The Male Reproductive System

The male reproductive system is composed of the testes, genital ducts, accessory glands, and penis. The dual function of the testis is to produce spermatozoa and hormones. The genital ducts and accessory glands produce secretions that, aided by smooth muscle contractions, conduct spermatozoa toward the exterior. These secretions also provide nutrients for spermatozoa while they are confined to the male reproductive tract. Spermatozoa and the secretions of the genital ducts and accessory glands make up the **semen** (from Latin, meaning seed), which is introduced into the female reproductive tract through the penis. Although testosterone is the main hormone produced in the testes, both testosterone and one of its metabolites, dihydrotestosterone, are necessary for the physiology of men.

Testes

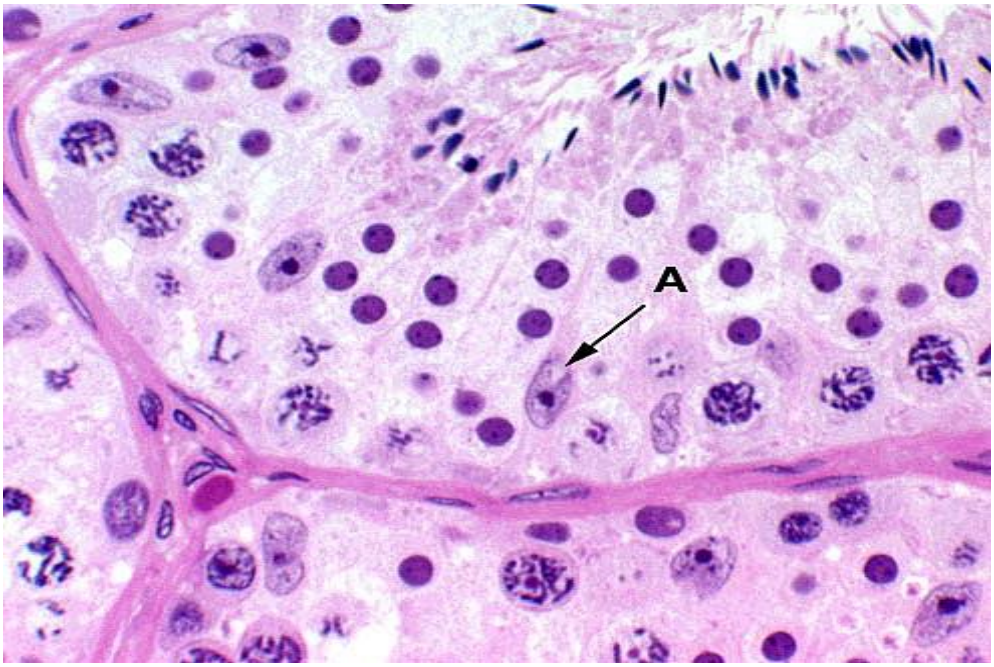
Each testis is surrounded by a thick capsule of dense connective tissue, the **tunica albuginea.** The tunica albuginea is thickened on the posterior surface of the testis to form the **mediastinum testis,** from which fibrous septa penetrate the gland, dividing it into about 250 pyramidal compartments called the **testicular lobules**. These septa are incomplete, and there is frequent intercommunication between the lobules. Each lobule is occupied by one to four **seminiferous tubules** enmeshed in a web of loose connective tissue that is rich in blood and lymphatic vessels, nerves, and **interstitial cells,** also known as **Leydig cells.** Seminiferous tubules produce male reproductive cells, the spermatozoa, whereas interstitial cells secrete testicular androgens. During embryonic development the testes develop retroperitoneally in the dorsal wall of the abdominal cavity. They migrate during fetal development and become positioned within the scrotum, at the ends of the spermatic cords. Because of this migration, each testis carries with it a serous sac, the **tunica vaginalis,** derived from the peritoneum. The tunic consists of an outer parietal layer and an inner visceral layer, covering the tunica albuginea on the anterior and lateral sides of the testis.

Seminiferous Tubules

Spermatozoids are produced in the seminiferous tubules at a daily rate of about 2×10^8 in the adult. Each testicle has 250-1000 seminiferous tubules that measure about 150-250 μm in diameter and 30-70 cm in length. The combined length of the tubules of one testis is about 250 m. The tubules are convoluted and have the form of loops at whose ends the lumen narrows and continues in short segments, known as **straight tubules,** or **tubuli recti**. These tubules connect the seminiferous tubules to an anastomosing labyrinth of epithelium-lined channels, the **rete testis.** About 10-20 **ductuli efferentes** connect the rete testis to the cephalic portion of the **epididymis**.

The seminiferous tubules are lined with a complex stratified epithelium called **germinal** or **seminiferous epithelium.** Their outer wall is surrounded by a well-defined basal lamina and a fibrous connective tissue consisting of several layers of fibroblasts. The innermost layer, adhering to the basal lamina, consists of flattened **myoid cells**, which have characteristics of smooth muscle. Interstitial (Leydig) cells occupy much of the space between the seminiferous tubules.

The seminiferous epithelium consists of two types of cells: **Sertoli,** or **supporting, cells** and cells that constitute the **spermatogenic lineage**. The cells of the spermatogenic lineage are stacked in four to eight layers; their function is to produce spermatozoa. The production of spermatozoa is called **spermatogenesis,** a process that includes cell division through mitosis and meiosis and the final differentiation of spermatozoids, which is called **spermiogenesis.**



Spermatogenesis

Spermatogenesis is the process by which spermatozoids are formed. It begins with a primitive germ cell, the **spermatogonium** (Gr. *sperma* + *gone,* generation), which is a relatively small cell, about 12 μm in diameter, situated next to the basal lamina of the epithelium. At sexual maturity, spermatogonia begin dividing by mitosis, producing successive generations of cells. The newly formed cells can follow one of two paths: they can continue dividing as stem cells, also called **type A spermatogonia,** or they can differentiate during progressive mitotic cycles to become **type B spermatogonia**. Type B spermatogonia are progenitor cells that will differentiate into **primary spermatocytes**. The primary spermatocyte has 46 (44 + XY) chromosomes and 4N of DNA. (N denotes either the haploid set of chromosomes [23 chromosomes in humans] or the amount of DNA in this set.) Soon after their formation, these cells enter the

prophase of the first meiotic division. Because this prophase takes about 22 days, the majority of spermatocytes seen in sections will be in this phase. The primary spermatocytes are the largest cells of the spermatogenic lineage and are characterized by the presence of chromosomes in various stages of the coiling process within their nuclei.

From this first meiotic division arise smaller cells called **secondary spermatocytes** with only 23 chromosomes (22 + X or 22 + Y). This decrease in number (from 46 to 23) is accompanied by a reduction in the amount of DNA per cell (from 4N to 2N). Secondary spermatocytes are difficult to observe in sections of the testis because they are short-lived cells that remain in interphase very briefly and quickly enter into the second meiotic division. Division of each secondary spermatocyte results in two cells that contain 23 chromosomes, the **spermatids**. Because no S phase (DNA synthesis) occurs between the first and second meiotic divisions of the spermatocytes, the amount of DNA per cell in this second division is reduced by half, forming haploid (1N) cells. The meiotic process therefore results in the formation of cells with a haploid number of chromosomes. With fertilization, the normal diploid number is again attained.

Spermiogenesis

Spermiogenesis is the final stage of production of spermatozoids. During spermiogenesis the spermatids are transformed into spermatozoa, cells that are highly specialized to deliver male DNA to the ovum. No cell division occurs during this process.

The spermatids can be distinguished by their small size (7-8 μm in diameter) and by nuclei with areas of condensed chromatin. Their position within the seminiferous tubules is close to the lumen. Spermiogenesis is a complex process that includes formation of the acrosome, condensation and elongation of the nucleus, development of the flagellum, and loss of much of the cytoplasm. The end result is the mature spermatozoon, which is then released into the lumen of the seminiferous tubule. Spermiogenesis can be divided into three phases.

The Golgi Phase

The cytoplasm of spermatids contains a prominent Golgi complex near the nucleus, mitochondria, a pair of centrioles, free ribosomes, and tubules of smooth endoplasmic reticulum. Small periodic acid Schiff (PAS)-positive granules called **proacrosomal granules** accumulate in the Golgi complex. They subsequently coalesce to form a single **acrosomal granule** within a membrane-limited **acrosomal vesicle**. The centrioles migrate to a position near the cell surface and opposite the forming acrosome. The flagellar axoneme begins to form, and the centrioles migrate back toward the nucleus, spinning out the axonemal components as they move.

The Acrosomal Phase

The acrosomal vesicle spreads to cover the anterior half of the condensing nucleus and is then known as the **acrosome**. The acrosome contains several hydrolytic enzymes, such as hyaluronidase, neuraminidase, acid phosphatase, and a protease that has trypsin-like activity. The acrosome thus serves as a specialized type of lysosome. These enzymes are known to dissociate cells of the corona radiata and to digest the zona pellucida, structures that surround the oocytes. When spermatozoa encounter an oocyte, the outer membrane of the acrosome fuses with the plasma membrane of a spermatozoon at several sites, liberating the acrosomal enzymes to the extracellular space. This process, the **acrosomal reaction,** is one of the first steps in fertilization

During this phase of spermiogenesis, the nucleus of the spermatid becomes oriented toward the base of the seminiferous tubule, and the axoneme projects into its lumen. In addition, the nucleus becomes more elongated and condensed. One of the centrioles grows concomitantly, forming the **flagellum.** Mitochondria aggregate around the proximal part of the flagellum, forming a thickened region known as the **middle piece**.

The Maturation Phase

Residual cytoplasm is shed and phagocytosed by Sertoli cells, and the spermatozoa are released into the lumen of the tubule.

Sertoli Cells

The **Sertoli cells** are important for the function of the testes. These **cells** are elongated pyramidal cells that partially envelop cells of the spermatogenic lineage. The bases of the Sertoli cells adhere to the basal lamina, and their apical ends frequently extend into the lumen of the seminiferous tubule. In the light microscope, the outlines of Sertoli cells appear poorly defined because of the numerous lateral processes that surround spermatogenic cells. Studies with the electron microscope reveal that these cells contain abundant smooth endoplasmic reticulum, some rough endoplasmic reticulum, a well-developed Golgi complex, and numerous mitochondria and lysosomes. The nucleus, which is often triangular in outline, possesses numerous infoldings and a prominent nucleolus; it exhibits little heterochromatin.

Adjacent Sertoli cells are bound together by occluding junctions at the basolateral part of the cell, forming a **blood-testis barrier**. The spermatogonia lie in a **basal compartment** that is situated below the barrier. During spermatogenesis, some of the cells resulting from division of spermatogonia somehow traverse these junctions and come to lie in the **adluminal compartment** situated above the barrier. Spermatocytes and spermatids lie within deep invaginations of the lateral and apical margins of the Sertoli cells, above the barrier. As the flagellar tails of the spermatids develop, they appear as tufts extending from the apical ends of the Sertoli cells. Sertoli cells are also

connected by gap junctions that provide ionic and chemical coupling of the cells; this may be important in coordinating the cycle of the seminiferous epithelium described above.

Sertoli cells in humans and in other animals do not divide during the reproductive period. They are extremely resistant to adverse conditions such as infection, malnutrition, and x-irradiation and have a much better rate of survival after these insults than do cells of the spermatogenic lineage.

Sertoli cells have several functions:

1-**Support, protection, and nutritional regulation of the developing spermatozoa.** As mentioned above, the cells of the spermatogenic series are interconnected via cytoplasmic bridges. This network of cells is physically supported by extensive cytoplasmic ramifications of the Sertoli cells. Because spermatocytes, spermatids, and spermatozoa are isolated from the blood supply by the bloodâ€“testis barrier, these spermatogenic cells depend on the Sertoli cells to mediate the exchange of nutrients and metabolites. The Sertoli cell barrier also protects the developing sperm cells from immunological attack.

2-**Phagocytosis.** During spermiogenesis, excess spermatid cytoplasm is shed as residual bodies. These cytoplasmic fragments are phagocytosed and digested by Sertoli cell lysosomes.

3-Secretion. Sertoli cells continuously secrete into the seminiferous tubules a fluid that flows in the direction of the genital ducts and is used for sperm transport. Secretion of an **ABP** by Sertoli cells is under the control of follicle-stimulating hormone (FSH) and testosterone and serves to concentrate testosterone in the seminiferous tubule, where it is necessary for spermatogenesis. Sertoli cells can convert testosterone to estradiol. They also secrete a peptide called **inhibin,** which suppresses synthesis and release of FSH in the anterior pituitary glan.

4-**Production of the anti-mollerian hormone.** Anti- mÍ¼llerian hormone (AMH, also called **mollerian-inhibiting hormone**), a glycoprotein that is a member of the transforming growth factor- family, acts during embryonic development to promote regression of the mÍ¼llerian (paramesonephric) ducts in the male fetus; testosterone fosters the development of structures derived from the Wolffian (mesonephric) ducts.

5-**The blood testis barrier.** The existence of a barrier between the blood and the interior of the seminiferous tubules accounts for the fact that few substances from the blood are found in the testicular fluid. The testicular capillaries are fenestrated and permit passage of large molecules. Spermatogonia have free access to materials found in blood. However, occluding junctions between the Sertoli cells form a barrier to the transport of large molecules along the space between Sertoli cells. Thus, the more advanced stages of spermatogenesis are protected from

blood-borne products protecting male germ cells against blood-borne noxious agents.

6-**Production of inhibin B.** Inhibin B inhibits the production of FSH by the hypophysis.

Interstitial Tissue

The interstitial tissue of the testis is an important site of production of androgens. The spaces between the seminiferous tubules in the testis are filled with connective tissue, nerves, fenestrated capillaries, and lymphatic vessels. The connective tissue consists of various cell types, including fibroblasts, undifferentiated connective cells, mast cells, and macrophages. During puberty, an additional cell type becomes apparent; it is either rounded or polygonal in shape and has a central nucleus and an eosinophilic cytoplasm rich in small lipid droplets. These are the **interstitial,** or **Leydig,** cells of the testis, and they have the characteristics of steroid-secreting cells. These cells produce the male hormone **testosterone** by enzymes present in mitochondria and in the smooth endoplasmic reticulum. Testosterone is important for spermatogenesis, sexual differentiation during embryonic and fetal development, and control of gonadotropin secretion. Dihydrotestosterone, a metabolite of testosterone secreted in small amounts by the testicle, is produced locally by enzymatic transformation of testosterone in several tissues. It acts on many organs and tissues of the body during puberty and adulthood (eg, muscle, hair pattern, and hair growth). Androgen-producing interstitial cell tumors can cause precocious puberty in males.

Both the activity and the number of the interstitial cells depend on hormonal stimuli. During human pregnancy, placental gonadotropic hormone passes from the maternal blood to the male fetus, stimulating the abundant fetal testicular interstitial cells that produce androgenic hormones. The presence of these hormones is required for the embryonic differentiation of the male genitalia. The embryonic interstitial cells remain fully differentiated for up to 4 months of gestation; they then regress, with an associated decrease in testosterone synthesis. They remain quiescent throughout the rest of the pregnancy and up to the prepubertal period, when they resume testosterone synthesis in response to the stimulus of luteinizing hormone (LH) from the hypophysis.

Genital Ducts

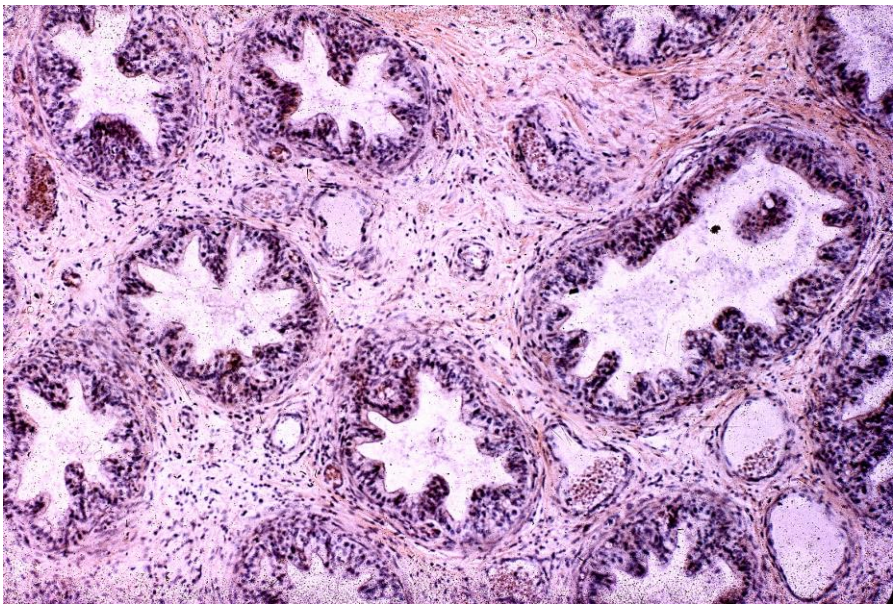
The intratesticular genital ducts are the **tubuli recti** (straight tubules), the **rete testis,** and the **ductuli efferentes**. These ducts carry spermatozoa and liquid from the seminiferous tubules to the ductus epididymidis.

Most seminiferous tubules are in the form of loops, both ends of which join the rete

testis by structures known as **tubuli recti.** These tubules are recognized by the gradual loss of spermatogenic cells, with an initial segment in which only Sertoli cells remain to form their walls, followed by a main segment consisting of cuboidal epithelium supported by a dense connective tissue sheath.

Tubuli recti empty into the **rete testis,** contained within the mediastinum, a thickening of the tunica albuginea. The rete testis is a highly anastomotic network of channels lined with cuboidal epithelium.

From the rete testis extend 10-20 **ductuli efferentes** . They have an epithelium composed of groups of nonciliated cuboidal cells alternating with ciliated cells that beat in the direction of the epididymis. This gives the epithelium a characteristic scalloped appearance. The nonciliated cells absorb much of the fluid secreted by the seminiferous tubules. The activity of ciliated cells and fluid absorption create a fluid flow that sweeps spermatozoa toward the epididymis. A thin layer of circularly oriented smooth muscle cells is seen outside the basal lamina of the epithelium. The ductuli efferentes gradually fuse to form the ductus epididymidis of the epididymis.

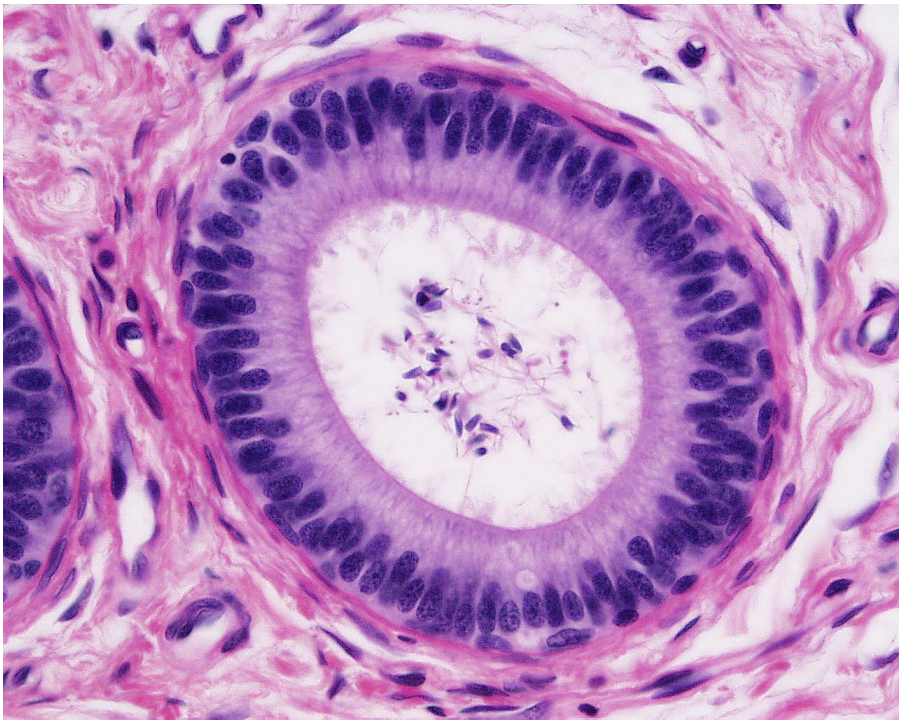


Excretory Genital Ducts

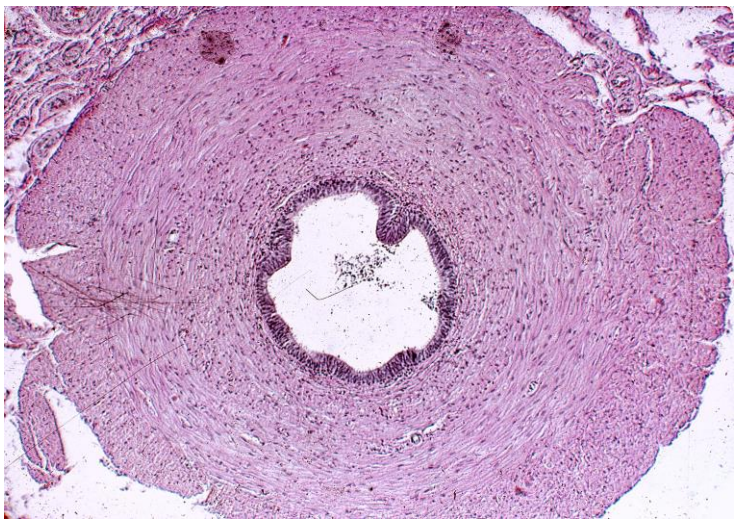
Excretory genital ducts transport the spermatozoa produced in the testis toward the penile meatus. These ducts are the **ductus epididymidis,** the **ductus** (**vas**) **deferens,** and the **urethra.**

The ductus epididymidis is a single highly coiled tube about 4-6 m in length. Together with surrounding connective tissue and blood vessels, this long canal forms the body and tail of the **epididymis.** It is lined with pseudostratified columnar epithelium composed of rounded basal cells and columnar cells. These cells are

supported on a basal lamina surrounded by smooth muscle cells, whose peristaltic contractions help to move the sperm along the duct, and by loose connective tissue rich in blood capillaries. Their surface is covered by long, branched, irregular microvilli called **stereocilia.** The epithelium of the ductus epididymidis participates in the uptake and digestion of residual bodies that are eliminated during spermatogenesis.



From the epididymis the **ductus** (**vas**) **deferens,** a straight tube with a thick, muscular wall, continues toward the prostatic urethra and empties into it. It is characterized by a narrow lumen and a mucosa with longitudinal folds, covered along most of its extent by pseudostratified columnar epithelium with stereocilia. The lamina propria is rich in elastic fibers, and the thick muscular layer consists of longitudinal inner and outer layers separated by a circular layer. The abundant smooth muscle produces strong peristaltic contractions that participate in the expulsion of the spermatozoa during ejaculation.

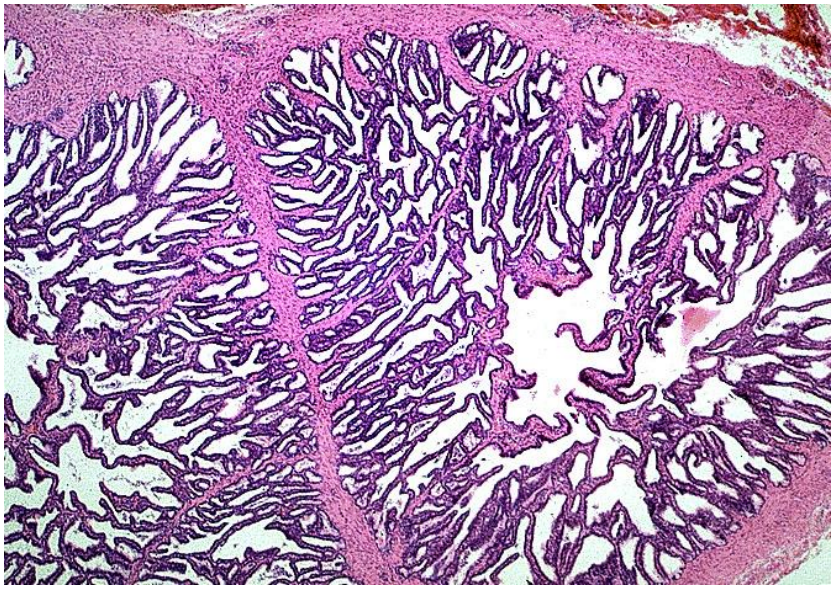


The ductus deferens forms part of the spermatic cord, which includes the testicular artery, the pampiniform plexus, and nerves. Before it enters the prostate, the ductus deferens dilates, forming a region called the **ampulla**. In this area, the epithelium becomes thicker and extensively folded. At the final portion of the ampulla, the seminal vesicles join the duct. From there on, the ductus deferens enters the prostate, opening into the prostatic **urethra.** The segment entering the prostate is called the **ejaculatory duct.** The mucous layer of the ductus deferens continues through the ampulla into the ejaculatory duct, but the muscle layer ends after the ampulla.

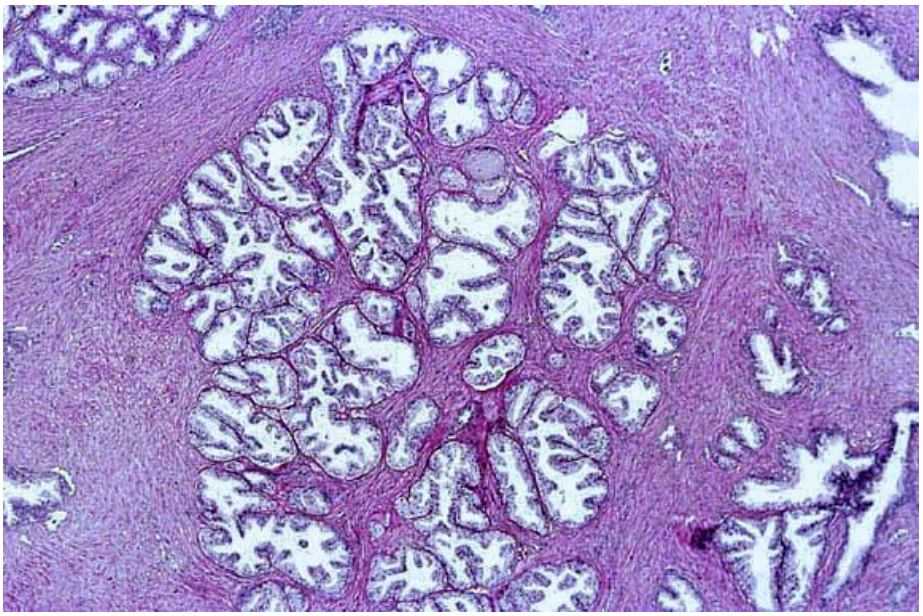
Accessory Genital Glands

The accessory genital glands produce secretions that are essential for the reproductive function in men. The accessory genital glands are the **seminal vesicles,** the **prostate,** and the **bulbourethral glands.**

The **seminal vesicles** consist of two highly tortuous tubes about 15 cm in length. When the organ is sectioned, the same tube is observed in different orientations. It has a folded mucosa that is lined with cuboidal or pseudostratified columnar epithelium rich in secretory granules. These granules have ultrastructural characteristics similar to those found in protein-synthesizing cells. The lamina propria of the seminal vesicles is rich in elastic fibers and surrounded by a thin layer of smooth muscle. The seminal vesicles are not reservoirs for spermatozoa. They are glands that produce a viscid, yellowish secretion that contains spermatozoa-activating substances such as carbohydrates, citrate, inositol, prostaglandins, and several proteins. The carbohydrates, of which **fructose** is the most abundant, are the source of energy for sperm motility. Seventy percent of human ejaculate originates in the seminal vesicles. The height of the epithelial cells of the seminal vesicles and the degree of activity of the secretory processes are dependent on testosterone levels.



The **prostate** is a collection of 30-50 branched tubuloalveolar glands. Their ducts empty into the prostatic urethra, which crosses the prostate. The prostate has three distinct zones: The **central zone** occupies 25% of the gland's volume. Seventy percent of the gland is formed by the **peripheral zone,** which is the major site of prostatic cancer. The **transition zone** is of medical importance because it is the site at which most benign prostatic hyperplasia originates. The tubuloalveolar glands of the prostate are formed by a cuboidal or a columnar pseudostratified epithelium. An exceptionally rich fibromuscular stroma surrounds the glands. The prostate is surrounded by a fibroelastic capsule rich in smooth muscle. Septa from this capsule penetrate the gland and divide it into lobes that are indistinct in adult men.



Benign prostatic hypertrophy is present in 50% of men more than 50 years of age and in 95% of men more than 70 years of age. It leads to obstruction of the urethra with clinical symptoms in only 5-10% of cases.

Penis

The main components of the penis are three cylindrical masses of erectile tissue, plus the urethra, surrounded by skin. Two of these cylinders, the **corpora cavernosa of the penis** are placed dorsally. The other the **corpus cavernosum of the urethra,** or **corpus spongiosum** is ventrally located and surrounds the urethra. At its end it dilates, forming the **glans penis**. Most of the penile urethra is lined with pseudostratified columnar epithelium; in the glans penis, it becomes stratified squamous epithelium. Mucus-secreting **glands of Littre** are found throughout the length of the penile urethra.

The prepuce is a retractile fold of skin that contains connective tissue with smooth muscle in its interior. Sebaceous glands are present in the internal fold and in the skin that covers the glans.

The corpora cavernosa are covered by a resistant layer of dense connective tissue, the **tunica albuginea**. The corpora cavernosa of the penis and the corpus cavernosum of the urethra are composed of erectile tissue. This is a tissue with a large number of venous spaces lined with endothelial cells and separated by trabeculae of connective tissue fibers and smooth muscle cells.

The arterial supply of the penis derives from the internal pudendal arteries, which give rise to the deep arteries and the dorsal arteries of the penis. Deep arteries branch to form nutritive and helicine arteries. Nutritive arteries supply oxygen and nutrients to the trabeculae, and helicine arteries empty directly into the cavernous spaces (erectile tissue). There are arteriovenous shunts between the helicine arteries and the deep dorsal vein.

Penile erection is a hemodynamic event that is controlled by neural input to both arterial muscle and smooth muscle in the walls of the vascular spaces in the penis; in the flaccid state, there is minimal blood flow in the penis. The nonerect state is maintained by both the intrinsic tone of penile smooth muscle and the tone induced by continuous sympathetic input. Erection occurs when vasodilator impulses of parasympathetic origin cause relaxation of the penile vessels and cavernous smooth muscle. Vasodilatation also involves the concomitant inhibition of sympathetic vasoconstrictor impulses to penile tissues. Opening of the penile arteries and cavernous spaces accounts for the increase in blood flow, the filling of the cavernous spaces, and the resulting rigidity of the penis. Contraction and relaxation of corpora cavernosa depend on intracellular calcium, which in turn is modulated by guanosine monophosphate.

After ejaculation and orgasm, parasympathetic activity declines, and the penis returns to its flaccid state.