

Microscopic Anatomy

MALE REPRODUCTIVE SYSTEM

I. Introduction

The male reproductive system (Figure 1) consists of a series of glandular, muscular, and ciliated tubes and diverticula dedicated to the production, storage, nourishment, and activation of spermatozoa, and to their transport into the female reproductive tract. There are three products of the system: the germ cells, the seminal fluid that bathes them when they are emitted, and hormones that regulate sperm production, development of secondary sex characteristics, and secretory activity in the tract.

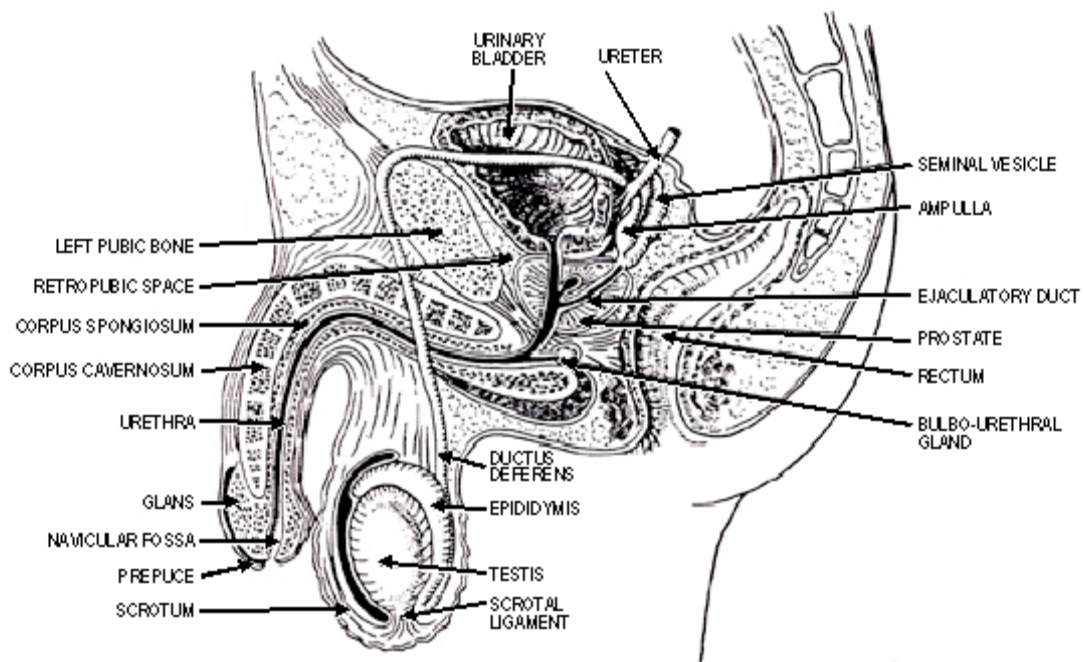


Figure 1: Median sagittal section of the male pelvis.

Sperm are produced in extraordinary quantities; an ejaculate may contain several hundred million sperm cells! This appears to be highly inefficient overproduction considering that less than 100 individual sperm cells will ever approach an ovum and only one will succeed in fertilizing it. Yet, there must be a selective advantage to the method because it has been perpetuated throughout evolutionary history.

II. Organs and Ducts of the Male Reproductive System

Sperm are produced in the **seminiferous tubules** in the **testes**. The lumens of these tubules are continuous with the lumens of the **straight tubules**, the **rete testes**, the **effluent ductules**, the **epididymis**, the **vas deferens**, and the **urethra** (Figure 1 and Table 1). Thus, once a spermatozoon makes it into the lumen of a seminiferous tubule, it has a continuous path to the

urethra and the outside world. However, It cannot traverse this pathway until it matures and is specifically released from its storage and maturation site, the **epididymis**.

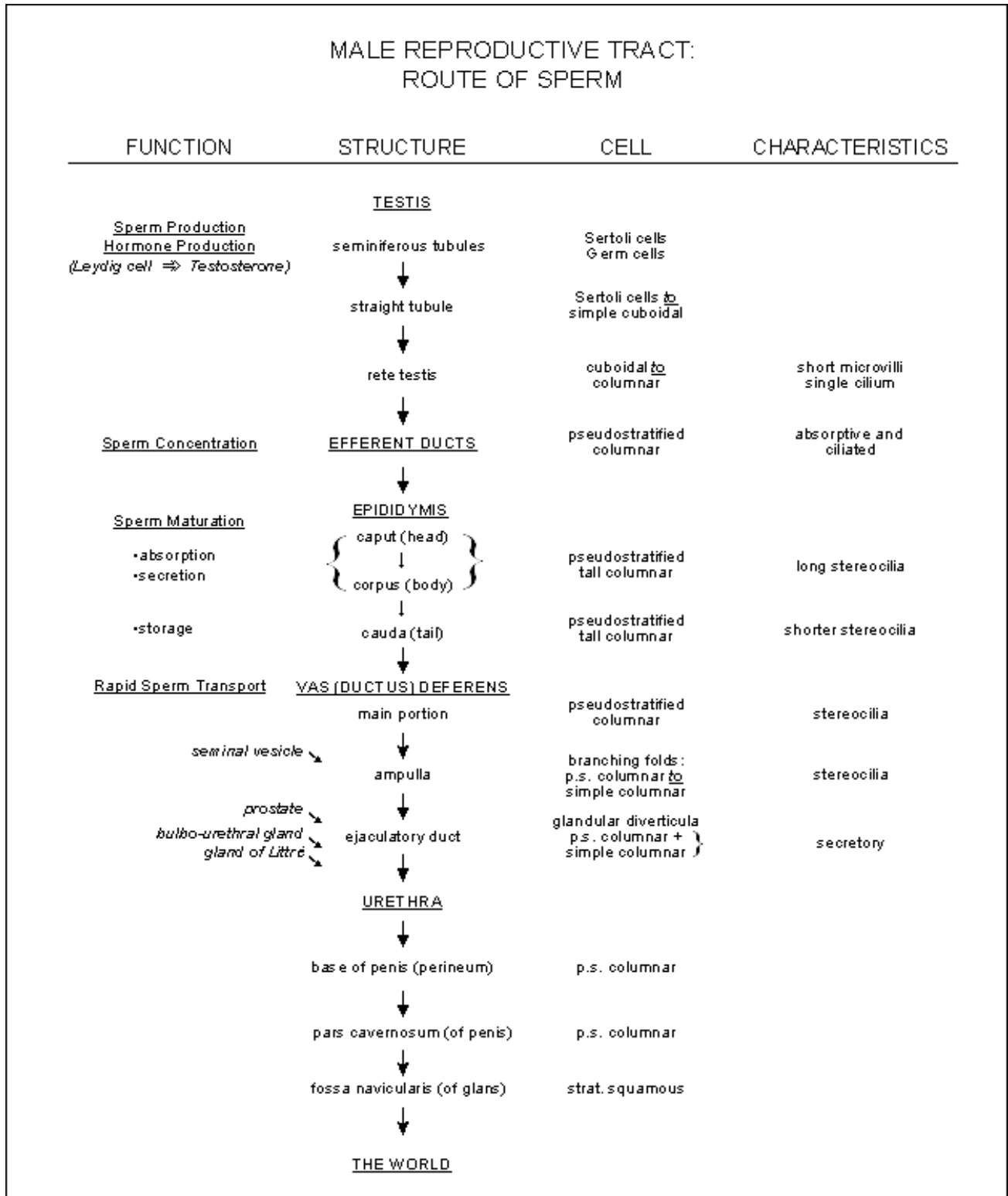


Table 1: Duct system of the male reproductive tract.

A. The Testes

1. Structure and cell types

The testes have both **exocrine** and **endocrine** functions: as exocrine glands they produce sperm, and as endocrine glands they synthesize and secrete steroid and glycoprotein hormones, including **testosterone**. Exocrine fluids secreted by the testis and other structures of the male genital duct system provide a medium for transport, nutrition, and further maturation of the sperm. Steroid hormones, primarily testosterone and dihydrotestosterone, are essential for the regulation of growth and development of spermatozoa and for the maintenance of accessory reproductive glands. These hormones also function in the development and maintenance of secondary sexual characteristics and, to some extent, sexual behavior.

In the adult human male, each testis is an ovoid structure approximately 4.5 cm in length, 2.5 cm in width and 3 cm in diameter. During fetal development, the testes descend into the **scrotum** (Figure 1), a cutaneous sac in which the testes and epididymides are located. The testes are external to the body cavity because spermatogenesis only occurs at 35 °C (core temp = 37 °C). An additional thermoregulatory mechanism is the arrangement of blood vessels: the testicular artery becomes very convoluted as it nears the testis and becomes surrounded by a pampiniform venous plexus. This permits the cooling of arterial blood prior to its entry into the testis.

The testes are suspended within the scrotum by the **spermatic cord**, which consists of the ductus deferens, arteries, pampiniform plexus of veins, nerve fibers and lymphatic vessels. Within the scrotum the testes are invested anteriorly and laterally in a peritoneal-derived serous sac, the **tunica vaginalis** that consists of an outer parietal layer and an inner visceral layer. This "tunic" protects the testes by allowing them to slide easily within the scrotum.

Each testis is encased in a dense fibrous capsule, the **tunica albuginea**. The tunica albuginea thickens posteriorly and projects into the interior of the testis forming the **mediastinum testis**. Blood vessels, lymphatics and nerves enter and exit the testis through the mediastinum. From the mediastinum, many thin fibrous **septa** of connective tissue pass into the interior of the testis, dividing it into about 250 pyramidal-shaped **lobules**. Each lobule contains one to four highly convoluted **seminiferous tubules**. **Spermatozoa** (sperm cells) are produced within the seminiferous tubules. Each tubule is 30-80 cm long, and though not continuous, together they comprise nearly 250 meters of sperm-producing ductules per testis. Each tubule is reinforced and supported by sheaths of connective tissue and smooth muscle, the latter serving to move mature sperm out of the tubules and into the duct system.

The coiled **seminiferous tubules** are lined with a specialized epithelium, consisting of two distinct classes of cells: **spermatogenic cells** (**spermatogonia**, **spermatocytes**, **spermatids**, and mature **spermatozoa**) and supporting **Sertoli** cells (Figure 2). In the adult, the Sertoli cells are non-proliferating whereas the spermatogenic cells undergo mitotic and meiotic divisions to produce spermatozoa.

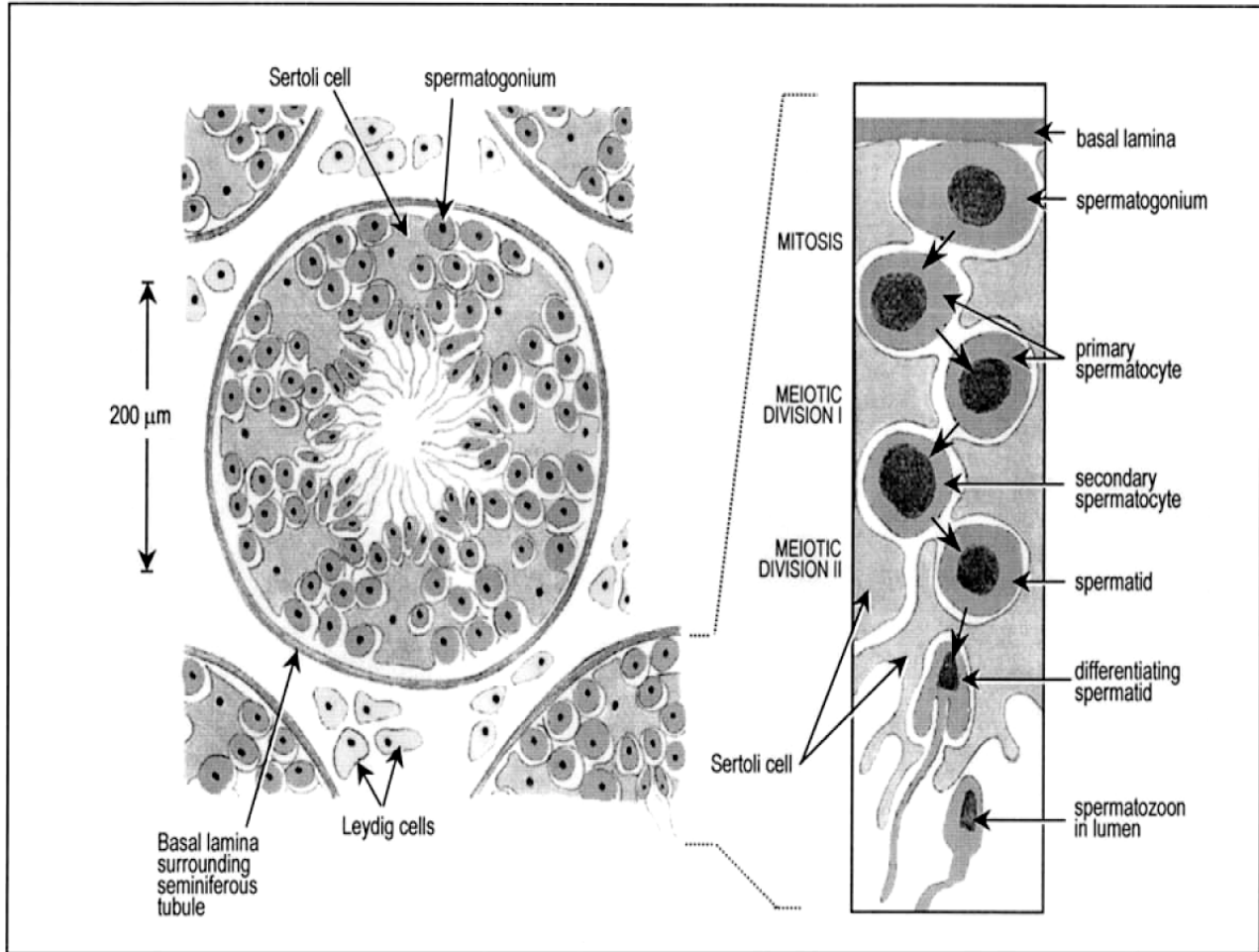


Figure 2: Schematic diagram of a cross section through a seminiferous tubule.

The **Sertoli cells** line the seminiferous tubules, one edge fixed at the basal lamina and the opposite edge extending to the lumen. These large cells constitute the basic epithelial cell of the seminiferous epithelium regardless of whether germ cells are present or not (as in certain pathological conditions). Sertoli cells perform many functions, including mechanical support and nutrition of the germ cells, control of germ cell migration and release into the lumen, secretion of androgen binding protein (ABP) and inhibin, phagocytosis of degenerating germ cells, and formation of the “blood-testis barrier”. In terms of this blood-testis barrier, the seminiferous epithelium is compartmentalized into **basal** and **adluminal compartments** by **zonula occludens (tight junctions)** between the basolateral processes of adjacent Sertoli cells. Mitotically replicating germ cells (**spermatogonia**) are located only in the basal compartment; whereas meiotically active germ cells (primary and secondary **spermatocytes**), morphologically differentiating germ cells (**spermatids**), and mature **spermatozoa** are located at increasingly higher levels of the adluminal compartment. The blood-testis barrier isolates spermatocytes, spermatids and mature sperm from the body’s immune system and thus prevents the production of sperm-specific antibodies. In addition, recent work with genetically modified animals has highlighted the importance of junctional complexes for the proper functioning of the testis. Male mice that do not express a testis-specific occludin (a tight junction protein), have testes that

appear normal until puberty. Thereafter, the seminiferous tubule literally falls apart, and these animals are completely infertile.

Communicating junctions (gap junctions) between adjacent Sertoli cells and between Sertoli cells and the germ cells are also critical in the proper functioning of the seminiferous tubules. While the importance of gap junctions in the function of the testis has been recognized for many years, recent work demonstrates this convincingly. Mice that are null for a particular gap junction protein are completely infertile due to the absence of bidirectional signaling between developing germ cells and the supporting Sertoli cells.

In the seminiferous epithelium the basal layer of cells (spermatogonia and the base of Sertoli cells) rests on a well-defined basal lamina that separates the lamina propria from the tubule epithelium. Immediately beneath this basal lamina are a few layers of modified contractile fibroblasts called **myoid cells** that exhibit rhythmic contractions, aiding in the movement of spermatozoa and fluids through the seminiferous tubules. .

2. Endocrine secretion

Leydig cells and **Sertoli cells** are the major endocrine cells of the testis. As described above, the Sertoli cells are within the seminiferous tubules, whereas Leydig cells are located in the connective tissue stroma surrounding the seminiferous tubules (Figure 2). Leydig cells, which synthesize the androgenic sex hormone **testosterone**, possess a large spherical nucleus with one or two prominent nucleoli. The cytoplasm is characterized by lipid-containing vacuoles and an abundance of smooth endoplasmic reticulum, typical features of steroid-secreting cells (such as you have previously observed in the adrenal cortex). The synthesis and release of testosterone is under anterior pituitary control via **luteinizing hormone (LH)**. Within the first trimester of fetal development, Leydig cells differentiate and secrete testosterone, necessary for the development of the male reproductive tract. Following this period, the Leydig cells involute and remain involuted until puberty. At puberty, the Leydig cells synthesize and secrete androgens in response to LH. Sertoli cells, in response to follicle stimulating hormone (**FSH**) from the anterior pituitary, synthesize and secrete **androgen binding protein (ABP)**, which binds testosterone, and this complex is released into the lumen of the seminiferous tubule.

3. Sperm Production/Sperm Structure

The compact and highly efficient spermatozoon is the end result of a unique series of intracellular differentiations and macromolecular alterations called **spermatogenesis**. These developmental events provide for perpetuation of the genetic information in future generations, but, at the same time, they determine the sperm's own ultimate demise as an independent cell. An extraordinary economy is evidenced during the later stages of spermatogenesis as the metabolic activities of the spermatid are shut down. The cell is reduced, by a series of radical alterations, to a semi-solid, structurally compact apparatus, geared only to conveying its tightly packaged payload of genetic material over quite long distances, and often through hostile environments, to (and into) the correct target, the egg. The cellular context of the process of spermatogenesis is centrally important. There are 4 to 5 layers of germ cells at different stages of development (Figure 2) grouped into predictable cellular associations and in close contact with Sertoli cells.

The arrangement of Sertoli and germ cells in the seminiferous tubule arises from several fundamental characteristics of spermatogenesis. First, the **stem cells (spermatogonia)** in the basal compartment of the seminiferous tubule supply a constantly renewable source of germ cells. Thus, some spermatogonia are considered to be quiescent "reserve" stem cells, whereas others divide mitotically to give rise to **primary spermatocytes**. Meiosis then takes place, resulting in a reduction (halving) of chromosome numbers, a requirement of gamete-forming cells (Figure 3). The meiotic process leads to the segregation of the diploid chromosome complement, derived from the mixing of haploid paternal and maternal chromosome sets, into two haploid sets that are passed on to the gametes. Thus, the diploid complement is 44 autosomes, and an X and a Y chromosome. At meiosis, equal numbers of sperm are produced containing 22 autosomes +X and 22 autosomes +Y. Each sperm chromosome is equivalent to one chromatid (Figure 3). Intercellular bridges connect spermatogenic cells in all animal species examined. These bridges are thought to be influential in determining subsequent meiotic and post-meiotic events. The syncytia that are formed comprise clones of 2 to 100 or more spermatogenic cells in different stages of proliferation. When the differentiation is triggered in a syncytial clone, its component cells all differentiate synchronously. Although both mitosis and meiosis occur in germ cells during spermatogenesis, the cell divisions (cytokinesis) are incomplete, leading to linked cohorts of cells developing coordinately (Figure 3). The differentiation proceeds on an invariant timetable. This holds for the initiation of stem cell division by any individual stem cell in the basal compartment (i.e., each spermatogonial stem cell will initiate mitosis every 16 days in the human). A rigidly fixed timetable is also found for the duration of each stage and substage of spermatogenesis. This means that differentiating spermatogenic cells are not randomly arranged along the seminiferous tubules, but rather appear in specific associations or stages. There are 6 stages in humans (that you are NOT required to learn) occurring in irregularly shaped regions in the tubules as illustrated in images in your text and in the Powerpoint lecture. Thus, small regions of a seminiferous tubule observed in pictures or with your glass slides will not show all stages of sperm development. So, with your slides look around to see the various types of differentiating cells.

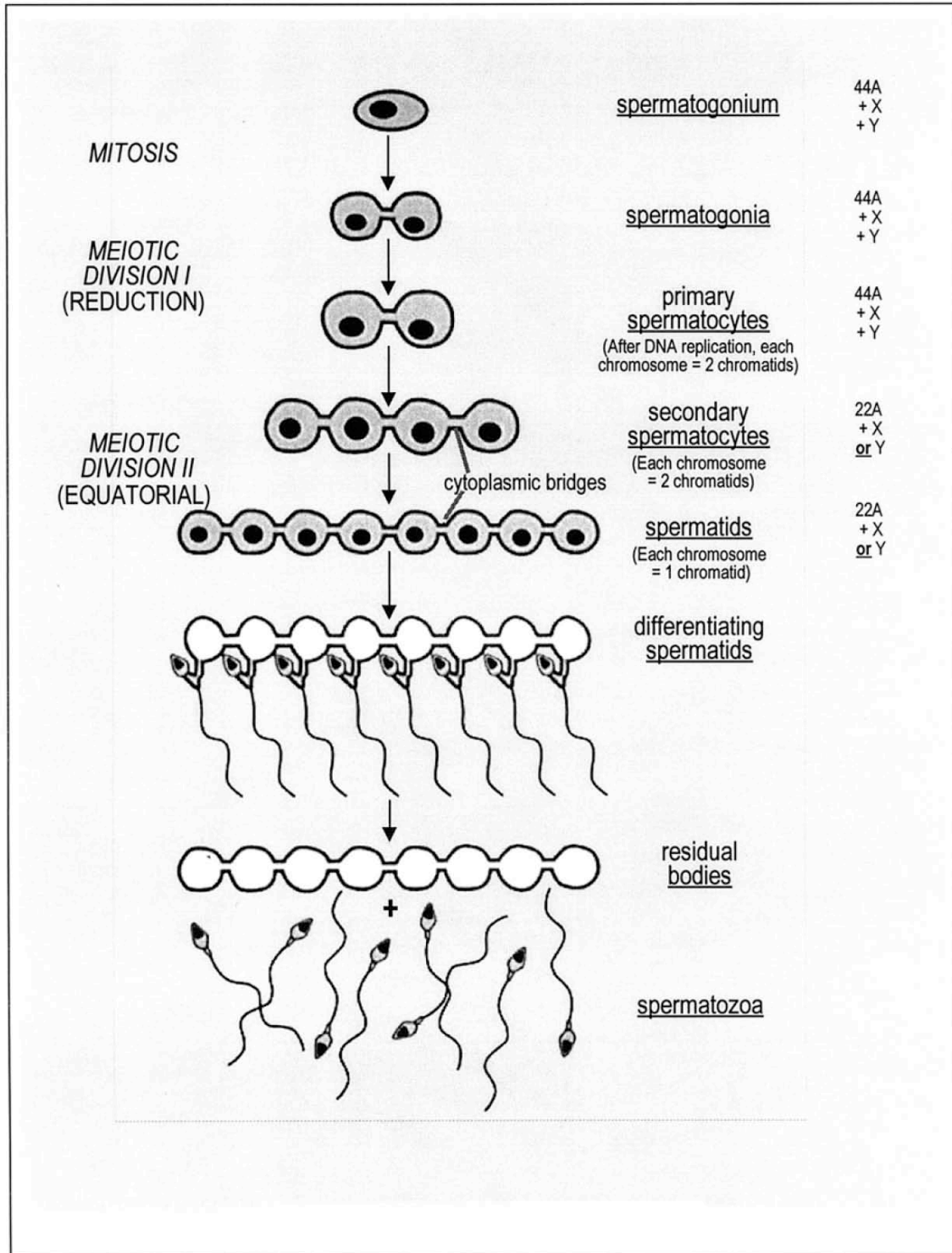


Figure 3: Schematic diagram of spermatogenesis.

The last stages of spermatogenesis are called **spermiogenesis**, and refer to the morphological transformation of **spermatids** into **spermatozoa**. As illustrated in Figure 4, during spermiogenesis there is no alteration of chromosomes, but morphological changes in: (1) the shape of nucleus, (2) the conversion of Golgi/secretion granule to the **acrosome**, (3) the

disposition of mitochondria, (4) the location of centrioles, (5) the formation of the flagellum, and (6) the loss of the residual body.

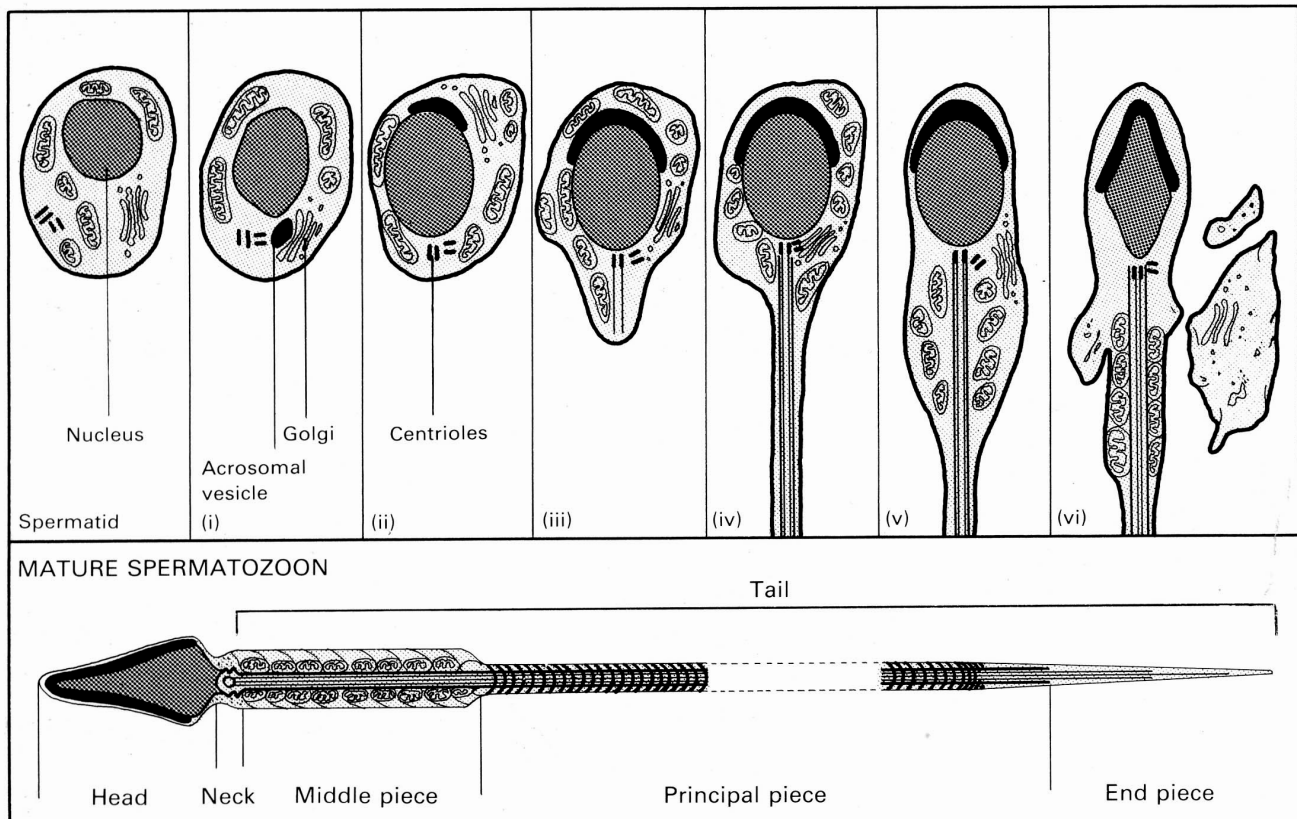


Figure 4: Stages in the transformation of a spermatid to a mature sperm.

The **acrosome** develops as a secretory granule in association with an elaborate Golgi apparatus. As maturation progresses, it collapses over the end of the nucleus to form part of the head cap (Figure 4). The secretory product consists of polysaccharide-protein and enzymes: hyaluronidase and proteases. The acrosome thus has characteristics of a modified lysosome; it also possesses antigenic specificity.

While the acrosome is being formed, the two spermatid **centrioles** migrate from a location near the nucleus to the peripheral cytoplasm opposite the acrosome. One (distal) centriole begins to elongate and move back toward the nucleus, serving as an organization center for assembly of the flagellar components. The **flagellum** contains the characteristic pattern of 9 doublet microtubules circularly arranged around a central pair of microtubules that is common to cilia and flagella throughout the animal and plant kingdoms. In the sperm this microtubular complex is called the **axoneme**. The other (proximal) centriole forms an attachment to the nucleus throughout fertilization and contributes centrosomal components to the embryo. Defects in sperm centrosomal components are associated with male-factor infertility.

During spermiogenesis, spermatid mitochondria aggregate and arrange themselves end-to-end in a double spiral fashion to form a sheath around the axoneme in the midpiece region. Enzymatic activity often persists, though it is not at all clear how mitochondrial metabolism is

related to sperm motility and function. (By careful observation of thin sections in the lab you may be able to see this spiral arrangement of mitochondria in mature sperm.)

The nucleus of the somatic cell contains mainly chromatin, comprising protein and RNA. During spermiogenesis, drastic morphological and chemical reorganization of the chromatin occurs, though the potential to reform functional somatic chromosomes after fertilization is retained. In the spermatid, there is a cessation of RNA transcription and loss of RNA. Histones are replaced by different basic proteins, usually arginine-rich **protamines** that are evidently synthesized in the spermatid. As transcription has shut down, messenger RNA for this protein must have been formed earlier and stored until needed. Nucleosome superstructure is lost. Aside from being symptomatic of metabolic inactivity, the structural alterations evidently provide protection and stability to the genetic apparatus during its passage through inimical environments. The folding, coiling and packing of sperm chromatin, stabilized by disulfide bonds, results in loss of binding sites and resistance to enzyme digestion, and is probably a major determinant of sperm head shape. Nuclear elongation is a usual concomitant of sperm maturation. A transitory microtubular sheath, the **manchette**, is probably an accessory to this change in shape.

Detailed diagrams of the mature sperm cell are shown in Figure 5. The two main regions of the sperm are the sperm **head** (including the acrosome and the nucleus) and the sperm **tail** (including mitochondria and the **flagellum**). In mammalian sperm flagella, prominent **outer dense fibers** are associated with the axoneme. A dense, ribbed **fibrous sheath** surrounds the whole flagellar structure. These structures appear to assist in stiffening the long flagellum, which aids in cellular translocation.

The **plasma membrane** of the mature spermatozoon is a mosaic of many different domains. Morphologically, the differentiation between domains is rather subtle, such as particular patterns of intramembranous particle distributions seen with the EM. But antigenically the distinction between domains is dramatic. The specific role that each of these domains plays in the selective recognition of and fusion with eggs is being studied currently. These restricted sperm antigens may appear on the cell during its residence in any of the many environments to which it is exposed; i.e., a particular antigen could be derived from the testis, the epididymis, the vas deferens, or the seminal fluid produced in the accessory glands.

It should also be realized that sperm are not capable of fertilization when they exit the male reproductive tract. They acquire fertilization capability in the female reproductive tract, in a complex process called **capacitation**. One of the first critical events in capacitation is removal of cholesterol from the sperm plasma membrane by cholesterol binding to proteins present in the female tract.

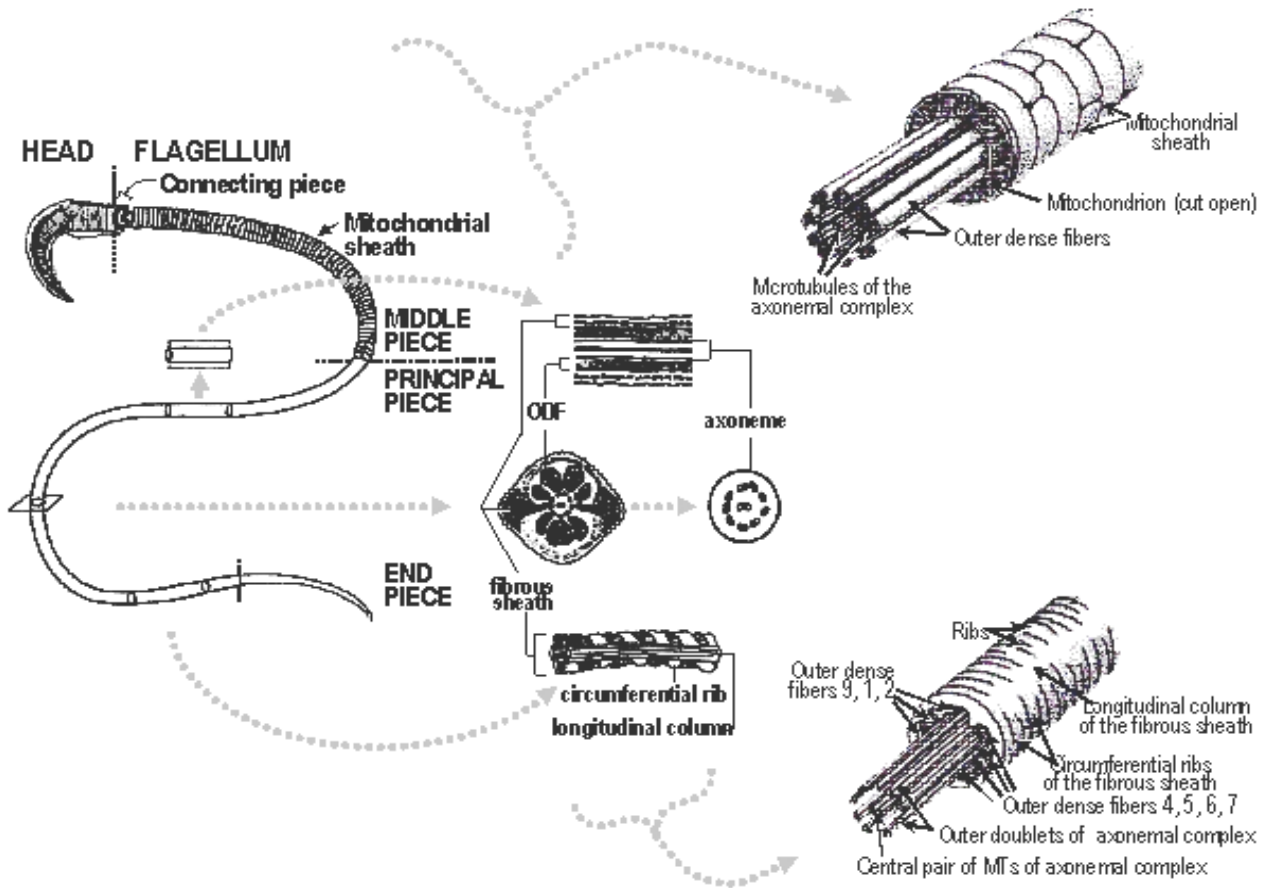


Figure 5: Structure of a mature sperm.

B. Rete Testis, Efferent Ducts, and Epididymis

Upon leaving the seminiferous tubules, the sperm pass through short **straight tubules** into a manifold region of anastomosing channels called the **rete testis**. Both the straight tubules and rete testes are lined by a simple cuboidal or simple columnar epithelium (Table 1). The sperm then travel through the **efferent ductules** to the **epididymis** (Figure 6), both lined by pseudostratified columnar epithelium. The mechanism by which sperm are released from the seminiferous tubule has not been fully elucidated but, because testicular sperm lack directed motility, they must be moved by tubule muscular contraction, the pressure and flow of the fluid medium produced in the tubules, or by motion of cilia in the **efferent ductules**. About a dozen spirally wound efferent ductules join at the head of the **epididymis**. A single highly coiled duct, about 5 meters in length, makes up the body of the epididymis. The pseudostratified epithelium of the epididymis is both secretory and absorptive in nature. It moves its contents by contractions of a layer of circular smooth muscle beneath the basement membrane. The epithelial surface is characterized by clumps of long, non-motile, branched microvilli termed **stereocilia**. Although incompletely understood in terms of function, stereocilia may serve to increase the absorptive and/or secretory surface of this epithelium.

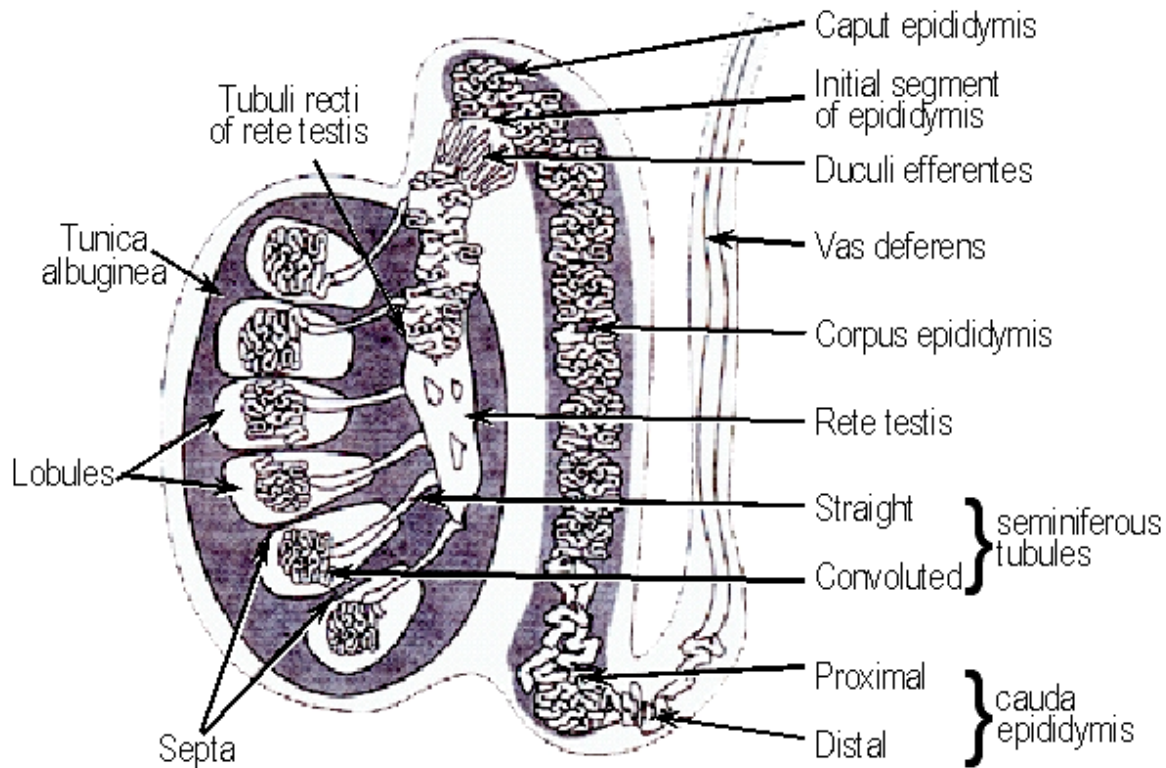


Figure 6: Arrangement of tubules and ducts in the testis and epididymis.

The efferent ducts probably absorb excess fluids and other materials, while the epididymis serves a number of functions, many details of which are emerging due to studies on transgenic and knockout mice. It is clear that while the epididymal ducts are both secretory and absorptive, they are also the principal sites of sperm storage. The secretory products have not been exhaustively identified, though histochemical tests show abundant intracellular glycogen, glycoprotein, lipid, phosphatases, and glycosidases. The secretions, together with a high K/Na ratio, provide a nutrient environment in which sperm mature and undergo subtle changes that prepare them for fertilization. Prominent characteristics that are acquired by sperm as they progress from the **caput** (*Lat.*, head) to **corpus** (*Lat.*, body) to **cauda** (*Lat.*, tail) regions of the **epididymis** include forward motility, a glycocalyx (or carbohydrate coat), and the ability to fertilize an egg. Although most excess, unejaculated sperm are disposed of in the bladder, some phagocytosis and absorption occurs in the epididymis.

Specific protein secretions of the epididymis immobilize sperm, decreasing their metabolic requirements; indeed sperm may reside in the epididymis for a month or more, immobile and protected, without losing fertilizing ability. Approximately 1 week is required for passage of sperm through the epididymis, propelled by muscular contractions of the duct walls.

The functions of the epididymis, exclusively directed toward sperm participation in fertilization, is controlled largely by testosterone, although subtle influences are also exerted by a variety of other regulators including estrogen. An active area of fertility research involves the influence of the environment on the maternal endocrine system during pregnancy; one line of evidence suggests that environmental estrogens may impact the activity of estrogen receptors within the fetal epididymal epithelium leading eventually to sub-normal epididymal function and sub-fertility in males.

C. Vas Deferens and Urethra

The remainder of the tract consists of the **ductus (vas) deferens** (one from each testis) that course out of the scrotal sac, through the inguinal canal, and into the abdominal cavity and pelvic regions (Figure 1). Here it passes to the back of the urinary bladder where it undergoes structural modifications. In association with the accessory glands (**seminal vesicle** and **prostate**), the vas becomes the **ejaculatory duct**, and, with its mate, joins the **urethra** in the prostate. The vas deferens is about 20 cm long and consists of three layers, a mucosa, muscularis, and adventitia.

The structure of the vas deferens changes during its journey from the epididymis to the urethra. Near the epididymis, the vas deferens contains a tall pseudostratified columnar epithelium with many stereocilia and three robust smooth muscle layers (inner longitudinal, middle circular, and outer longitudinal). In the ampulla, the distal region of the vas deferens near the seminal vesicle, the pseudostratified epithelium becomes shorter and contains fewer basal cells, the muscular coat becomes thinner, and the mucosa is thrown into longitudinal folds. Bilateral ligation of the vas deferens (vasectomy) has become a common contraceptive procedure.

The urethra, serving both as urinary and seminal duct, continues through the prostate on its way from the urinary bladder to the **penis**. The epithelium lining the urethra changes from transitional, as it passes through the prostate, to pseudostratified columnar to stratified squamous, as it passes through the penis. In the penis the urethra becomes surrounded by a venous plexus, the **corpus spongiosum**, which extends through the length of the penis together with two other vascular structures, the **corpora cavernosa**. The filling of the corpora cavernosa with blood as a consequence of erotic stimulation leads to erection of the penis. Collapse of the urethra by pressure from the swollen corpora cavernosa is prevented by the corpus spongiosum.

III. Accessory glands

Several accessory glands, including the **seminal vesicles**, the **prostate**, and the **bulbo-urethral** glands, produce the bulk of the volume of the seminal fluid. These glands provide lubricating secretions and the seminal fluid in which sperm are discharged. Although the function of the seminal fluid is not entirely clear, it does contain various substrates, such as fructose from the seminal vesicles, presumably used by the sperm for energy metabolism. While sperm maintain their motility for longer periods while bathed in seminal fluid, it is evidently an accessory, rather than an essential medium. Sperm are motile without it, and in any case, are only mixed with it at the moment of ejaculation. Upon deposition in the vagina, the fertilizing sperm remain with the seminal fluid for only a few moments before entering the cervix.

A. Seminal Vesicles

The paired **seminal vesicles** are mainly secretory and do not store sperm in man. Each consists of an elongated (about 5 cm in length) coiled sac-like diverticulum of the ductus deferens, from which branch about 10 tubular blind diverticula. All are lined with an extensively folded mucosa of secretory epithelium consisting of pseudostratified columnar or simple columnar. The secretory product, which makes up a major portion of the seminal fluid, is viscid, yellowish, alkaline and contains reducing substances, especially fructose, together with citric acid, sorbitol, inositol, ergothioneine and prostaglandins. The size of the vesicle and the activity of the epithelium are under the direct influence of male hormones. The engorgement of the vesicles resulting from accumulation of the secretions may be a contributory factor in arousing the sex urge in the male. Thus, as testosterone production decreases with age, secretory activity declines, as does the sex urge.

B. Prostate

The **prostate** is a round, lobulated collection of 30-50 compound tubulo-acinar glands emptying by numerous ducts into the urethra, which it surrounds. The epithelium is variable, ranging from simple squamous to cuboidal to columnar to pseudostratified columnar. The glands can be separated on the basis of their size, location and secretory products into 3 kinds, forming 3 more or less concentric areas around the urethra. (Note that these 3 types of glands are difficult to distinguish in your slides.) The innermost glands are small and mucus-secreting; their overgrowth into non-malignant adenomatous (aden = gland; oma = tumor) nodules produces an enlargement, common in older men, that obstructs the urethral outlet from the bladder causing benign prostatic hyperplasia (BPH). The outermost, main prostatic glands are responsible for the bulk of the secretion of the gland. It is in this area that carcinomas are apt to develop. The secretion of the prostatic agglomerate makes up much of the fluid in the 3-6 ml of seminal ejaculate; it is a colorless fluid, slightly acid (pH 6.5), with a distinctive odor, contributed by spermine, spermidine, and related compounds. It also contains proteolytic enzymes, such as fibrinolysin and diastase. It is the main source of citric acid and acid phosphatase, the amount of the latter in the seminal fluid being used as an index in assaying the functional state of the prostate. The gland is also high in its content of zinc. The highly folded mucosal lining allows storage of the products, one of the abnormal consequences of which is the accumulation of lamellated, calcified concretions (also termed corpora amyloacea) that obstruct the glandular lumens in older males. Like the seminal vesicles, the prostate is highly responsive to hormones; androgens from the testis are required for the gland to reach full development, and

castration leads to its atrophy.

Prostatic adenocarcinoma is the most frequently diagnosed carcinoma in males. It occurs at an increasing rate with advancing age. It is rare before the age of 50 years and most patients are over 60 years at the time of diagnosis. Both early and advanced carcinoma of the prostate may be asymptomatic at the time of diagnosis and in the past more than 80% of patients had advanced or metastatic disease at the time of diagnosis. Screening programs employ digital rectal examination and biochemical detection of serum prostatic specific antigen (PSA). Serum PSA is elevated in most patients with prostatic carcinoma, including many with disease confined to the gland. However, PSA is an imperfect marker because of relatively low sensitivity (does not detect all cases of prostatic carcinoma due to false negative results) and lack of specificity (many false positive cases as PSA may also be increased in some benign prostatic conditions such as BPH).

C. Bulbo-Urethral Glands

At the point where the urethra passes through the urogenital diaphragm, two small tubuloalveolar glands, the **bulbo-urethral (Cowper's) glands**, embedded in the diaphragm, open into the urethra. Their viscous mucous secretion containing sialoprotein is expressed during erotic stimulation by contraction of the smooth and voluntary muscle with which they are surrounded, and probably serves as a lubricant.

D. Glands of Littre

These glands, located along the length of the urethra in the penis, produce a watery, mucous lubricating material that is expressed ahead of the sperm ejaculate.

The bulbo-urethral glands and glands of Littre are difficult (if not impossible) to see in your slides in lab, so please: (1) do not spend your medical school career looking for them and (2) do not ask your lab instructor to spend his/her career looking for them.