1. *Male reproductive organs.*

3. External genitalia : These are penis and scrotum. (Secondary sex characters include the features characteristic of a male, *i.e.*, body appearance, hair distribution, voice, etc. These are not directly related to reproduction).

ANDROGENS

The hormones which stimulate male characteristics are called **androgens**. Some androgens are secreted from the suprarenal cortex (p. 349) but the testes are the main source.

The main functional components of the testes are the seminiferous tubules (see later) and the interstitial cells of Leydig (Fig. 10.2). These cells are the source of androgens. There is another type of cell in the seminiferous tubules, called Sertoli cells (see Fig. 10.6), which secrete inhibin and probably some amount of oestrogens as well.

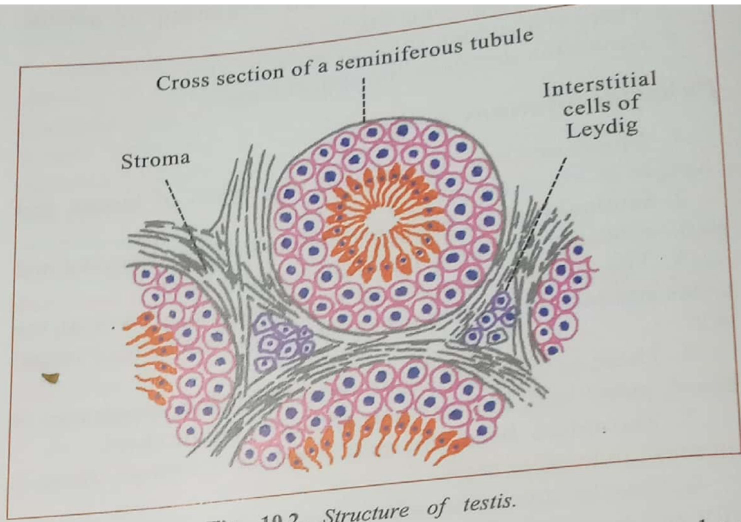

Fig. 10.2. *Structure of testis.*

The androgens are steroid hormones having 19 carbon atoms in them with OH at 17C (see below). The main hormones are **testosterone** and its derivative **dihydrotestosterone**. The other androgens, secreted in small amounts, are **dehydroepiandrosterone** and **androstenedione**. Testosterone, which is secreted from testes will be considered in relation to male reproduction.

Synthesis

The androgens are synthesised from cholesterol as follows :

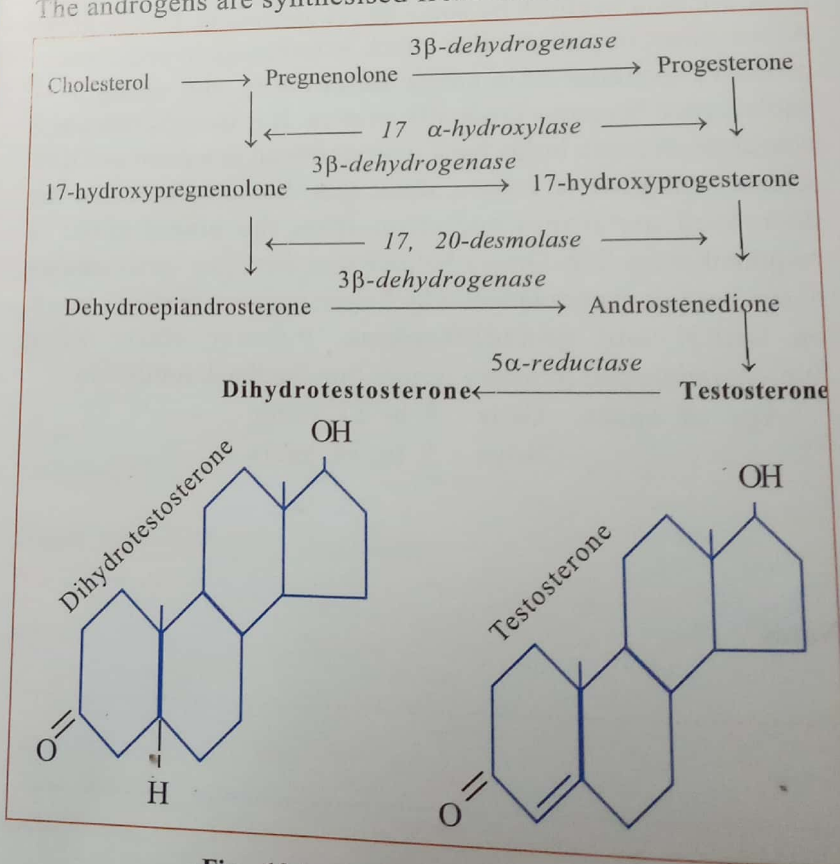

Fig. 10.3. *Synthesis of androgens.*

Plasma Hormones

Most of the secreted hormones are bound to the gonadal steroid binding globulin (GBG) and only a small portion circulates freely in the plasma. The free hormone is responsible for the physiological actions.

Dihydrotestosterone is produced in some target organs. A small amount of oestrogen is also produced from testosterone in circulation. Daily output of androgens is about 4 to 9 mg in an adult male, which is mostly testosterone and the plasma level is about 0.65 μg/100ml. In females also, a small amount of androgens are secreted. Most of the testosterone is converted into 17-ketosteroid in liver. This source contribute 1/3rd of the 17-ketosteroid excreted in urine in an adult male, the rest is from the suprarenal cortex.

Functions of Testosterone

(1) Metabolic actions

(a) Increases BMR.

(b) Testosterone is strongly anabolic and it increases protein synthesis and prevents protein breakdown.

(c) Helps to retain Na^+, K^+, Ca^{2+}, PO_4^{3-}, SO_4^{2-}, etc. along with water.

(2) On growth : Testosterone is responsible for the spurt of growth seen during adolescence. It is mainly due to stimulation of growth hormone secretion, protein anabolic effect and growth of bones.

At the same time the testosterone is also responsible for early epiphyseal closure in male, which arrests the growth in height.

(3) Testosterone causes development of secondary sexual characters in boys, *e.g.*, growth of beards, axillary hair, pubic hair, temporal recession of hair line, and so on (it brings about all the pubertal changes in boys, p. 367). It is responsible for growth of the external genitalia during adolescence. In adults it maintains the sex organs.

(4) It is responsible for the development of male psychology and aggressive behaviour.

(5) Testosterone is essential for male gametogenesis (spermatogenesis) and for this, a very high local concentration of testosterone is maintained inside the seminiferous tubules (see below). It is also responsible for motility of the sperms.

(6) It stimulates erythropoiesis.

(7) It is responsible for male libido, particularly at puberty and also in adults.

(8) In intrauterine life, testosterone from the foetal testes acts on foetal brain to develop the male psyche. It causes sex differentiation; development of the wolffian ducts into epididymis, vas deferens and seminal vesicles. External genitalia of male foetus also develop under its influence.

Mechanism of Action

Like all other steroid hormones, testosterone has intracellular receptors through which it regulates intracellular protein synthesis. Testosterone in some target organs is converted into dihydrotestosterone (DHT) by the enzyme 5α-reductase. This DHT is responsible for the development of prostate, growth of facial, axillary and pubic hairs, temporal recession of hair line. It also causes development of male external genitalia and probably causes growth of penis at puberty.

Rest of the functions, *e.g.*, anabolic effects, growth of penis, male libido, development of the wolffian system into male internal genitalia, are due to testosterone itself.

Regulation of Secretion

(1) Secretion of testosterone from the Leydig cells of foetal testes is caused by the HCG (Human chorionic gonadotrophin) from placenta. This testosterone is required for sex differentiation and for development of the sex organs of the male embryo.

(2) After birth, testosterone secretion does not occur up to adolescence. During adolescence it starts again and continues under the influence of GnRH (Gonadotrophin releasing hormone).

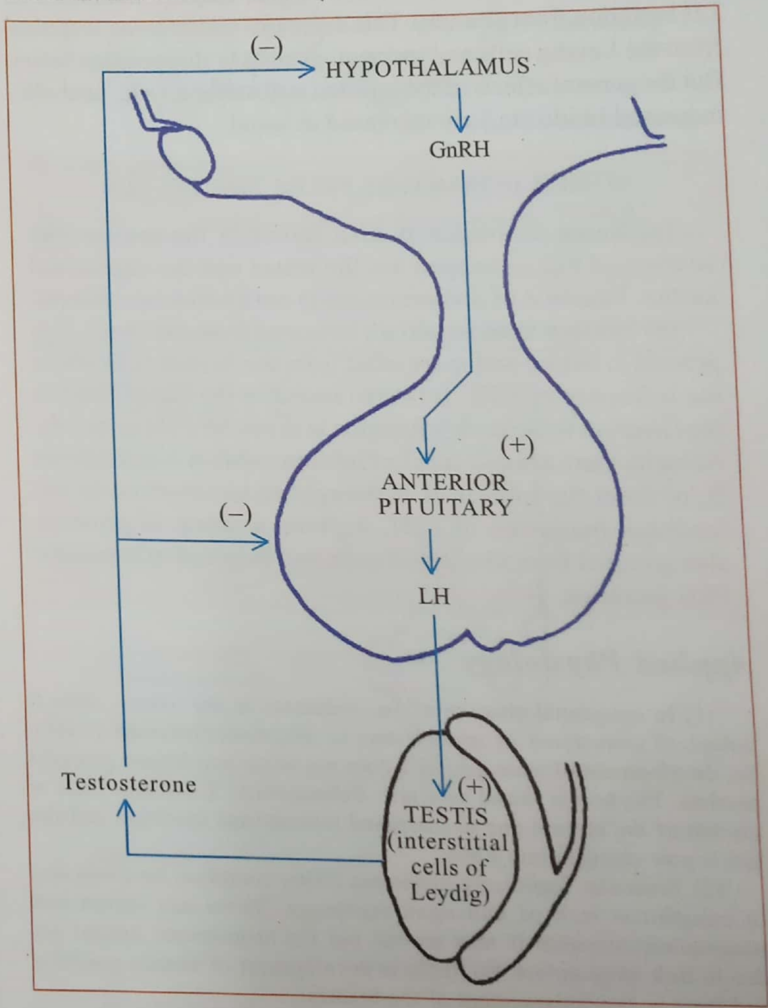

Fig. 10.4. *Regulation of testosterone secretion.*

GnRH from hypothalamus stimulates pituitary gonadotrophs to secrete LH (Luteinising hormone) (Fig. 10.4). LH then stimulates the interstitial cells of Leydig in testes to secrete testosterone.

GnRH : It is a decapeptide secreted from the mid-hypothalamic region (median eminence, arcuate nucleus and ventromedial N). GnRH is also found in other parts of the brain. GnRH acts on the pituitary gonadotrophs through its receptors and stimulates them to secrete LH and FSH (Follicle

Plasma Hormones

Most of the secreted hormones are bound to the gonadal steroid binding globulin (GBG) and only a small portion circulates freely in the plasma. The free hormone is responsible for the physiological actions.

Dihydrotestosterone is produced in some target organs. A small amount of oestrogen is also produced from testosterone in circulation. Daily output of androgens is about 4 to 9 mg in an adult male, which is mostly testosterone and the plasma level is about 0.65 μg/100ml. In females also, a small amount of androgens are secreted. Most of the testosterone is converted into 17-ketosteroid in liver. This source contribute 1/3rd of the 17-ketosteroid excreted in urine in an adult male, the rest is from the suprarenal cortex.

Functions of Testosterone

(1) Metabolic actions
- (a) Increases BMR.
- (b) Testosterone is strongly anabolic and it increases protein synthesis and prevents protein breakdown.
- (c) Helps to retain Na^+, K^+, Ca^{2+}, PO_4^{3-}, SO_4^{2-}, etc. along with water.

(2) On growth : Testosterone is responsible for the spurt of growth seen during adolescence. It is mainly due to stimulation of growth hormone secretion, protein anabolic effect and growth of bones.

At the same time the testosterone is also responsible for early epiphyseal closure in male, which arrests the growth in height.

(3) Testosterone causes development of secondary sexual characters in boys, *e.g.*, growth of beards, axillary hair, pubic hair, temporal recession of hair line, and so on (it brings about all the pubertal changes in boys, p. 367). It is responsible for growth of the external genitalia during adolescence. In adults it maintains the sex organs.

(4) It is responsible for the development of male psychology and aggressive behaviour.

(5) Testosterone is essential for male gametogenesis (spermatogenesis) and for this, a very high local concentration of testosterone is maintained inside the seminiferous tubules (see below). It is also responsible for motility of the sperms.

(6) It stimulates erythropoiesis.

(7) It is responsible for male libido, particularly at puberty and also in adults.

(8) In intrauterine life, testosterone from the foetal testes acts on foetal brain to develop the male psyche. It causes sex differentiation; development of the wolffian ducts into epididymis, vas deferens and seminal vesicles. External genitalia of male foetus also develop under its influence.

Mechanism of Action

Like all other steroid hormones, testosterone has intracellular receptors through which it regulates intracellular protein synthesis. Testosterone in some target organs is converted into dihydrotestosterone (DHT) by the enzyme 5α-reductase. This DHT is responsible for the development of prostate,

growth of facial, axill... of hair line. It also causes dev... genitalia and probably causes g...

Rest of the functions, *e.g.*, ana... male libido, development of th... internal genitalia, are due to tes...

Regulation of Secretion

(1) Secretion of testosterone... testes is caused by the HCG (H... from placenta. This testos... differentiation and for develo... male embryo.

(2) After birth, testosteron... adolescence. During adolesce... under the influence of GnRH (C...

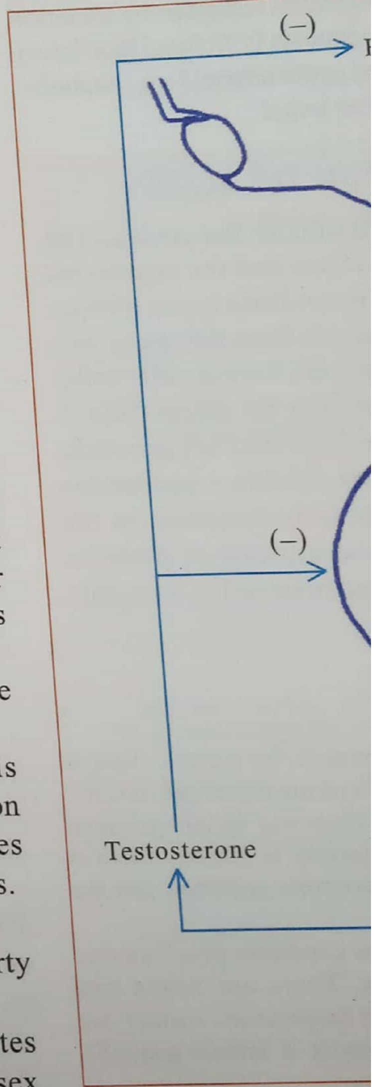

Fig. 10.4. *Re...*

GnRH from h... gonadotrophs to secre... LH then stimulates t... secrete testosterone...

GnRH : It is a... hypothalamic regio... ventromedial N). C... brain. GnRH acts c... receptors and stimu...

stimulating hormone). Secretion of GnRH occurs in the form of pulses (no steady plasma level). There is intermittent rise and fall, preventing down regulation of its receptors in pituitary.

LH : It is a glycoprotein hormone secreted from the pituitary gonadotrophs. It also has no steady plasma level and is secreted in pulses like the GnRH. 2 to 4 pulses occur within 6 hours. It increases production of testosterone in the Leydig cells (prolactin probably potentiates this action).

Testosterone feedback : Testosterone ultimately regulates its own secretion. It acts both at pituitary and at hypothalamus to cause feedback inhibition of GnRH and LH secretion (Inhibin leads to feedback inhibition of FSH).

Oestrogen from testes (see below) also inhibits LH secretion, this may be the role of the oestrogen secreted from the testes.

Injection of testosterone from outside leads to inhibition of LH secretion from pituitary. This decreases testosterone secretion from the Leydig cells and spermatogenesis is stopped (see later). But the general effects of the injected testosterone, (*e.g.*, anabolic, increased libido etc.) are increased as usual.

OTHER HORMONES FROM THE TESTES

(a) Some oestrogen is also found in the males. The sources of this oestrogen are the testes and the suprarenal cortex. Function of this oestrogen is not known (see above).

(b) **Inhibin** is an important hormone from the testes. It is protein in nature and is secreted from the Sertoli cells under the influence of FSH. It is also found in the antral fluid in the Graafian follicle. It's function is to inhibit FSH secretion. Actually there are two types of inhibin; inhibin A and inhibin B, of them the inhibin B is thought to be involved in the feedback inhibition of FSH. Activin, a group of proteins also secreted from the Sertoli cells and believed to stimulate FSH secretion.

Applied Physiology

(1) In congenital absence of 5α- reductase in the tissues, there is failure of conversion of testosterone to dihydrotestosterone (DHT). ... italia does not occur and female genitalia

UG - 6th Sem
Paper - C13T (Reproductive Physiology)
Dept. of Physiology

Ref. → ① Medical Physiology - Guyton & Hall
② " - Anil Baran Singha Mahapatra