Male Reproductive System
Revised 11.13.15

Reading Assignment: Chapter 22: Male Reproductive System; pay special attention to Boxes 22.2, 22.3, 22.4 and 22.5

Outline:
I. Components of male reproductive system
II. Testes
   A. Seminiferous tubules
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III. Extra-testicular Excurrent duct system
IV. Development of testes and ducts
   A. Spermatic cord
V. Accessory glands (seminal vesicle, prostate, bulbourethral)
VI. Penis

I. Components of the male reproductive system

The male reproductive system consists of 4 components:
1. testes – the male gonads are the site of gamete and hormone production (androgens, MIF) and the intra-testicular duct system (straight tubules (tubuli recti) and rete testes)
2. extra-testicular excurrent duct system – this series of tubes has a common embryonic origin and conducts sperm away from the testes to the copulatory organ; it consists of the efferent ductules, ductus epididymis, ductus deferens, and ejaculatory duct.
3. accessory sex glands – these contribute to semen volume and function; they include the seminal vesicles, prostrate gland and bulbourethral glands
4. penis – the copulatory organ; its duct, the urethra, serves as the terminal passage for both the urinary and reproductive systems.

II. Testes

The testes are bilateral gonads lying within a common musculocutaneous sac, the scrotum. The scrotum is actually an out-pocketing of the abdominal wall and not surprisingly contains bilateral (left and right) remnants of the peritoneum carried along in the descent of the testes during development. These peritoneal remnants are called the tunicae vaginali (plural; singular, tunica vaginalis), and like the peritoneum, consist of parietal and visceral layers surrounding a cavity, called, logically enough, the cavum of the tunica vaginalis. Like the fetal ovaries, the testes are “retroperitoneal” (more specifically retro-vaginalis) and the visceral layer covers only one surface of the testes. Confused? Excellent!

Each testis is invested in a thick, dense connective tissue capsule called the tunica albuginea. The posterior border of the tunica albuginea is thickened and projects inward to form a portal for the passage of vessels and ducts called the mediastinum testis. Septa extending internally from the capsule incompletely divide the parenchyma (= seminiferous tubules) into lobules. Each lobule contains 1-4 seminiferous tubules that are separated from one another by a connective tissue stroma (= tunica propria) within which are found the hormone producing interstitial (Leydig) cells. The seminiferous tubules are highly convoluted loops whose terminal straight portion, the straight tubule (L., tubulus rectus) enters the mediastinum where they form an anastomising network of ducts, the rete testis.

The seminiferous tubules are formed by the seminiferous epithelium, a complexly stratified epithelium resting upon a basement membrane and containing 2 cell populations: nurse (Sertoli) cells and germ (spermatogenic) cells.

The stroma of the testes is a connective tissue called the tunica propria. It consists of collagen fibrils, capillaries, lymphatics, myoid cells and interstitial (Leydig) cells. The myoid cells are contractile cells that also produce the collagen
of the stroma; their peristaltic contractions propel the newly formed spermatozoa through the seminiferous tubules. Interstitial (Leydig) cells are the testosterone producing endocrine cells located in the spaces between adjoining tubes. Electron microscopy of these cells shows a cytoplasm rich in sER, lipid droplets, mitochondria and the presence of Reinke crystals, a crystallized protein of unknown composition.

A. Seminiferous tubules

The seminiferous tubules consist of a stratified epithelium resting upon a thickened basement membrane. The epithelial consists of 2 types of cells, nurse (Sertoli) and germ cells.

Nurse cells (also called Sertoli or sustenacular cells) are columnar, non-replicating (post-mitotic) support cells that extend from the basement membrane to the lumen of the tubule. They have extensive apical and lateral projections that envelop the adjacent germ cells and make contact with adjacent nurse cells. At these contacts, highly modified zonula occludens create two (2) epithelial compartments: basal and lumenal. The basal compartment lies below the occluding junctions and houses the spermatagonia (stem cells) and early primary spermatocytes (see below). The lumenal compartment houses the later stage spermatocytes and spermatids. The occluding junctions of the nurse cells also establish the blood-testis barrier. This barrier is both physiological and immunological in function; the barrier permits the lumenal fluid to differ from that of the interstitium creating a more nutritive environment for the gametes and prevents an immunological response to the antigenic haploid spermatids.

Ultra-structurally, the nurse cells exhibit an active synthesizing profile. The nucleus is euchromatic with a prominent nucleoli. Extensive sER and rER and abundant mitochondria fill the cytoplasm. Like the interstitial (Leydig) cells, nurse cells contain diagnostic crystalloids of unknown function known as Charcot-Bottcher inclusion bodies.

Functionally, the nurse cells serve, logically enough, as nurse cells to the spermatogenic cells, exchanging metabolic and waste substances with them. They also phagocytose the residual bodies produced in the last stage of spermatogenesis (see below). Finally, they secrete androgen-binding protein (ABP) into the lumenal compartment to elevate the concentration of testosterone in this space.

The germ cells are comprised of spermatagonia, spermatocytes, spermatids and spermatozoa. The spermatagonia divide by mitosis to create stem cells and primary spermatocytes; the latter undergo further differentiation as they move apically through the seminiferous epithelium to form secondary spermatocytes, then spermatids and finally spermatozoa.

Spermatagonia are the stems cells found in the basal compartment of the seminiferous tubule adjacent to the basement membrane. There are 3 types (Ad, Ap, and B) that differ in their nuclear morphology and cell fate. Spermatagonia type A are stem cells whose daughter cells (arising through mitosis) either (1) remain as a pair of stem cells (Type Ad (dark)) or (2) turn into a pair that initiate a spermatogenic lineage (Type Ap (pale)). Not surprisingly, type Ad has an oval, dark staining nucleus whereas type Ap has an oval, light staining nucleus. Spermatagonia type B are simply differentiated descendents of type Ap with spherical nuclei and obvious clumps of chromatin.

Interestingly, the type Ap daughter cells do not undergo cytokinesis following mitosis, nor does it occur in subsequent mitotic and meiotic cell divisions until the differentiated cells (actually gametes) are released into the lumen as spermatozoa. The resulting multi-nucleated mass is called a plasmodium and its intercellular connection accounts for the synchronous development of all the daughter cells derived from the initial type Ap division.

Definitions

- **plasmodium** — a protoplasmic mass containing several nuclei resulting from multiplication of the nucleus without cell division (e.g., spermatogenesis)
- **syncytium** — a protoplasmic mass containing several nuclei resulting from secondary union of originally separate cells (e.g., osteoclasts, skeletal muscle fibers)

Primary spermatocytes result from the mitotic division of spermatagonia type B. These cells will undergo the first stage of meiosis (meiosis I) which in the male has a prolonged prophase (up to 22 days), thus these cells are commonly
observed in histological preparations. They are large cells with coarse chromatin threads; these are the cells that migrate through the nurse cell junctional complex to enter the lumenal compartment.

Secondary spermatocytes result from the first meiotic division (chromosome reduction; hence, these cells have 23 chromosomes, each chromosome consisting of paired chromatids). These cells rapidly move to the second meiotic division and thus are not commonly observed. They are small cells with indistinguishable chromatin found in the lumenal compartment.

Spermatids are haploid cells (23 chromosome) resulting from the second meiotic division (chromatid splitting). Found within the lumenal compartment, they are small cells with condensed chromatin. Early spermatids are spherical in shape whereas late spermatids develop flagella and acrosomal caps.

Spermatozoa represent the final stage in differentiation of the spermatids and separate from their intercellular bridges to enter the lumen. However, they do not acquire motility until after transport to the epididymis.

B. Spermatogenesis

Spermatogenesis (gamete formation) can be divided into 3 phases:
1. spermatogonial phase: Spermatagonia divide by mitosis to create stem cells and primary spermatocytes.
2. spermatocyte phase: primary spermatocytes undergo two meiotic divisions (first reducing their chromosome number (chromosome reduction) and then the amount of DNA (chromatid splitting) to produce haploid spermatids.
3. spermatid phase: Spermatids differentiate into mature sperm cells (spermatozoa)

During the spermatogonial phase the type Ap spermatogonia undergo repeated cell divisions (mitotic) to produce multiple clones; cytokinesis during these divisions is incomplete and the daughter cells are all linked by a cytoplasmic bridge forming a plasmodium. As noted above, this cytoplasmic continuity is responsible for the synchronous development of all the linked “cells”. At the end of this phase the linked type Ap spermatogonia differentiate into type B spermatagonia.

During the spermatocyte phase mitotic division of each type B spermatagonia produces 2 daughter primary spermatocytes that migrate into the lumenal compartment of the seminiferous tubule. Prior to undergoing meiosis I, these cells replicate their DNA so that each chromosome consists of paired chromatids. As meiosis I begins crossing over can occur between homologous chromosomes (one source of genetic variation) and during metaphase the maternal and paternal chromosome are randomly segregated (2nd source of genetic variation). At the end of meiosis I, two secondary spermatocytes (containing 23 chromosomes each consisting of paired chromatids) are formed. The secondary spermatocytes move rapidly into meiosis II without DNA synthesis (S phase) resulting in the formation of spermatids (23 single strand chromosomes)

During the spermatid phase (spermiogenesis) the spermatids (immature gametes) develop into spermatozoa (mature gametes) while remaining physically attached to the nurse cells. This occurs in 4 stages: Golgi, cap, acrosome and maturational.

During the Golgi stage the polarity of the spermatids is established. The acrosomal vesicle (rich in glycoproteins) develops from the Golgi complex and marks the anterior (head) pole of the sperm. Following this, the centrioles migrate to the opposite end to establish the posterior pole by initiating formation of the axoneme core of the future flagellum.

During the cap stage the acrosomal vesicle spreads over the nucleus as the acrosomal cap. The nucleus begins to condense and the flagellum starts to form around the axoneme.

During the acrosome stage the spermatid re-orient so the flagellum projects into the lumen and the acrosome points toward the basement membrane. The nucleus flattens and elongates and the cytoplasm moves posteriorly to concentrate the mitochondria around the flagellum. The centrioles migrate back to the nucleus and form the connecting piece (neck).
During the maturational phase the connecting residual bodies of cytoplasm are shed and the spermatids are released into the lumen as spermatozoa or sperm.

**Intratesticular ducts and acquisition of motility**

The newly released sperm are non-motile. Suspended in a fluid secreted by the nurse cells, they are transported to the epididymis by peristaltic contraction of the myoid cells. In doing so, they pass through the length of the seminiferous tubule into the intra-testicular duct system formed by the straight tubules (tubuli recti) and the rete testis. The straight tubules (tubuli recti) are the terminal straight portions of the seminiferous tubules that are lined only by nurse cells. The straight tubules feed into the rete testis, a labyrinth of ducts within the highly vascularized mediastinum testis. These channels are lined by a simple low cuboidal epithelium with apical cilium and short microvilli.

The spermatozoa reach the epididymis by passing through the first part of the extra-testicular excurrent duct system, the efferent ductules. Within the ductus epididymis the sperm become motile; however, transport through the remainder of the male reproductive system is accomplished largely by peristalsis of the smooth muscle lining the duct system, the sperm resting themselves in preparation for the external exertions to come.

**Structure of mature sperm**

A mature spermatozoa is approximately 60 micrometers long and 1 micrometer wide. The head consists of the nucleus and acrosomal cap; the latter is rich in enzymes responsible for producing the acrosome reaction at fertilization. The neck contains the centrioles. The tail contains the locomotory flagellum and is divided into the middle, principal and end pieces. In the middle piece the flagellum is surrounded by a sheath of mitochondria that provide energy for movement. In the principal piece the flagellum is covered by a fibrous sheet that is lacking in the end piece.

**III. Extra-testicular excurrent duct system**

The extra-testicular excurrent duct system transports sperm from the rete testis (terminus of the intratesticular duct system) to the urethra within the prostate gland. It has a different developmental origin than the testes (specifically the mesonephric or Wolffian duct) and is divided into 4 parts: efferent ductules, duct of the epididymis, ductus deferens, and ejaculatory ducts.

The epididymis is a crescent shaped organ lying along the superior and posterior surfaces of the testis. It contains the efferent ductules and the duct of the epididymis (ductus epididymis). Surrounding the ducts are vessels, smooth muscle and a connective tissue covering. The epididymis is divided into a head (adjacent to the testis), body and tail, with the tail serving as a site of sperm storage.

The efferent ductules lie within the head of the epididymis and connect the channels of the rete testis to the duct of the epididymis. [Thus, the efferent ductules span two organs: The testes (specifically in the tunica albuginea) and the epididymis.] They consist of approximately 20 convoluted ducts lined with a pseudostratified columnar epithelium. The epithelium consists of basal stem cells, taller ciliated cells and shorter cells with apical microvilli. The different cell heights of the epithelium result in a characteristic saw-tooth outline to the lumen. The microvilli absorb seminal fluid and the cilia help propel the sperm. The epithelium is surrounded by a thin smooth muscle layer which also assists in transport of the sperm.

The ductus epididymis is a highly coiled tube (~4-6 m in length!) that receives the efferent ductules in the head of the epididymis. Its wall consists of a mucosa, muscularis and adventitia. The pseudostratified columnar epithelium of the mucosa consists of basal (stem cells) and columnar principal cells. The principal cells have stereocilia (= long microvilli) projecting into the lumen. [Stereocilia are long, non-motile cilia which are better termed long microvilli as they lack the microtubules that form true cilia and consist solely of cytoplasmic projections like normal microvilli.] These cells’ secretions aid in the maturation of sperm and they resorb any remnants of the residual bodies. The epithelium in the head is surrounded by a thin layer of circumferential smooth muscle that elaborates and thickens along the length of the duct so that in the tail it is tri-laminar. Neural stimulation of this tail muscle during ejaculation moves the sperms out of the tail storage site. Although the sperm within the epididymis are motile, transport through the epididymis is largely by peristalsis.
The ductus deferens runs from the tail of the epididymis to the seminal vesicles, a distance of approximately 30 cm. Like the ductus epididymis, it is a tubular organ whose wall is formed by a mucosa, muscularis and adventitia/serosa (i.e., some portions of the ductus along its length are covered by peritoneum). The lumen is lined with the same epithelium as the ductus epididymis but with a highly irregular lumen formed by numerous mucosal plicae. Beneath the lamina propria is a thick muscularis consisting of three layers of smooth muscle surrounded by a connective tissue adventitia. The distal termination of the ductus deferens is dilated to form the ampulla (yet another stinkin’ ampulla; where did you see the last one?). In the ampulla the lumen is expanded and the muscular wall thinned to serve as a (yet another) sperm storage site.

The terminal portion of the excurrent duct system, the ejaculatory duct, is formed by the union of the ductus deferens (ampulla) and duct of the seminal vesicle. The ejaculatory ducts (bilateral) run within the prostate to the prostatic portion of the urethra. Its epithelium is similar to that of the ductus deferens but the muscular wall is replaced by the fibromuscular tissue of the prostate gland.

Urethra

The urethra is not part of the excurrent duct system but we’ve gotten the boys this far so let’s get them out the door, so to speak. Derived from the urogenital sinus, the urethra in males serves as the common final duct for both the urinary (urine) and reproductive (semen) tracts. It is divisible into three (toponymic) portions: prostatic, membranous and penile. The prostatic urethra lies within the prostate gland and is lined by transitional epithelium. The membranous urethra lies within the urogenital diaphragm (UG membrane) and is lined by a stratified or pseudostratified columnar epithelium. The penile urethra lies within the corpus spongiosum of the penis and transitions from a pseudostratified columnar at its beginning to a stratified squamous at the urethral orifice.

V. Development of the gonads and extra-testicular ducts

As noted in the urinary system, the urinary and reproductive systems share a common developmental origin. In males, the testes and excurrent ducts arise from the 3 different tissues: intermediate mesoderm, mesodermal epithelium and primordial germ cells. The intermediate mesoderm forms the urogenital ridge on the posterior abdominal wall and gives rise to the (1) stroma of the testes and (2) mesonephric (Wolffian) duct (the duct of a fetal renal system). The mesodermal (coelomic) epithelium gives rise to the (1) nurse (Sertoli) cells and (2) paramesonephric (Müllerian) duct. The primordial germ cells, originally of epiblastic origin, migrate from the allantoic wall and give rise to the spermatagonia.

During embryonic development the mesonephric duct (Wolffian) develops tubules that connect to the developing seminal vesicles. These tubules form the (1) efferent ductules and (2) proximal ductus epididymis. The mesonephric duct proper forms the remainder of the ductus epididymis, ductus deferens, seminal vesicles, and ejaculatory ducts. The paramesonephric (Müllerian) duct degenerates but small portions persist as the prostatic utricle (male homolog of the uterus) and appendix testis. The urethra develops from the urogenital sinus, the primitive cloaca that serves as the common terminus of the digestive, reproductive and urinary systems.

Sex determination

As mammals, genetic sex in humans is determined at fertilization by the presence/absence of the Y-chromosome. Gonadal sex determination begins at 7 weeks gestation. At this time the transcription of the SYR gene on the Y-chromosome begins synthesis of a protein called testis-determining factor (TDF). Secretion of this protein stimulates (1) the nascent Leydig cells to produce testosterone leading to an elaboration of the mesonephric duct (see above) and (2) nurse cells to secrete Mullerian-inhibiting factor (MIF) leading to the regression of the paramesonephric duct. Conversion of testosterone to DHT (dihydrotestosterone) induces the urogenital sinus to form the male external genitalia, prostate and urethra.

In the absence of SYR, the default program is female. Specifically, without TDF the mesonephric duct fails to elaborate and persists as vestigial structures in the adults (see attached figure). Instead the paramesonephric ducts, in the absence of MIF, elaborate to form the uterus and uterine tube (oviduct). In the absence of DHT the urogenital sinus forms female external genitalia.

A. Spermatic cord
Spermatogenesis is temperature sensitive requiring a cooler environment than the body cavity. Thus, the testes are located peripherally in an out-pocketing of the abdominal wall called the scrotum. As noted above, during their descent into the scrotum the testes carry along portions of the peritoneum and abdominal wall (muscle and connective tissue). The peritoneal cavity becomes the cavity of the tunica vaginalis and the fibrous and muscular layers of the abdominal wall becomes the coats (tunics) of the spermatic cord.

The spermatic cord extends from the interior abdominal wall to the testes and contains the proximal half of the ductus deferens and the vascular supply to the testes (testicular artery and venous pampiniform plexus). The cremaster muscle also lies within its tunics. The pampiniform plexus and cremaster muscle assist in the cooling of the seminiferous tubules.

Thus, cooling of the testes is promoted by the following mechanisms:
1. Peripheral location within the scrotum
2. Dartos muscle – this is a layer of smooth muscle within the dermis of the scrotum. Contraction decreases the surface area (SA) of the scrotum conserving heat; relaxation increase SA to release heat and promote spermatogenesis.
3. Vascular counter-current heat exchange: The testicular artery within the spermatic cord is encased within the venous pampiniform plexus; heat of the arterial blood is transferred to the cooler returning venous blood, thus delivering cooled arterial blood to the testes.
4. Cremaster muscle: This muscle elevates the testes closer to the body to conserve heat and inhibit spermatogenesis; conversely, relaxation lowers the testes and promotes spermatogenesis; this muscle typically has a limited range of motion in human.

V. Associated glands (seminal vesicle, prostate, bulbourethral)

Seminal vesicles

The seminal vesicles occur bilaterally on the posterior aspect of the urinary bladder. They develop as an evagination of the ductus deferens. They consist of a single, highly convoluted tube whose wall is comprised of a mucosa (epithelium and lamina propria), muscularis (smooth muscle) and adventitia/serosa (again, some portions are covered by peritoneum). The lining epithelium is variable but most typically presents as a pseudostratified columnar/cuboidal epithelium. The columnar cells are secretory and the basal cells are stem cells. The epithelium produces a viscous secretion containing fructose that serves as the principal metabolite for sperm. Secretory activity is stimulated by testosterone.

Prostate gland

The prostate gland is a large, midline (unpaired) gland underlying the urinary bladder and perforated by the prostatic urethra and ejaculatory ducts. Covered by a fibroelastic capsule, it consists of 30-50 tubuloalveolar glands which open to the urethra. The epithelium is extremely variable (squamous, cuboidal, pseudostratified) and secretes semen components including citric acid (nutrient) fibrinolysin (keeps semen liquefied) and serine protease (PSA). Like the seminal vesicle, secretory activity of the prostate is stimulated by testosterone. The glands are surrounded by a fibromuscular stroma which contracts during ejaculation to empty the glands’ lumens. In older individuals (e.g., Drs. Swartz and Brokaw) the lumen may contain prostatic concretions (corpora amyloidea), a precipitate of the secretions.

The bulbourethral (Cowper’s) glands are small, bilateral glands within the urogenital diaphragm. These tubuloalveolar glands secrete a mucous that lubricates the urethra prior to ejaculation. The glands are formed by a simple columnar epithelium and their ducts open to the penile urethra. Secretory activity is stimulated by testosterone.

VII. Penis

The penis is the male copulatory organ. It is formed by three erectile bodies surrounded by a dense fibroelastic capsule called the tunica albuginea. The three erectile bodies are bilateral corpora cavernosa which are positioned dorsally and the unpaired ventral corpus spongiosum. The corpus spongiosum contains the spongy urethra and its erectile tissues expand distally as the glans.
The erectile tissue consists of numerous wide spaces lined with vascular endothelium and surrounded by smooth muscle. Erection is mediated by vasodilation of the incoming arteries and constriction of the venous outflow; this results in the vascular spaces becoming engorged with blood and creating a rigid body for intromission.

The skin of the penis is thin and loose except over the glans. It is highly innervated by both somatic sensory and autonomic nerves which are important in erection and ejaculation. These nerves cross the prostate to reach the penis and damage to them during prostate surgery can result in impotence.

Surprisingly, the penis in humans lacks a baculum (os penis) positioned between the erectile bodies, as would be expected given the phylogenetic distribution of these bones in mammals.