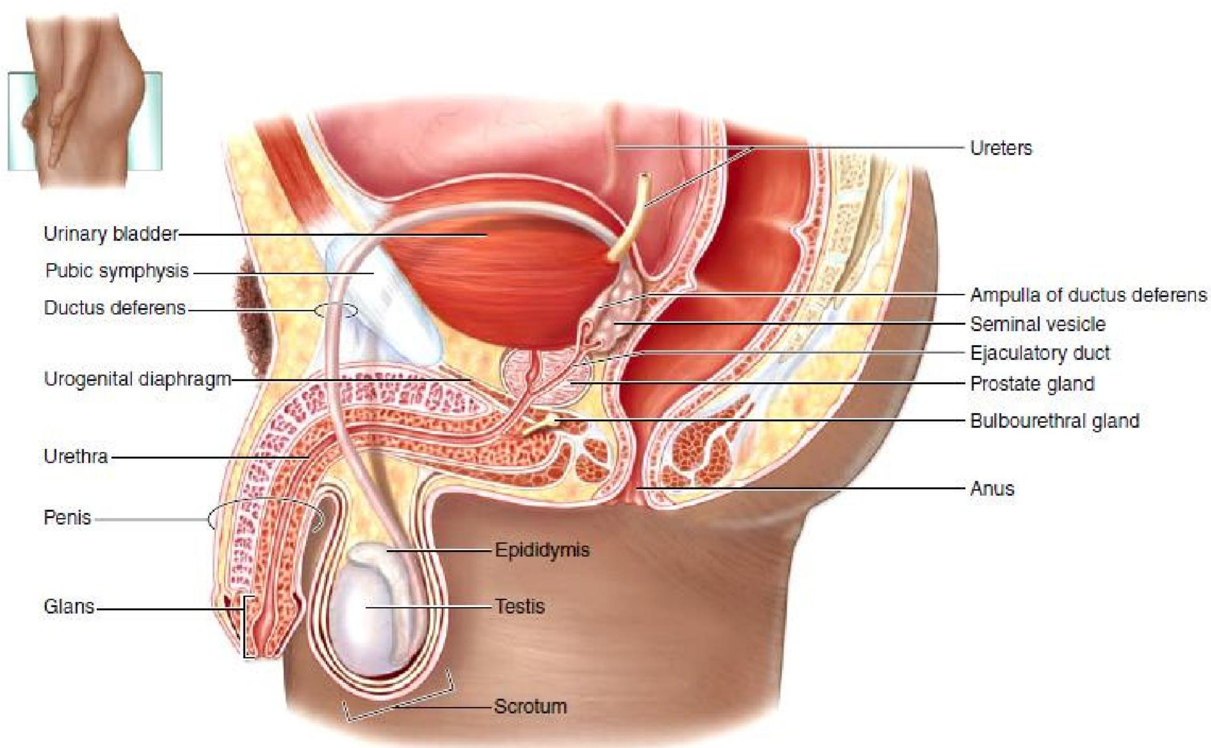
The male reproductive system consists of the testes, genital ducts, accessory glands, and penis. Testes produce sperm but also contain endocrine cells secreting hormones such as testosterone, which drives male reproductive physiology. Testosterone is important for spermatogenesis, sexual differentiation during embryonic and fetal development, and control of gonadotropin secretion in the pituitary. A metabolite of testosterone, dihydrotestosterone, also begins to act on many tissues during puberty (eg, male accessory glands and hair follicles).

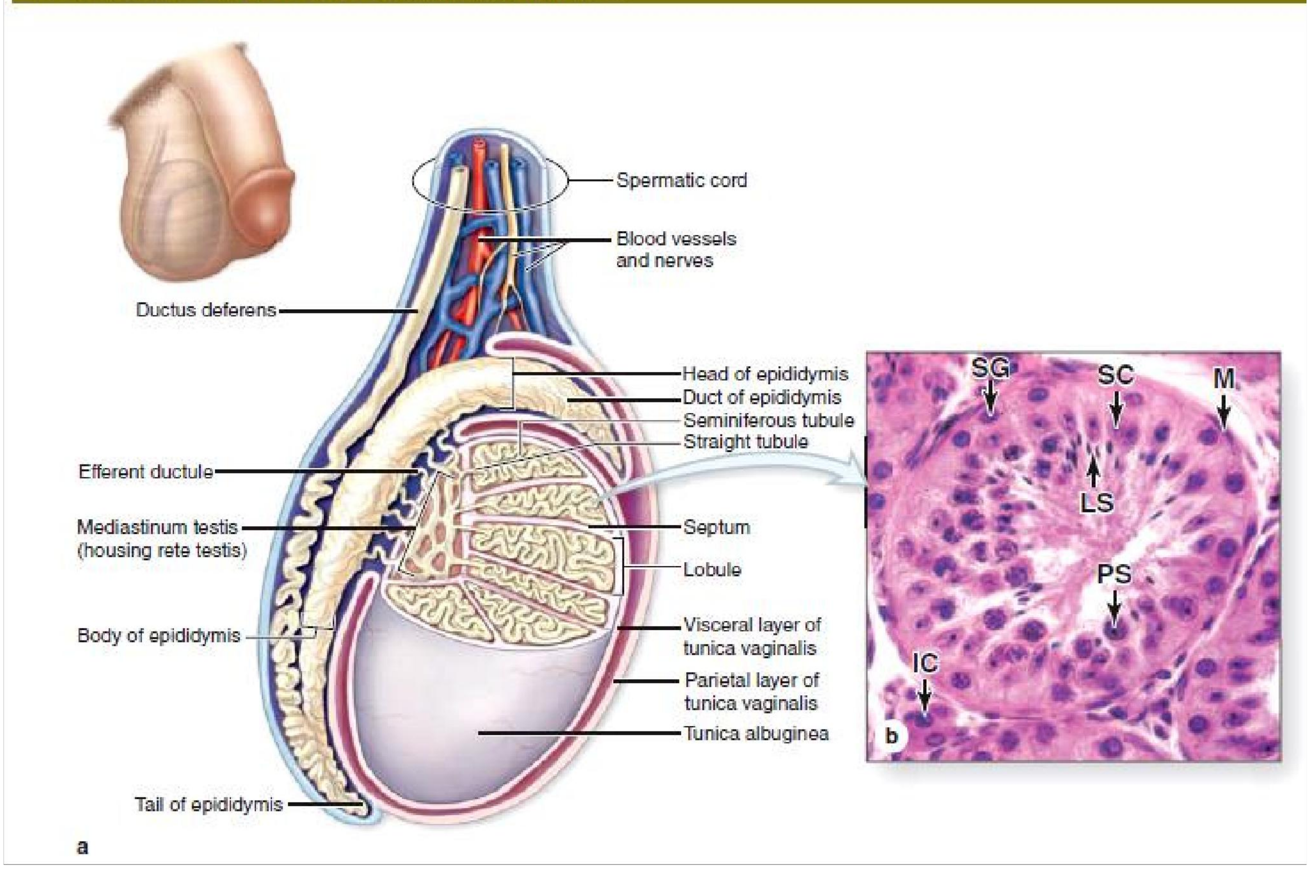
FIGURE 21–1 The male reproductive system.



TESTES

Each **testis** (or testicle) is surrounded by a dense connective tissue capsule, the **tunica albuginea**, which thickens on the posterior side to form the **mediastinum testis** . From this fibrous region, septa penetrate the organ and divide it into about 250 pyramidal compartments or testicular lobules. Each lobule contains sparse connective tissue with endocrine **interstitial cells** (or **Leydig cells**) secreting testosterone, and one to four highly convoluted **seminiferous tubules** in which sperm production occurs. The testes develop retroperitoneally in the dorsal wall of the embryonic abdominal cavity and are moved during fetal development to become suspended in the two halves of the scrotal sac, or scrotum, at the ends of the spermatic cords. During migration from the abdominal cavity, each testis carries with it a serous sac, the **tunica vaginalis**, derived from the peritoneum. This tunic consists of an outer parietal layer lining the scrotum and an inner visceral layer, covering the tunica albuginea on the anterior and lateral sides of the testis.

FIGURE 21–2 **Testes and seminiferous tubules.**



The anatomy of a testis is shown. **(a)** The diagram shows a partially cutaway sagittal section of the testis. **(b)** A seminiferous tubule cross section shows spermatogonia (**SG**) near the periphery, near nuclei of Sertoli cells (**SC**), primary spermatocytes (**PS**), and late spermatids (**LS**) near the lumen, with interstitial cells (**IC**) in the surrounding connective tissue. X400. H&E.

Interstitial Tissue

The interstitial tissue of the testis between the seminiferous tubules consists of sparse connective tissue containing fibroblasts, lymphatics, and blood vessels including fenestrated capillaries. During puberty **interstitial cells**, or **Leydig cells**, develop as large round or polygonal cells with central nuclei and eosinophilic cytoplasm rich in small lipid droplets (Figures). These cells produce the steroid hormone testosterone, which promotes development of the secondary male sex characteristics. Testosterone is synthesized by enzymes present in the smooth ER and mitochondria similar to the system in adrenal cortical cells. Testosterone secretion by interstitial cells is triggered by the pituitary gonadotropin, **luteinizing hormone** (**LH**), which is also called **interstitial cell stimulating hormone** (**ICSH**). Testosterone synthesis thus begins at puberty, when the hypothalamus begins producing gonadotropin-releasing hormone.

Seminiferous Tubules

Sperm are produced in the seminiferous tubules at a rate of about 2 × 108 per day in the young adult. Each testis has from 250 to 1000 such tubules in its lobules, and each tubule measures 150 to 250 μm in diameter and 30 to 70 cm in length. The combined length of the tubules of one testis totals about 250 m.

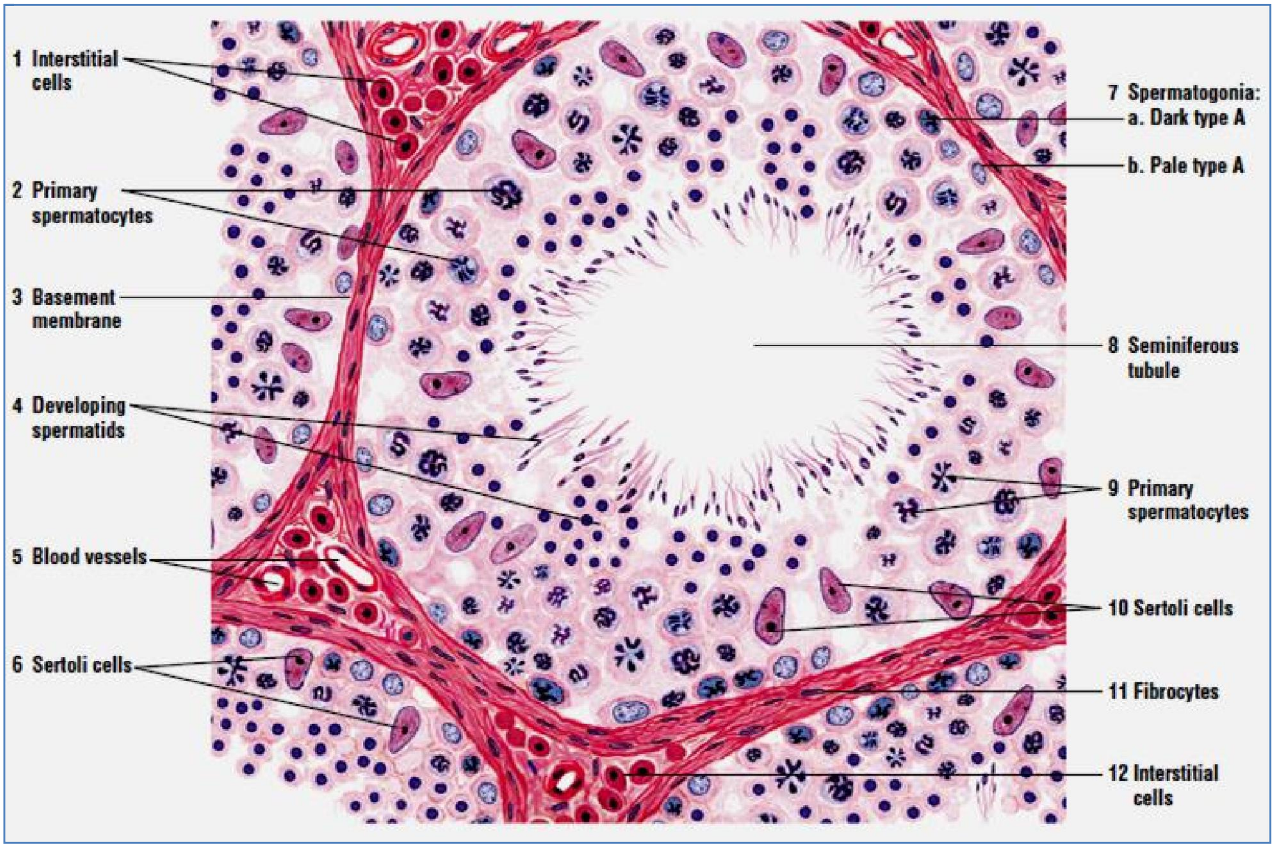


FIGURE. Seminiferous tubule

Each tubule is actually a loop linked by a very short, narrower segment, the straight tubule, to the **rete testis**, a labyrinth of epithelium-lined channels embedded in the **mediastinum testis** (see Figures). About 10-20 **efferent ductules** connect the rete testis to the head of the **epididymis** (Figure). Each seminiferous tubule is lined with a complex, specialized stratified epithelium called **germinal** or **spermatogenic epithelium** (Figure). The basement membrane of this epithelium is covered by fibrous connective tissue, with an innermost layer containing flattened, smooth muscle-like **myoid cells** (Figure), which allow weak contractions of the tubule. The germinal epithelium consists of two types of cells:

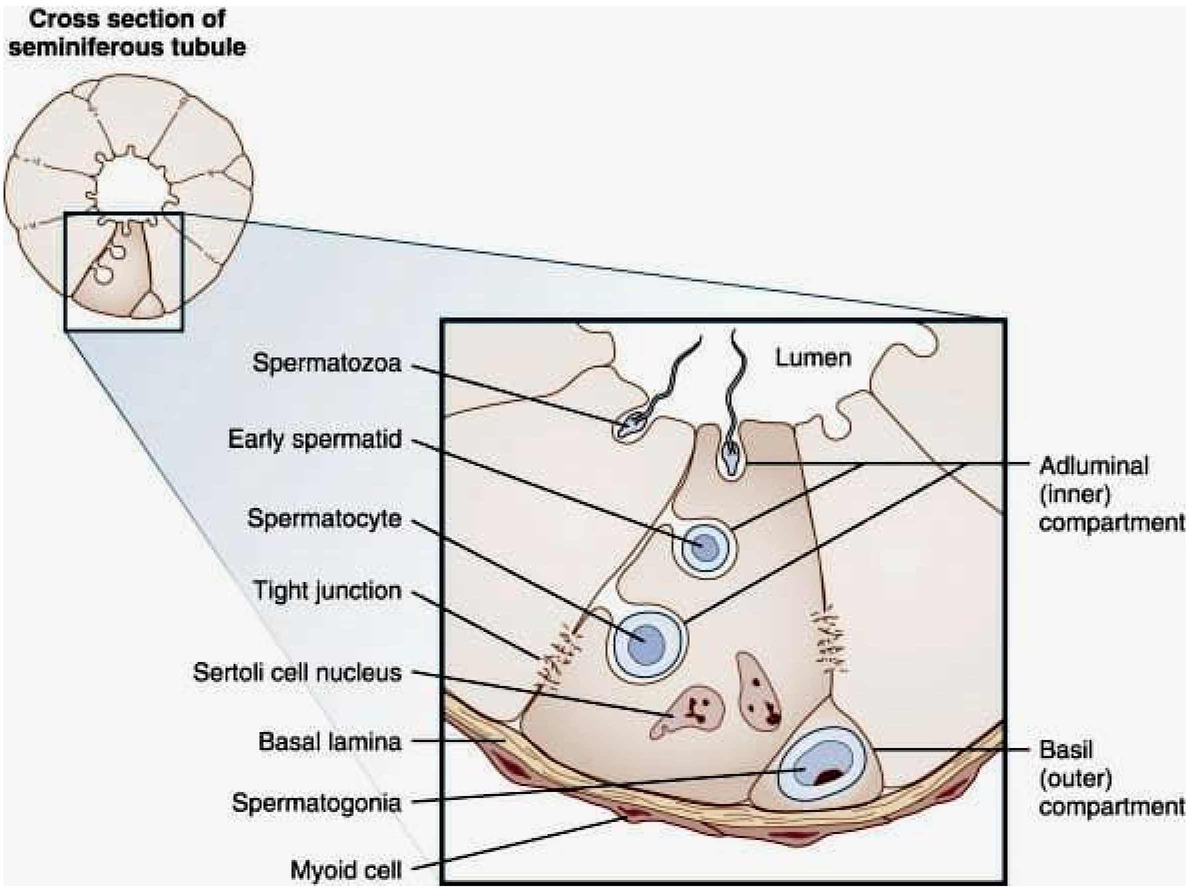
■ Large nondividing Sertoli cells (Figure), which physically and metabolically support developing sperm cell precursors.

■ Dividing cells of the spermatogenic lineage (Figure).

The cells of the spermatogenic lineage comprise four to eight concentric cell layers and produce the cells that become sperm. As shown in Figure, spermatogenesis is the first part of sperm production, including stem cell mitosis and meiosis, and spermiogenesis is the final differentiation process occurring in the haploid male germ cells.

Sertoli Cells

The **supporting or sustentacular** or **Sertoli cells**, named after Enrico Sertoli (1842-1910) who first demonstrated their physiologic significance, are tall columnar or pyramidal epithelial cells that form the basal lamina of the seminiferous tubules. All cells of the spermatogenic lineage are closely associated with the extended surfaces of Sertoli cells and depend on them for metabolic and physical support. Sertoli cells adhere to the basal lamina and their apical ends extend to the lumen. Each Sertoli cell supports 30 to 50 developing germ cells. Ultrastructurally Sertoli cells are seen to contain abundant SER, some rough ER, well-developed Golgi complexes, numerous mitochondria, and lysosomes. Their nuclei are typically ovoid or triangular, euchromatic, and have a prominent nucleolus, features that allow Sertoli cells to be distinguished from the neighboring germ cells. Important in Sertoli cell function are elaborate tight occluding junctions between their basolateral membranes that form a **blood-testis barrier** within the seminiferous epithelium. The tightest blood-tissue barrier in mammals, this physical barrier is one part of a system that prevents autoimmune attacks against the unique spermatogenic cells.



Spermatogonia lie in a **basal compartment** of the tubule, below the tight junctions and not sealed off from the vascularized interstitial tissue containing lymphocytes and other immune cells. Newly formed primary spermatocytes temporarily disassemble the adhesion molecules of the local occluding junctions and move into the tubule's **adluminal compartment** while still adhering to Sertoli cells (Figure). Like the spermatogonia, all spermatocytes and spermatids lie within invaginations of the Sertoli cells surfaces. Sertoli cells are also connected and coupled ionically by gap junctions, which help to regulate activities of occluding junctions and spermatogenic cells. As the flagellar tails of the spermatids develop, they appear as tufts extending from the apical ends of the Sertoli cells.

They perform numerous important functions in the testes, among which are the following:

• Physical support, protection, and nutrition of the developing spermatids
• Phagocytosis of excess cytoplasm (residual bodies) from the developing spermatids as well as degenerating germ cells
• Release of mature sperm, called **spermiation**, into the lumen of seminiferous tubules containing fluid produced by Sertoli cells
• Secretion of fructose-rich testicular fluid for the nourishment and transport of sperm to the excurrent ducts
• Production and release of **androgen-binding protein** (ABP) that binds to testosterone and increases the concentration of testosterone in the lumen of the seminiferous tubules that is necessary for spermatogenesis; ABP secretion is under the control of **follicle-stimulating hormone** (FSH) from the pituitary gland
• Secretion of the hormone **inhibin**, which suppresses the release of FSH from the pituitary gland
• Production and release of the **anti-Müllerian hormone**, also called **Müllerian inhibiting hormone**, that suppresses the development of Müllerian ducts in the male and inhibits the development of female reproductive organs

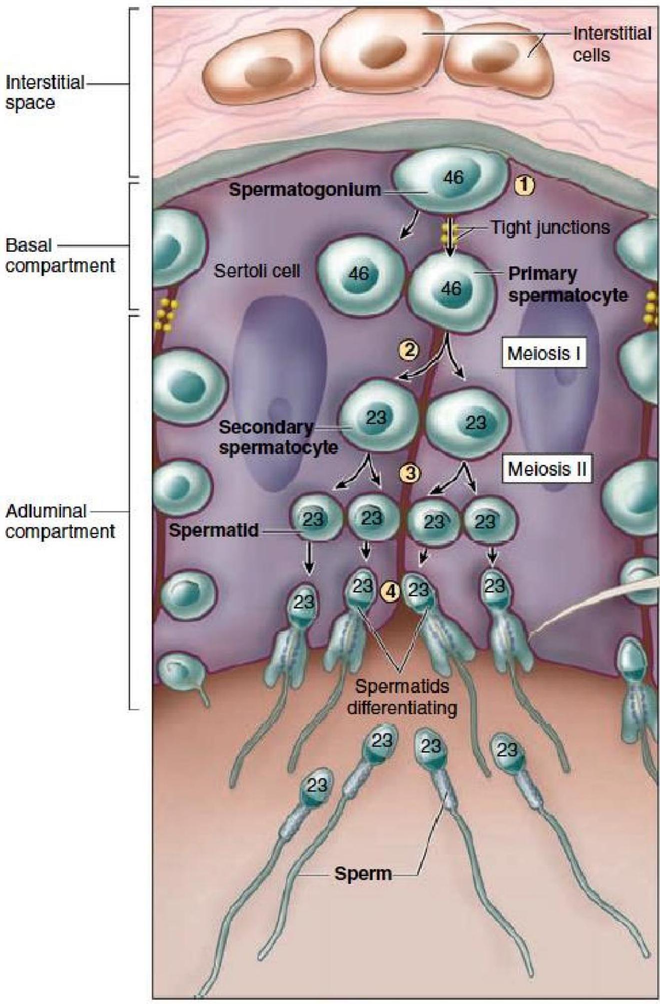
Spermatogenesis

The process of sperm formation is called **spermatogenesis**. Spermatogenesis begins at puberty with proliferation of stem and progenitor cells called **spermatogonia** (Gr. *sperma* +*gone*, generation), small round cells about 12 μm in diameter. These cells occupy a basal niche in the epithelial wall of the tubules, next to the basement membrane and closely associated with Sertoli cell surfaces.
Spermatogenic cells are subdivided into **type A spermatogonia** and **type B spermatogonia**. **Dark type A spermatogonia** with dark, ovoid nuclei act as stem cells that divide infrequently to give rise to new dark stem cell and **pale type A spermatogonia** with pale and ovoid nucleus. Pale type A spermatogonia divide more rapidly to give rise to type B cells with more spherical and pale nuclei.
Each type B spermatogonium then undergoes a final mitotic division to produce two cells that grow in size and become **primary spermatocytes**, which are spherical cells with euchromatic nuclei. The primary spermatocyte has 46 (44 + XY) chromosomes, the diploid number, and a DNA content of 4N. Soon after their formation, these cells enter the first meiotic prophase that lasts about 3 weeks. The primary spermatocytes are the largest cells of the spermatogenic lineage. Homologous chromosomes separate in the first meiotic division, which produces smaller cells called **secondary spermatocytes** with only 23 chromosomes (22 + X or 22 + Y), but each still consists of two chromatids so the amount of DNA is 2N. Division of each secondary spermatocyte separates the chromatids of each chromosome and produces two haploid cells called **spermatids** each of which contains 23 chromosomes.

Spermiogenesis

Spermiogenesis, the final phase of sperm production, is the temperature-sensitive process by which spermatids differentiate into spermatozoa, which are highly specialized to deliver male DNA to the ovum.

FIGURE 21–5 Spermatogenesis and spermiogenesis.



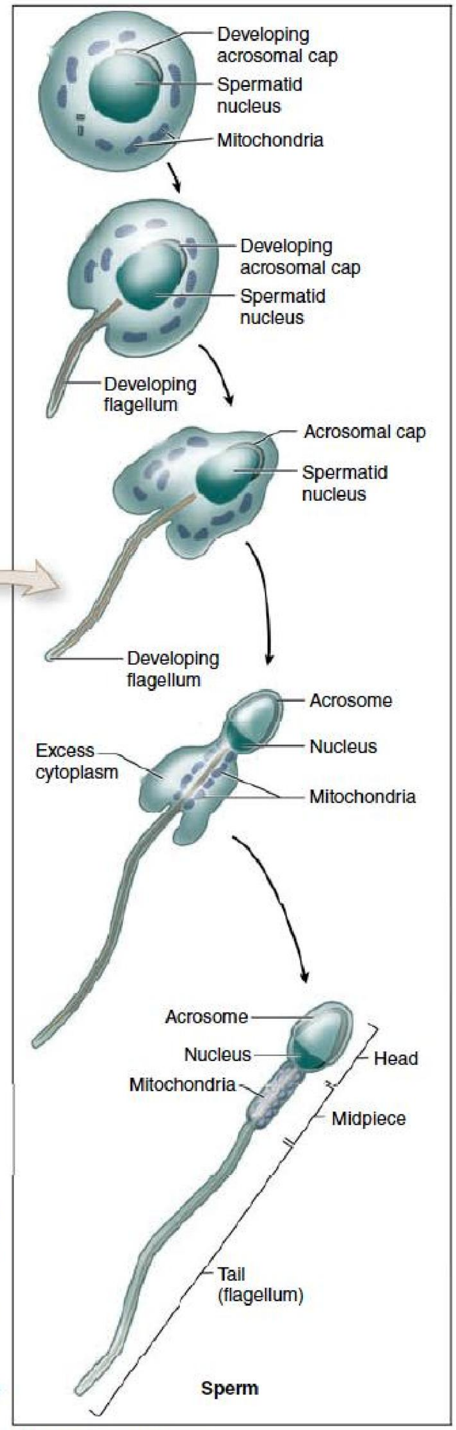
(a) Spermatogenesis

(1) The spermatogenic progenitor cells, called spermatogonia, are diploid cells containing 46 chromosomes (23 pairs). Mitotic divisions of these cells each produce a new spermatogonium and a cell called a primary spermatocyte committed to meiosis.

(2) Each new primary spermatocyte transiently disassembles the tight junctions of the blood-testis barrier and moves from the tubule's basal compartment to the adluminal compartment. At the same time these cells replicate their DNA, enter meiosis I, and undergo synapsis. The first meiotic division produces two haploid secondary spermatocytes each with 23 chromosomes.

(3) Meiosis II is rapid as chromatids in the secondary spermatocyte chromosomes separate into two smaller haploid cells, the spermatids.

(4) Near the lumen but still embedded in Sertoli cells, the spermatids differentiate and undergo the morphological changes required to become motile and capable of fertilization.



(b) Spermiogenesis

(a) The diagram shows two large, columnar Sertoli cells with their surfaces binding many germ cells in various stages of spermatogenesis. Near the basement membrane are **spermatogonia,** which divide by mitosis to produce both more spermatogonia and also **primary spermatocytes** that undergo meiosis to produce haploid spermatids that differentiate as sperm. Newly formed spermatocytes temporarily disassemble the tight junctions between Sertoli cells

(b) Spermiogenesis is the process of cell differentiation by which spermatids become sperm. The major changes that occur during spermiogenesis are shown here. These involve flattening of the nucleus, formation of an **acrosome** that resembles a large lysosome, growth of a **flagellum** (tail) from the basal body, reorganization of the mitochondria in the **midpiece** region, and shedding of unneeded cytoplasm.

No cell division occurs during this process, and as with spermatogenesis the cells involved remain associated with Sertoli cells. The haploid spermatids are small (7-8 μm in diameter) cells near the lumen of the seminiferous tubules. Spermiogenesis includes formation of the acrosome (Gr. *akron*, extremity + *soma*, body), condensation and elongation of the nucleus, development of the flagellum (L, whip), and the loss of much of the cytoplasm. The end result is the mature spermatozoon, which is released from the Sertoli cell surface into the tubule's lumen. Spermiogenesis is commonly divided into four phases:

■ In the **Golgi phase** the cytoplasm contains a prominent Golgi apparatus near the nucleus, mitochondria, paired centrioles, and free ribosomes. Small **proacrosomal vesicles** from the Golgi apparatus coalesce as a single membrane-limited acrosomal cap close to one end of the nucleus. The centrioles migrate to a position farthest from the **acrosomal cap** and one acts as a basal body, organizing the axoneme of the flagellum which is structurally and functionally similar to that of a cilium.

■ In the **cap phase** the acrosomal cap spreads over about half of the condensing nucleus. The acrosome is a specialized type of lysosome containing hydrolytic enzymes, mainly hyaluronidase and a trypsinlike protease called **acrosin**. These enzymes are released when a spermatozoon encounters an oocyte and the acrosomal membrane fuses with the sperm's plasma membrane. They dissociate cells of the corona radiata and digest the zona pellucida, both structures that surround the egg. This process, the **acrosomal reaction**, is one of the first steps in fertilization.

■ In the **acrosome phase** the head of the developing sperm, containing the acrosome and the condensing nucleus, remains embedded in the Sertoli cell while the growing axoneme extends into the lumen of the tubule. Nuclei become more elongated and very highly condensed, with the histones of nucleosomes replaced by small basic peptides called **protamines**. Flagellum growth continues as the tail and mitochondria aggregate around its proximal region to form a thickened middle piece where the ATP for flagellar movements is generated.

■ In the **maturation phase** of spermiogenesis, unneeded cytoplasm is shed as a **residual body** from each spermatozoon and remaining intercellular bridges are lost. Mature but not yet functional sperm are released into the lumen of the tubule.

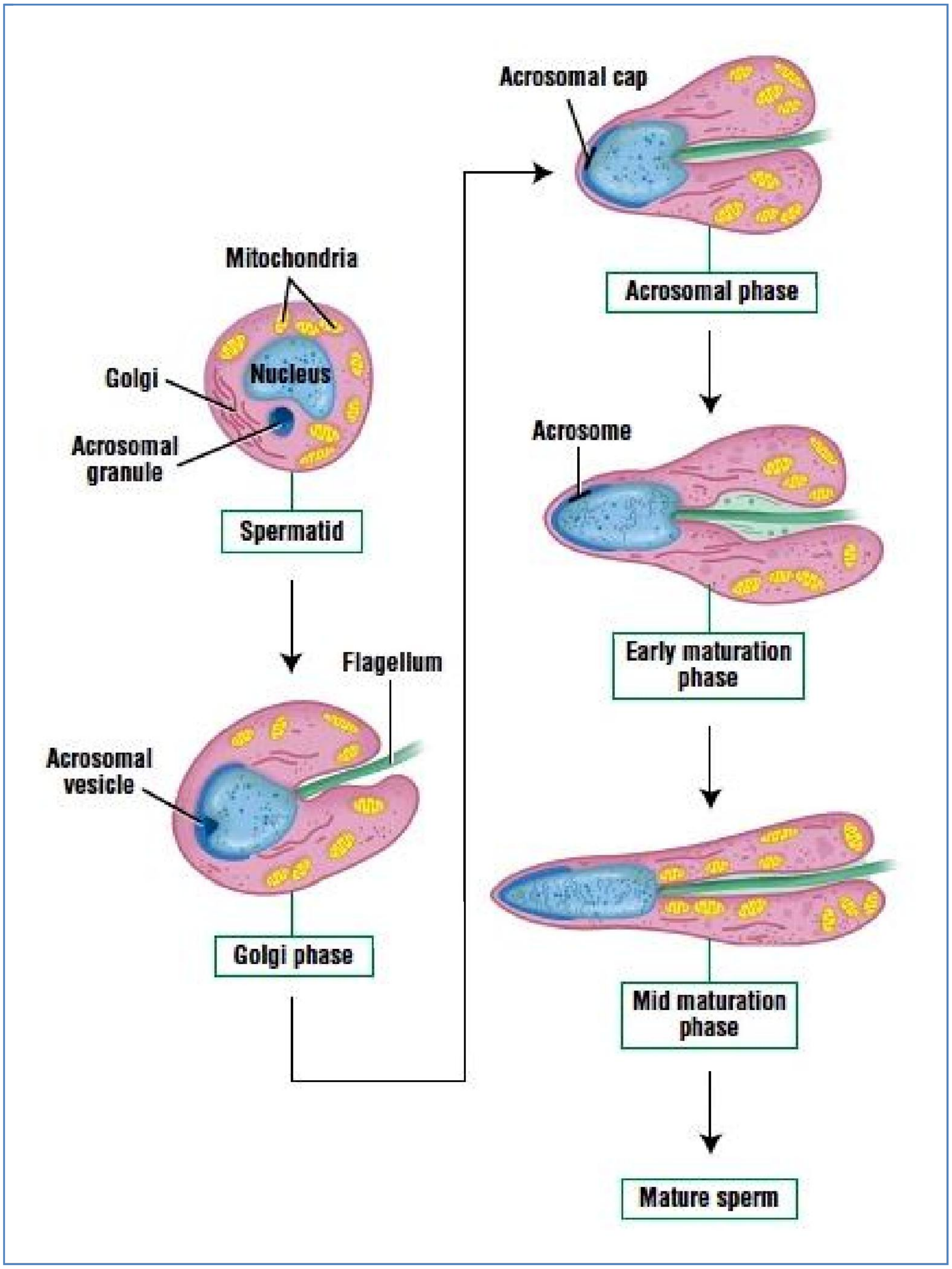


FIGURE. **Spermiogenesis**