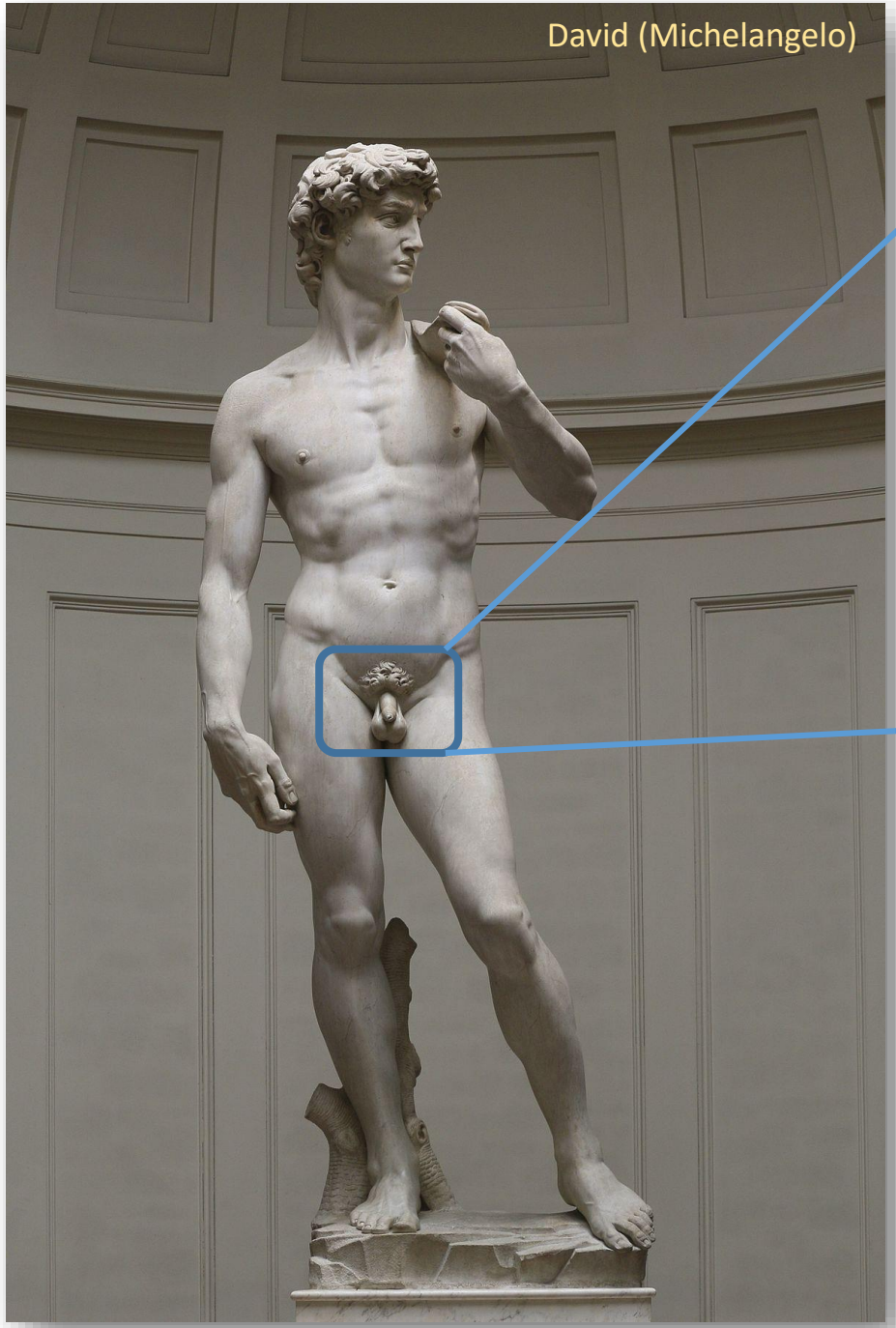


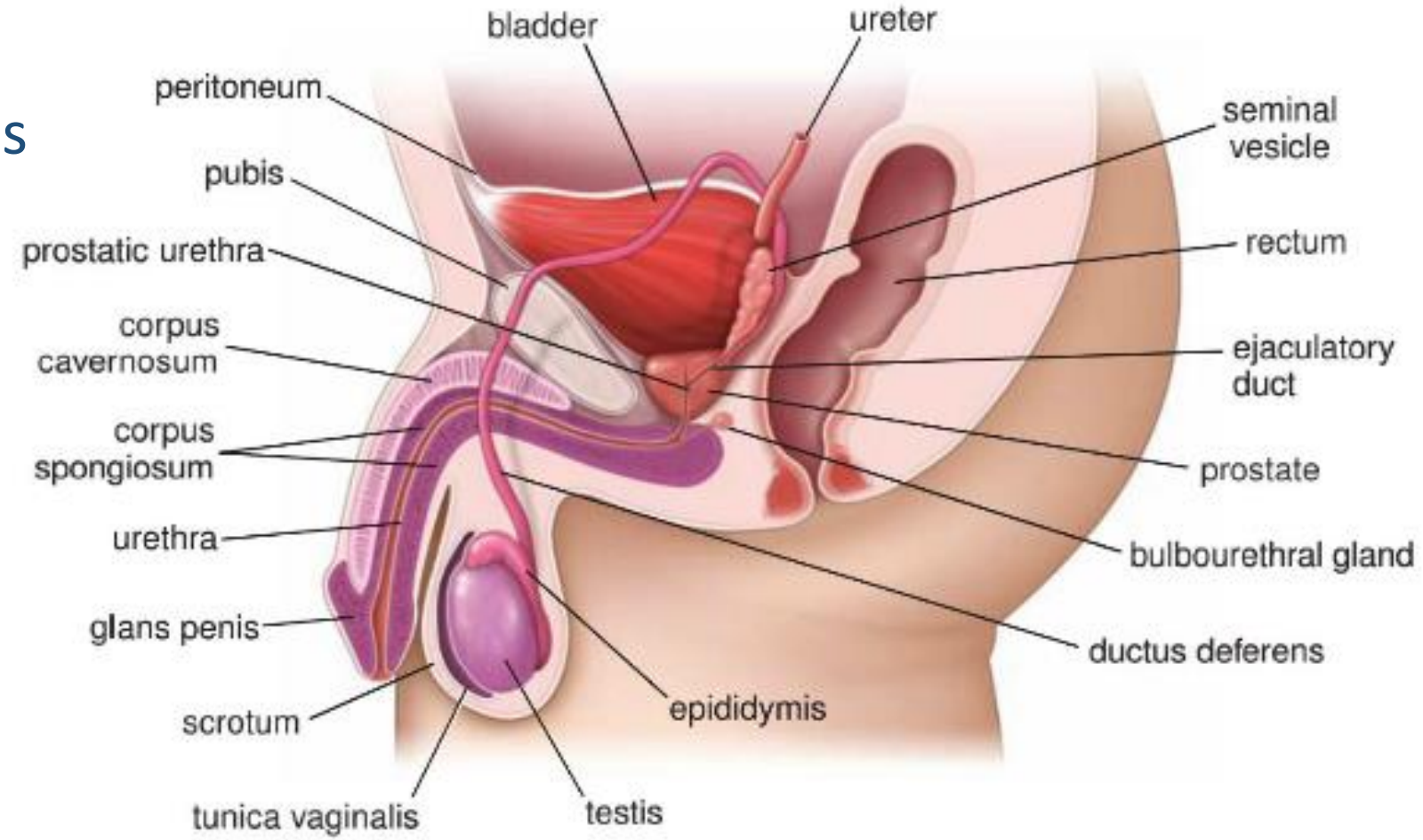
MED316
REPRODUCTIVE SYSTEM AND DISORDERS
HISTOLOGY OF THE MALE REPRODUCTIVE SYSTEM

Histology of Testes and Spermatogenesis

Dr. Sinan Özkavukcu
Ankara University Faculty of Medicine
Dept. of Histology – Embryology
Lab Director - Center for Assisted Reproduction

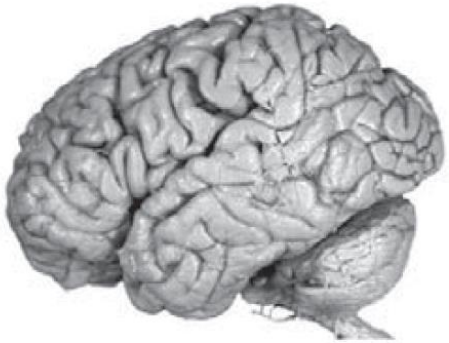
Male Reproductive System

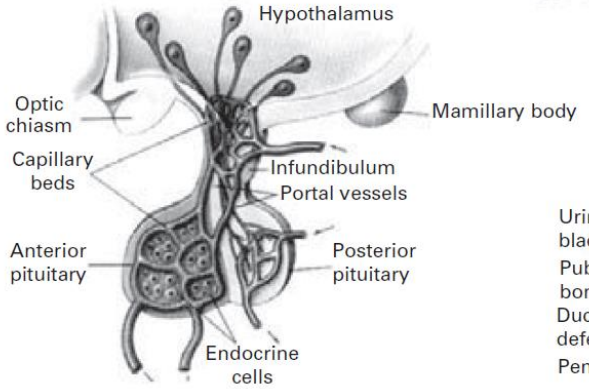
- Testes
- Genital excurrent ducts
  - Ductuli efferentes
  - Ductus epididymis
  - Ductus deferens
- Accessory sex glands
  - Seminal vesicles
  - Prostate
  - Bulbourethral glands
- External genitalia
  - Penis
  - Scrotum

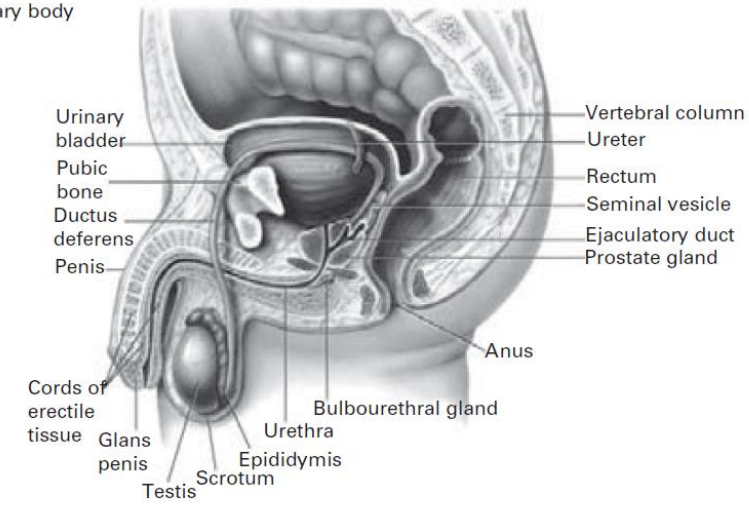


Endocrine control of male reproduction

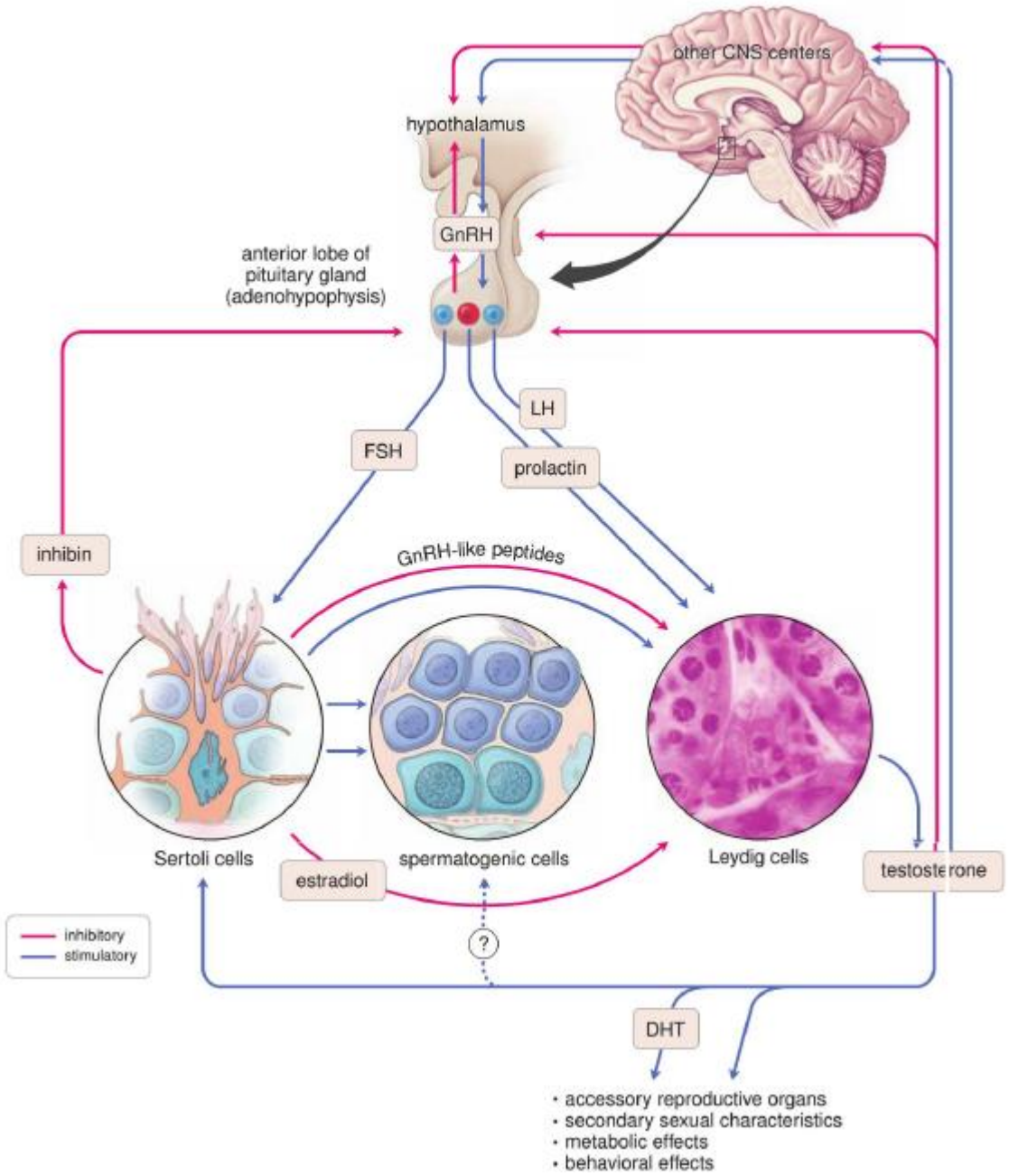
- Onset of puberty
  - **brain** determines the timing of onset of puberty
  - crucial role in controlling sexual behavior and reproduction is played by the **hypothalamus**
- Terminals of gonadotropin-releasing hormone (GnRH)-secreting neurons release their secretions in the median eminence and infundibulum, where they enter the hypophyseal portal system
- GnRH is then driven to the anterior pituitary, precisely to the gonadotrophs, basophil-staining cells, which constitute 10%–15% of anterior pituitary cells and are located throughout the entire anterior lobe
- The gonadotrophs synthesize follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and release them into the systemic circulation; both hormones reach the testis by testicular arteries.







An Introduction to Male Reproductive Medicine, Niederberger



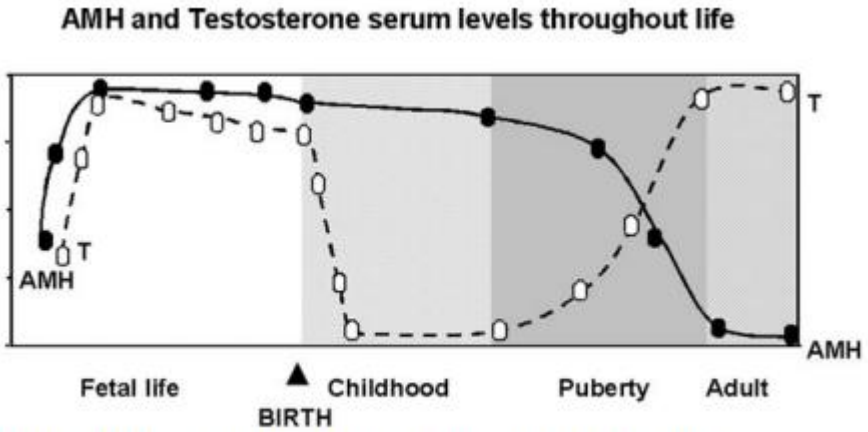


Figure 4. Profiles of serum levels of testosterone and AMH in the male.

Anti-Müllerian Hormone in Disorders of Sex Determination and Differentiation
Arq Bras Endocrinol Metab vol 49 nº 1 Fevereiro 2005

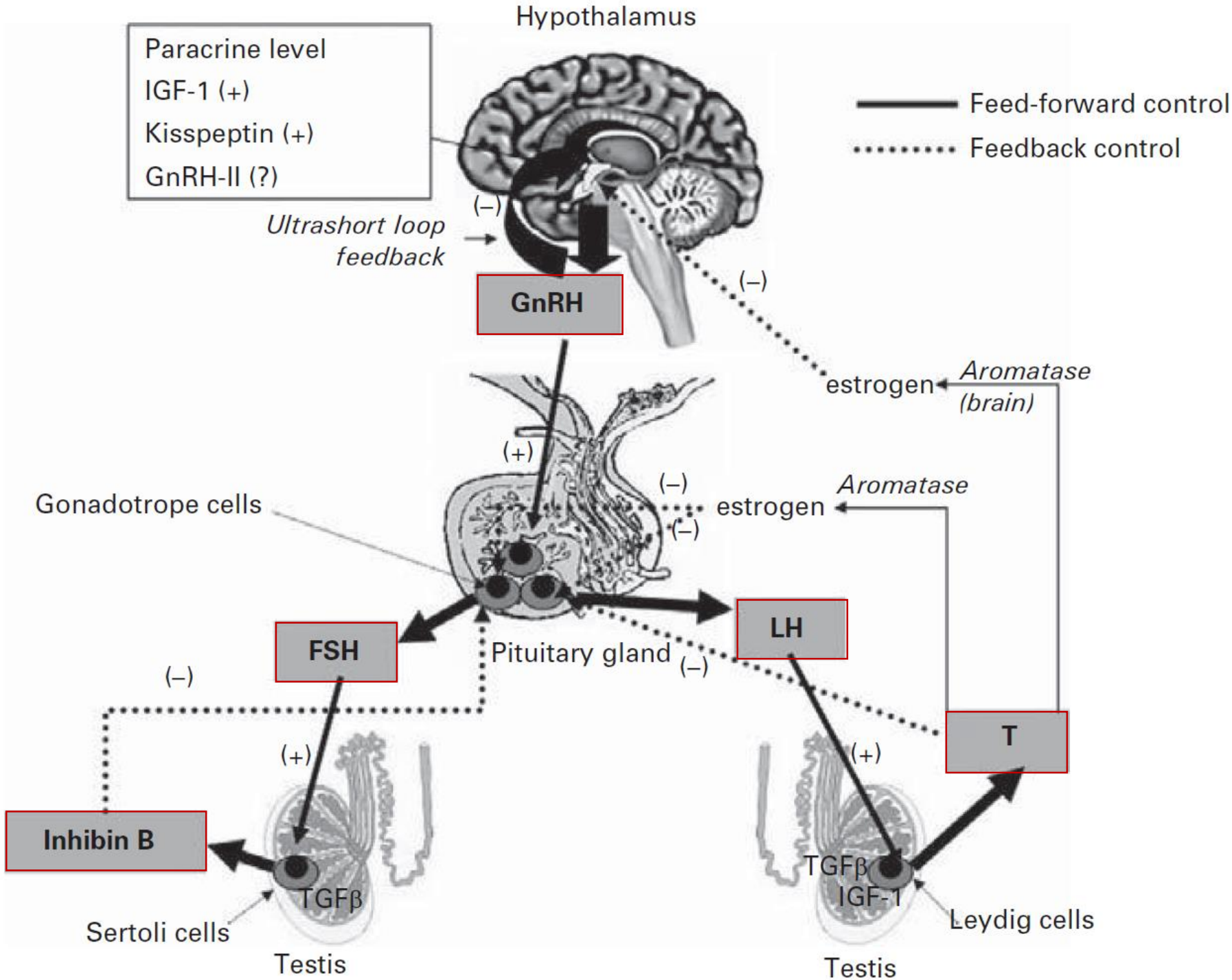

Hypothalamus
Paracrine level
IGF-1 (+)
Kisspeptin (+)
GnRH-II (?)
Feed-forward control
Feedback control
Ultrashort loop feedback
(–)
GnRH
(–)
estrogen
Aromatase (brain)
(+)
(–)
Gonadotrope cells
Aromatase
estrogen
(–)
FSH
Pituitary gland
LH
(–)
(–)
T
(+)
(+)
Inhibin B
TGFβ
Sertoli cells
TGFβ
IGF-1
Leydig cells
Testis
Testis

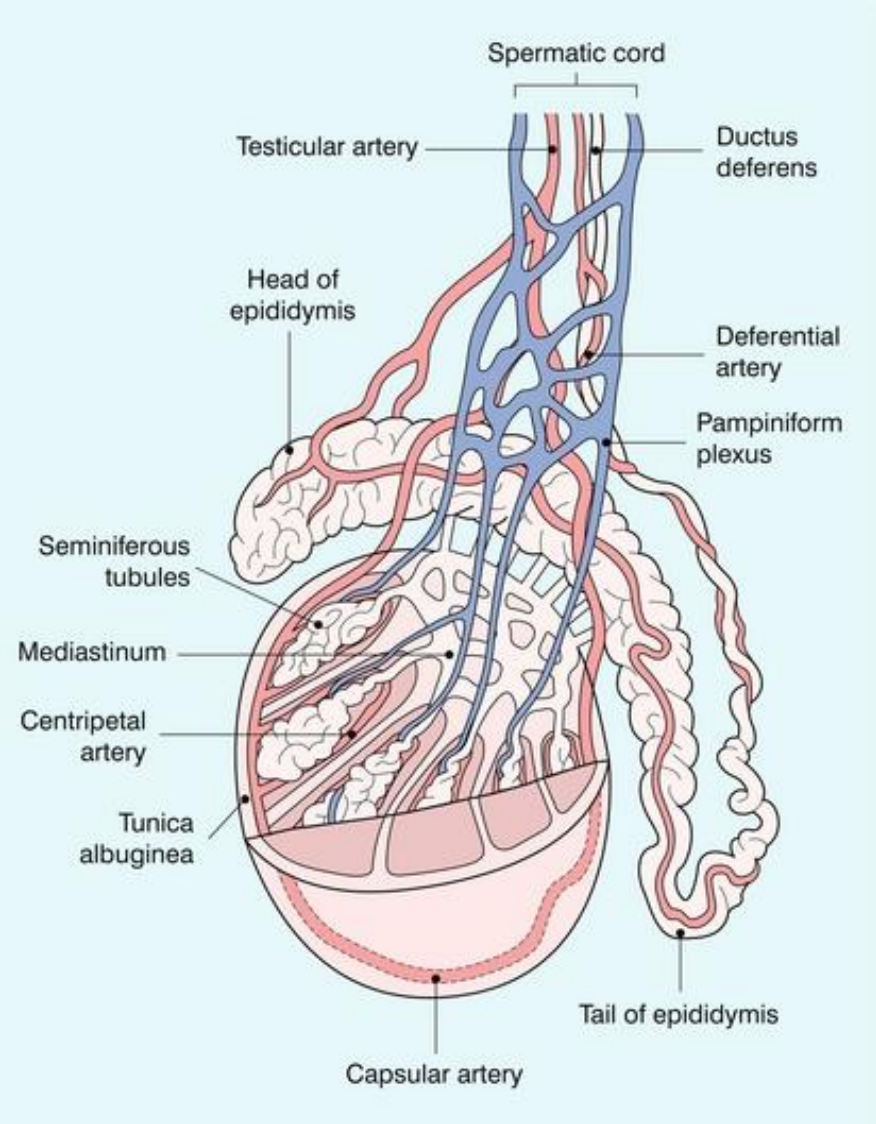
Table 1.1 Regulation of hypothalamic–pituitary–gonadal axis hormone release

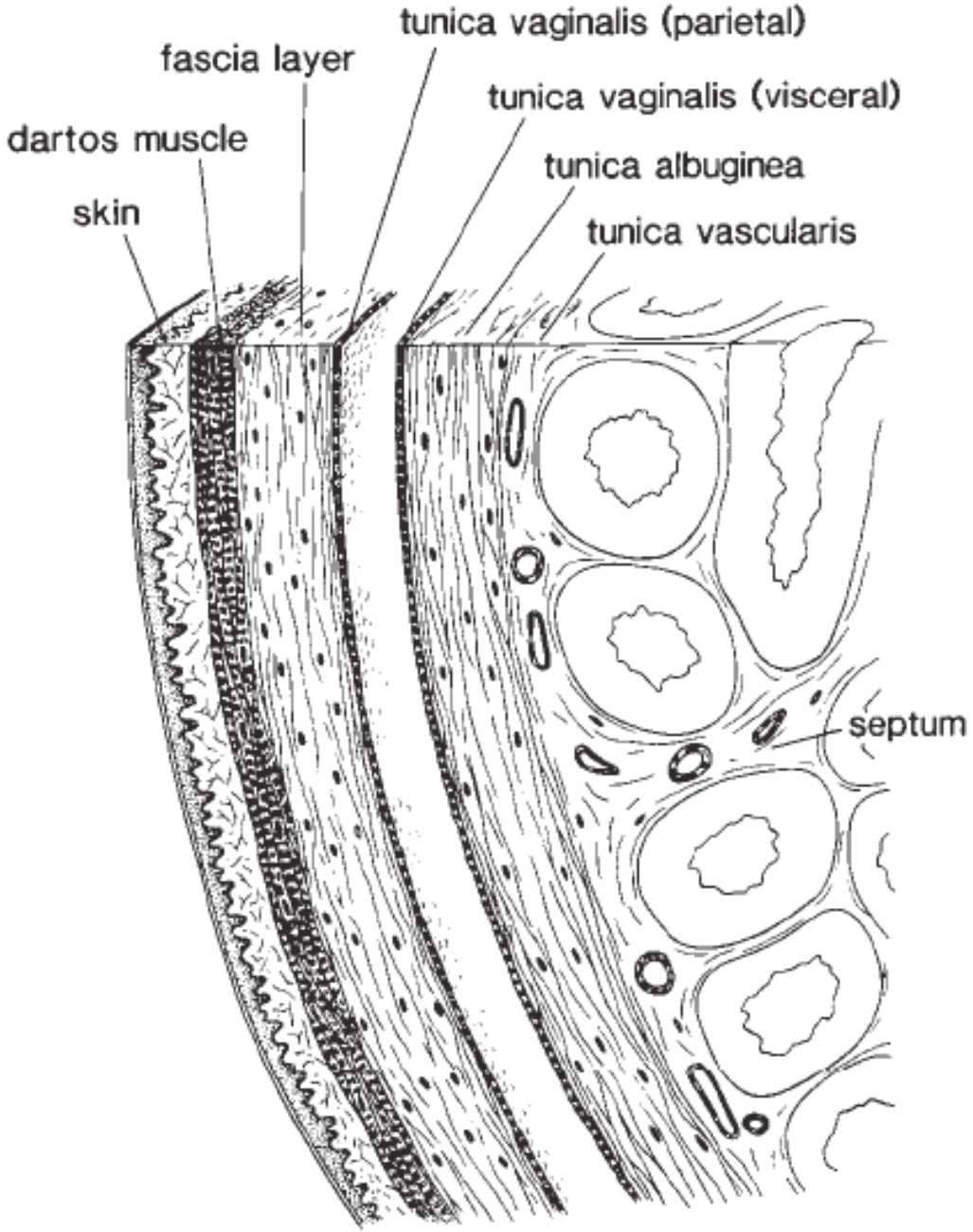
Hormone	Autocrine regulation	Paracrine regulation	Endocrine regulation
GnRH	GnRH itself (−)	GnRH II (+), IGF-1 (+), kisspeptin (+)	Testosterone (−), estrogens (−), neurotensin (+), norepinephrine (+)
FSH	–	Activin (+), follistatin (−)	GnRH (+), estrogens (−), inhibin B (−)
LH		Activin (+), follistatin (−)	GnRH (+), testosterone (−)
Testosterone	–	IGF-1 (+), GH(+), CRH (−), TGF-β (−), IL-1α (±)	LH (+)

+ Stimulatory effect, – Inhibitory effect. Transforming growth factor-β (TGF-β), corticotropin-releasing hormone (CRH), interleukin 1α (IL-1α), growth hormone (GH), insulin-like growth factor 1 (IGF-1).

Circulation of testes

- The arterial supply to the testes follows the lobular division of seminiferous tubules,
- Each lobulus is supplied by one recurrent artery; segmental arteries and capillaries become branched between the Leydig cells and then give rise to the venous system.
- **The pattern of blood supply to the testis is also essential for maintaining a lower testicular temperature compared with body temperature.**
- In the pampiniform plexus, the convoluted testicular artery is surrounded by several veins coiling around the artery many times, so arterial blood is cooled down by surrounding venous blood.
  - Within the scrotum, the temperature of the testes is 2°C to 3°C below body temperature only needed for spermatogenesis

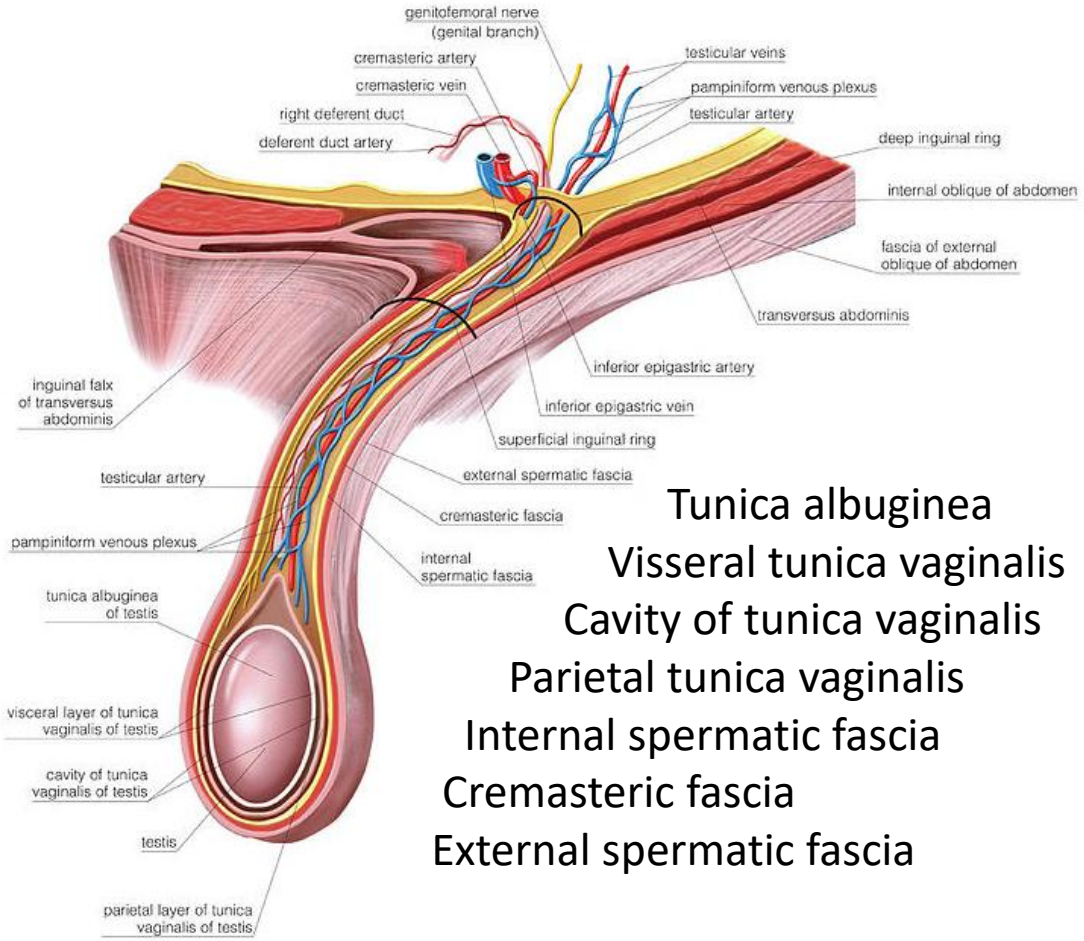




The scrotum

elongated musculofascial pouch, which is continuous with layers of the anterior abdominal wall and projects into the scrotum

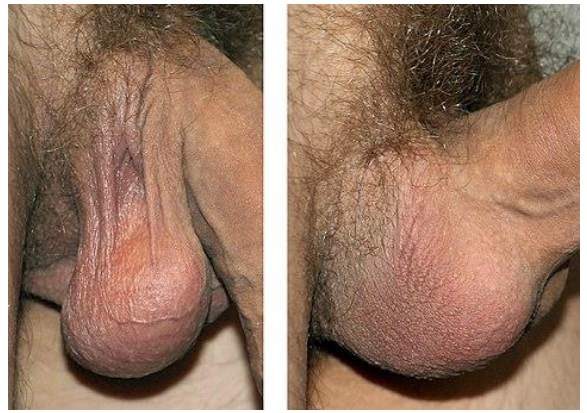
- adult testes are paired ovoid organs that lie within the scrotum, located outside the body cavity



Tunica albuginea
Visseral tunica vaginalis
Cavity of tunica vaginalis
Parietal tunica vaginalis
Internal spermatic fascia
Cremasteric fascia
External spermatic fascia

Temperature control inside the testes is essential for spermatogenesis, but not for steroidogenesis

- The pampiniform plexus
  - The pampiniform venous plexus is a paired network of several small veins found within the spermatic cords of males.
- Cremaster muscle *Ancient Greek translation: "I hang" (Greek: κρεμάννυμι)*
  - the cremaster muscle is a thin layer of striated muscle found in the inguinal canal and scrotum between the external and internal layers of spermatic fascia
  - Anatomically, it originates from the internal oblique muscle, but receives distinctly different innervation and vascular supply in comparison to the internal oblique
  - raise and lower the testes in order to regulate scrotal temperature
  - Contraction and retraction occur in cold, fear, arousal and ejaculation
- Dartos
  - a layer of connective tissue found in the penile shaft, foreskin, and scrotum
  - in the scrotum, it consists mostly of smooth muscle. The tone of this smooth muscle is responsible for the wrinkled (rugose) appearance of the scrotum.
  - dartos acts to regulate the temperature of the testicles

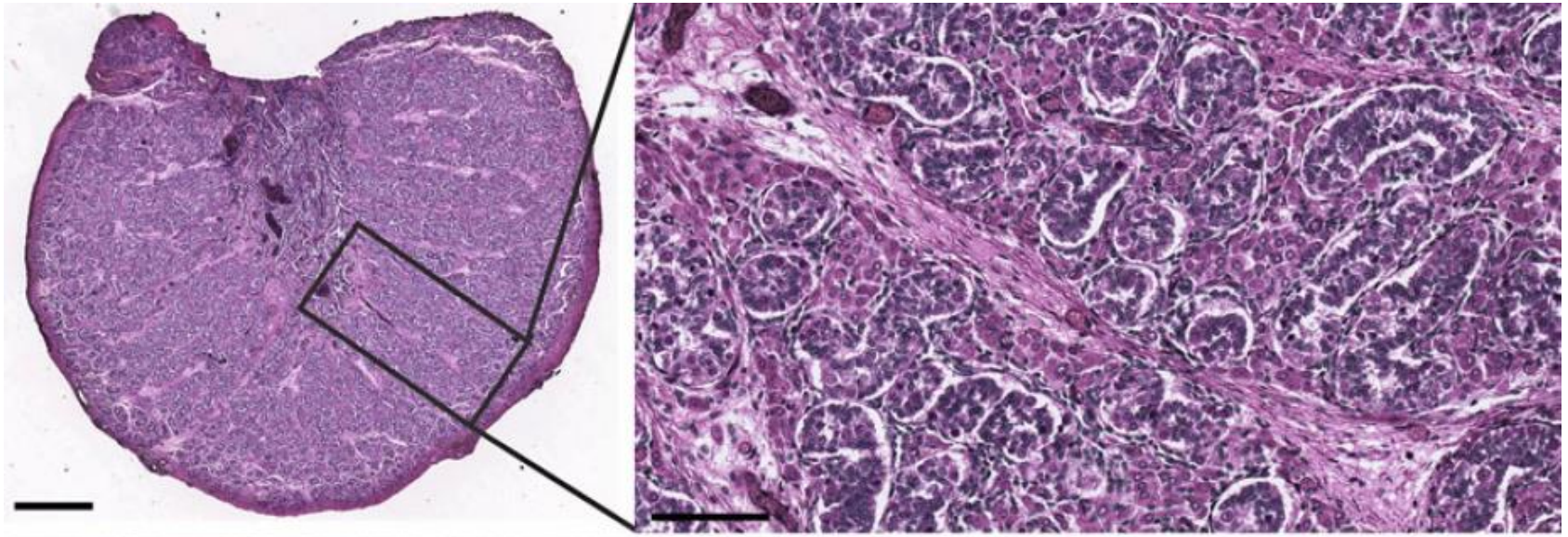


wikipedia

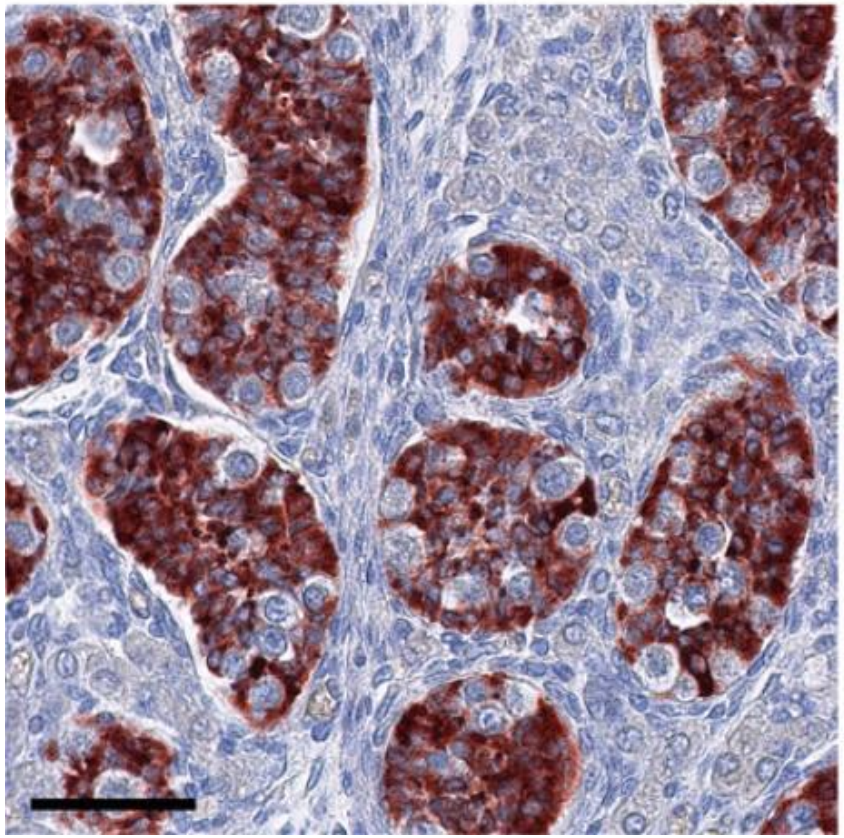
Histology of the pre-pubertal testes

- The control of testicular descent is still controversial. It appears to involve at least four factors;
    1. insulin-like factor 3 (INSL3, also known as Leydig cell insulin-like factor or relaxin-like factor);
    2. calcitonin gene-related peptide (CGRP);
    3. Mullerian inhibiting substance (MIS), also known as anti-Mullerian hormone;
    4. Androgens
- In general, the histology of the infantile testis is similar to that of the third-trimester fetal testis.
- The seminiferous tubules contain infantile spermatogonia and undifferentiated Sertoli cells, which produce large amounts of anti-Müllerian hormone (AMH) and inhibin B
- A few gonocyte-like cells may be seen during the first few months after birth. These cells express some of the embryonic germ cell markers (e.g., placental-like alkaline phosphatase [PLAP], M2A/D2-40/PDPN) and pluripotency markers, such as OCT4, NANOG, and AP2 g)
- Serum levels of gonadotropins, testosterone, insulin-like factor 3 (INSL3), and inhibin B peak around age 2–3 months, but receptors of androgens are lacking on Sertoli cells so no maturation occurs. At 6th month LH and testosteron are un-measurable
- Sertoli cells remain immature and highly positive for AMH and podoplanin (M2A/D2-40/PDPN) until puberty, when both proteins are rapidly downregulated, whereas serum testosterone increases again
- Leydig cells, which initiate testosterone production in response to sharply increased LH stimulation, increase in number and display the typical morphology of adult Leydig cells.
- This is associated with rapid growth of seminiferous tubules and the onset of spermatogenesis. The pubertal period during which the testis grows often lasts a couple of years and concludes when the gonad has reached an orchidometer-measured volume of 15–30 mL.
- Descent of the testis is sometimes obstructed, resulting in **cryptorchidism** or **undescended testes.** This condition is common (30%) in premature newborns and about 1% of full-term newborns. Cryptorchidism can lead to irreversible histologic changes in the testis and increases the risk of testicular cancer. Therefore, an undescended testis requires surgical correction (**Orchiopexy**) .

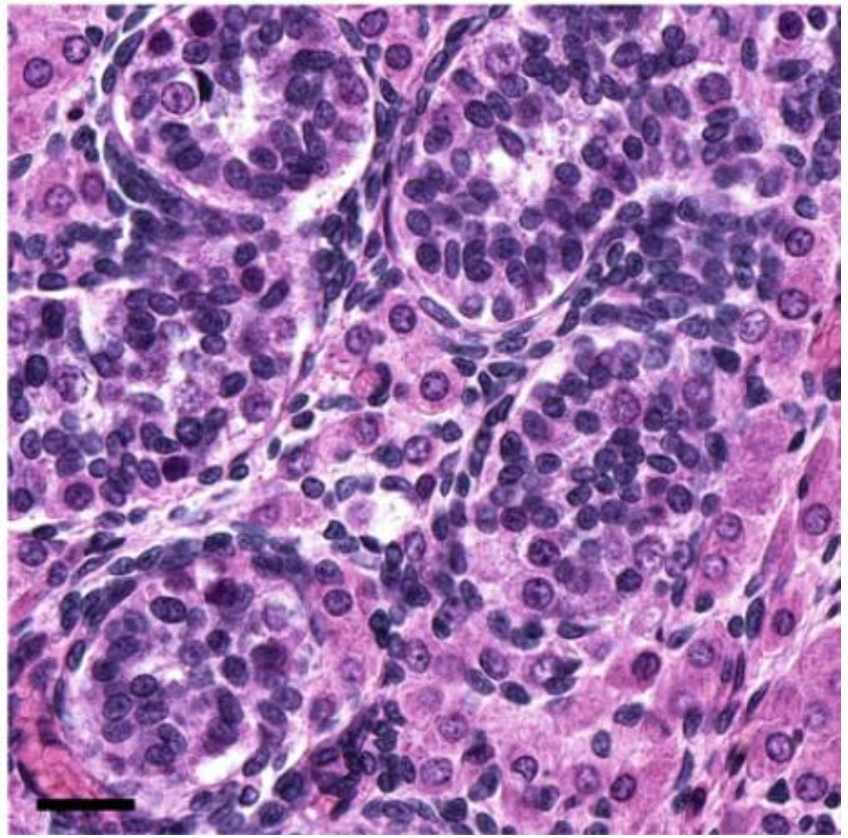
Atlas on the Human Testis, Jezek D. (ed)



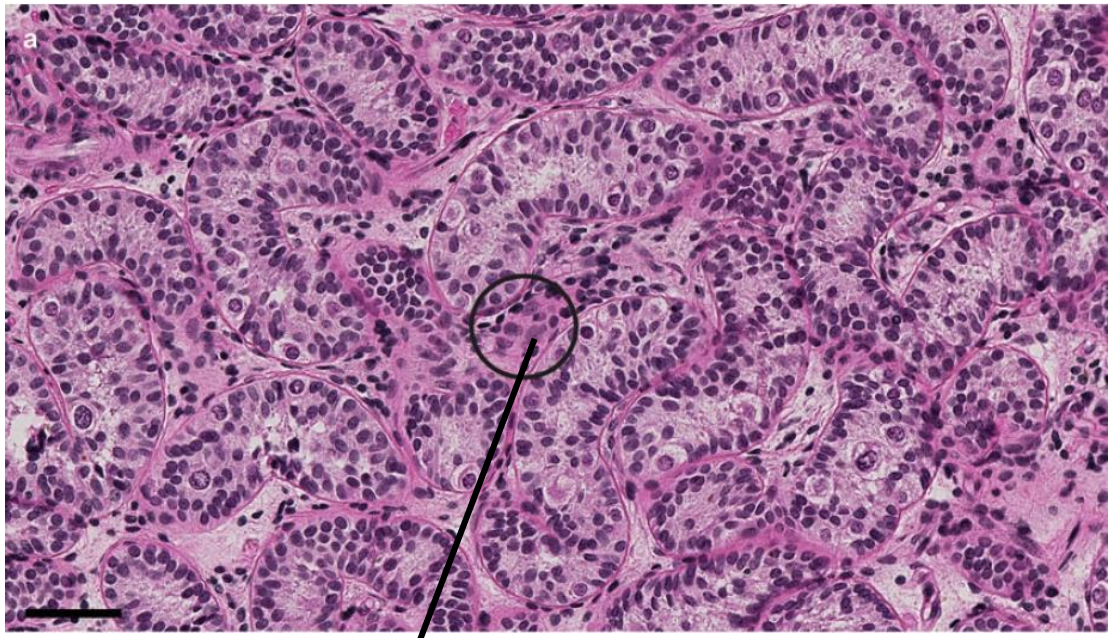
New born testis



AMH immunostaining

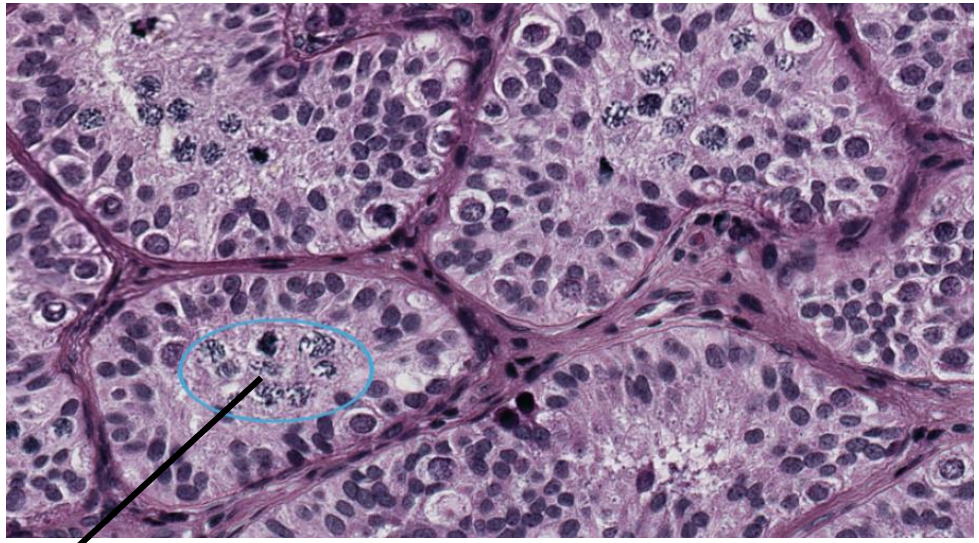


Hematoxylin-eosin



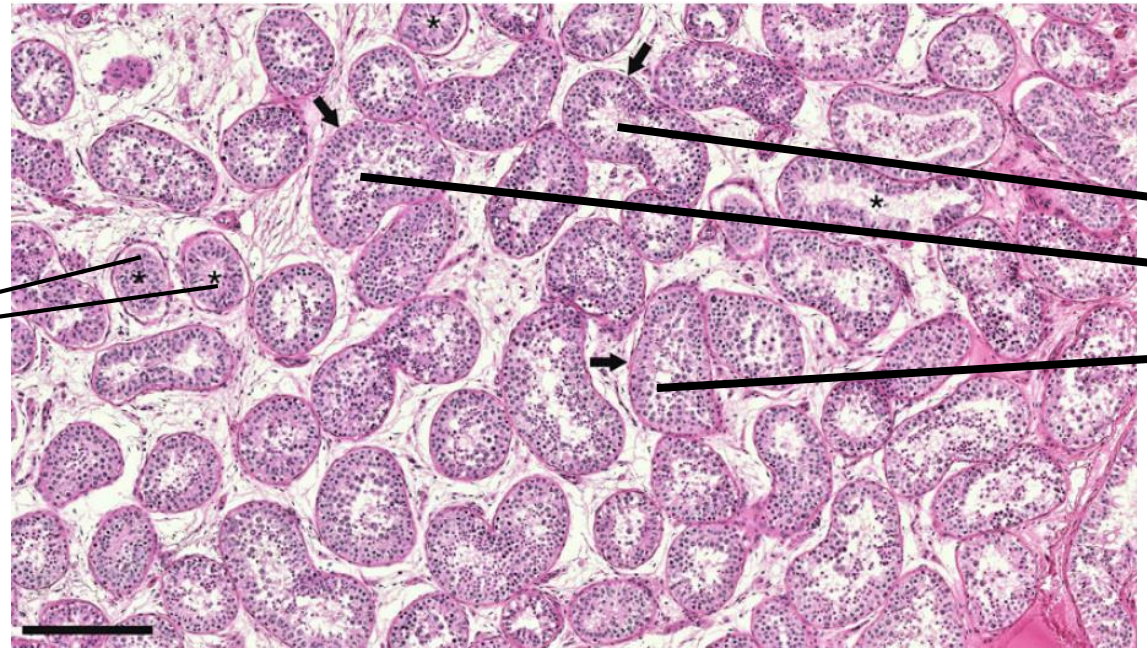
6.5 y.o

Leydig cells



11 y.o

Maturing spermatocytes upto pachytene stage



14 y.o

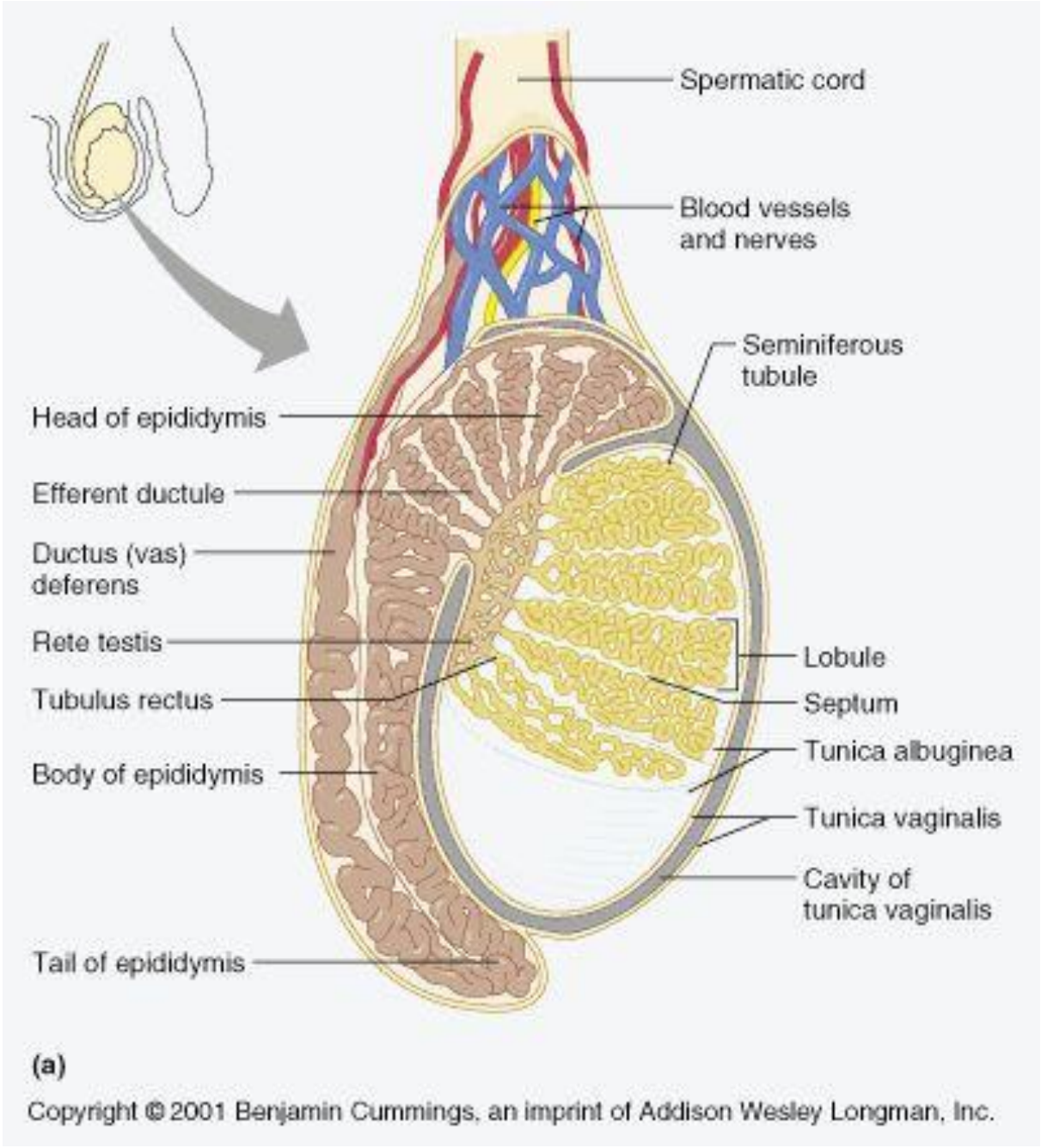
immature tubules without spermatids

complete spermatogenesis and late spermatids (type Sd)

Atlas on the Human Testis, Jezek D. (ed)

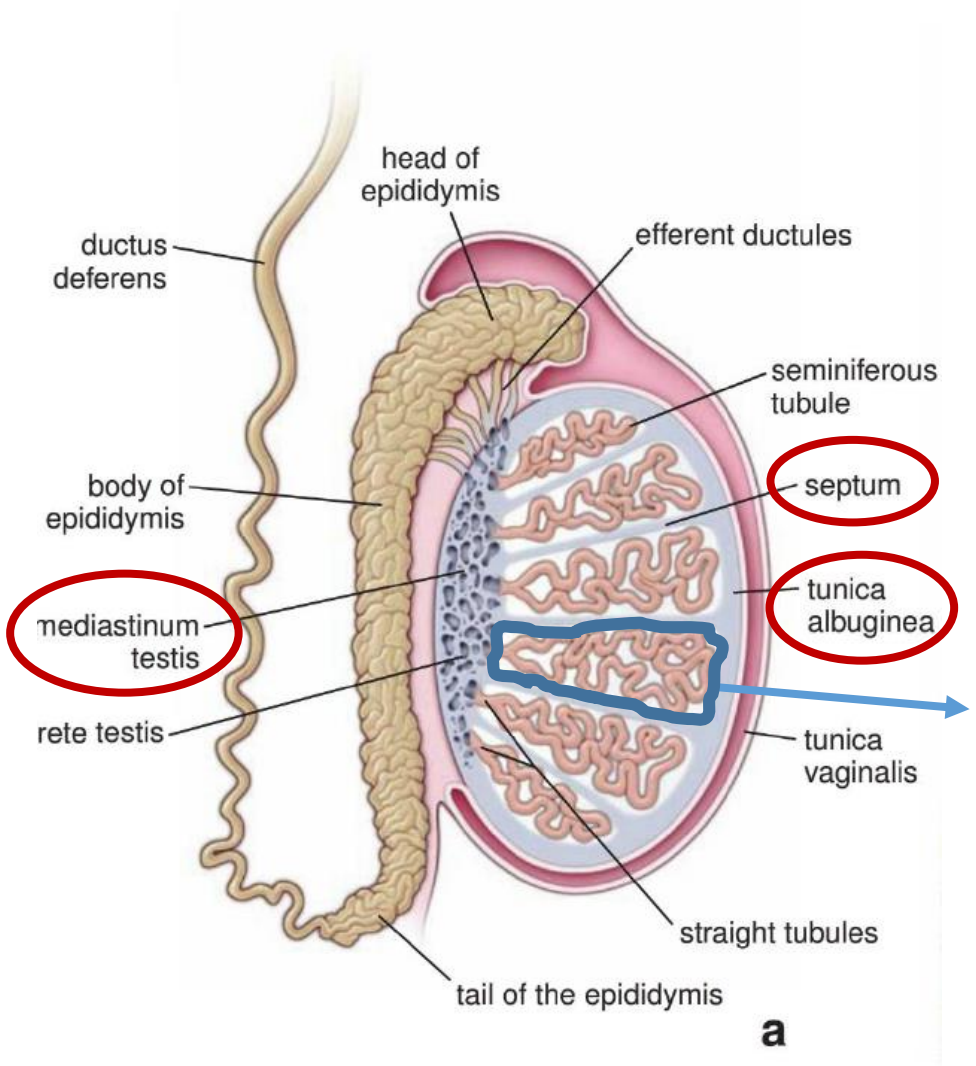
Adult testes

- Stereoidogenesis
- Spermatozoa production and journey
  - Seminiferous tubule
  - Tubulus rectus (straight tubules)
  - Rete testis
  - Ductuli efferentes
  - Epididymis (D. epididymis)
    - Head (Caput)
    - Body (Corpus)
    - Tail (Cauda)
  - Ductus deferens (vas deferens)



Stroma and Paranchyme

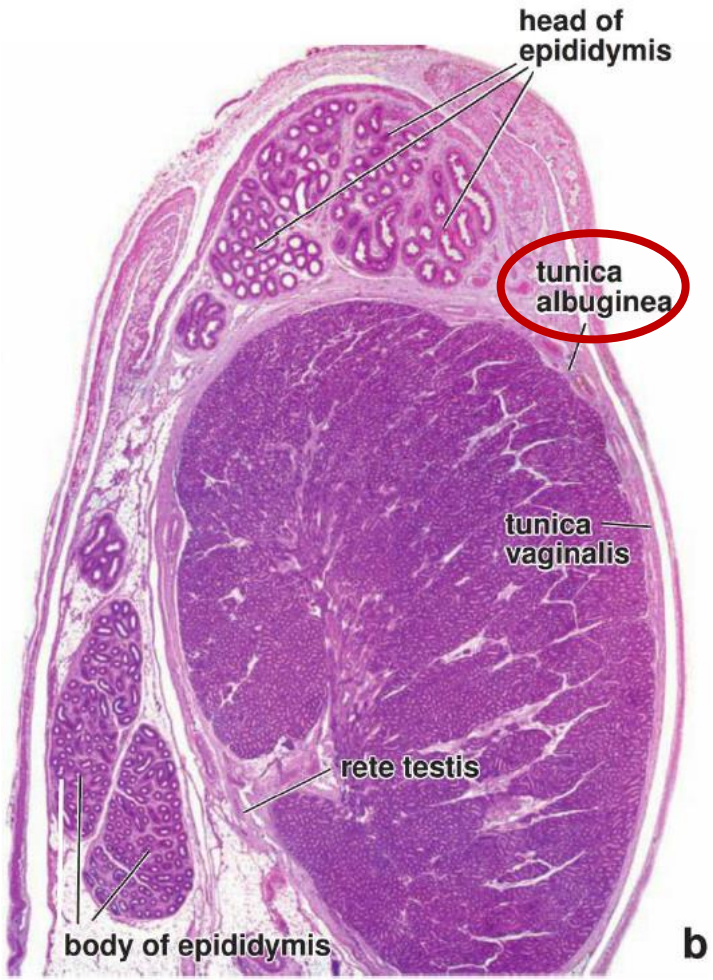
An adult man has a pair of testis which measures about 4–5 cm in length, 3 cm in width, and 2.5 cm in thickness, weighing around 10–15 g each.



lobule

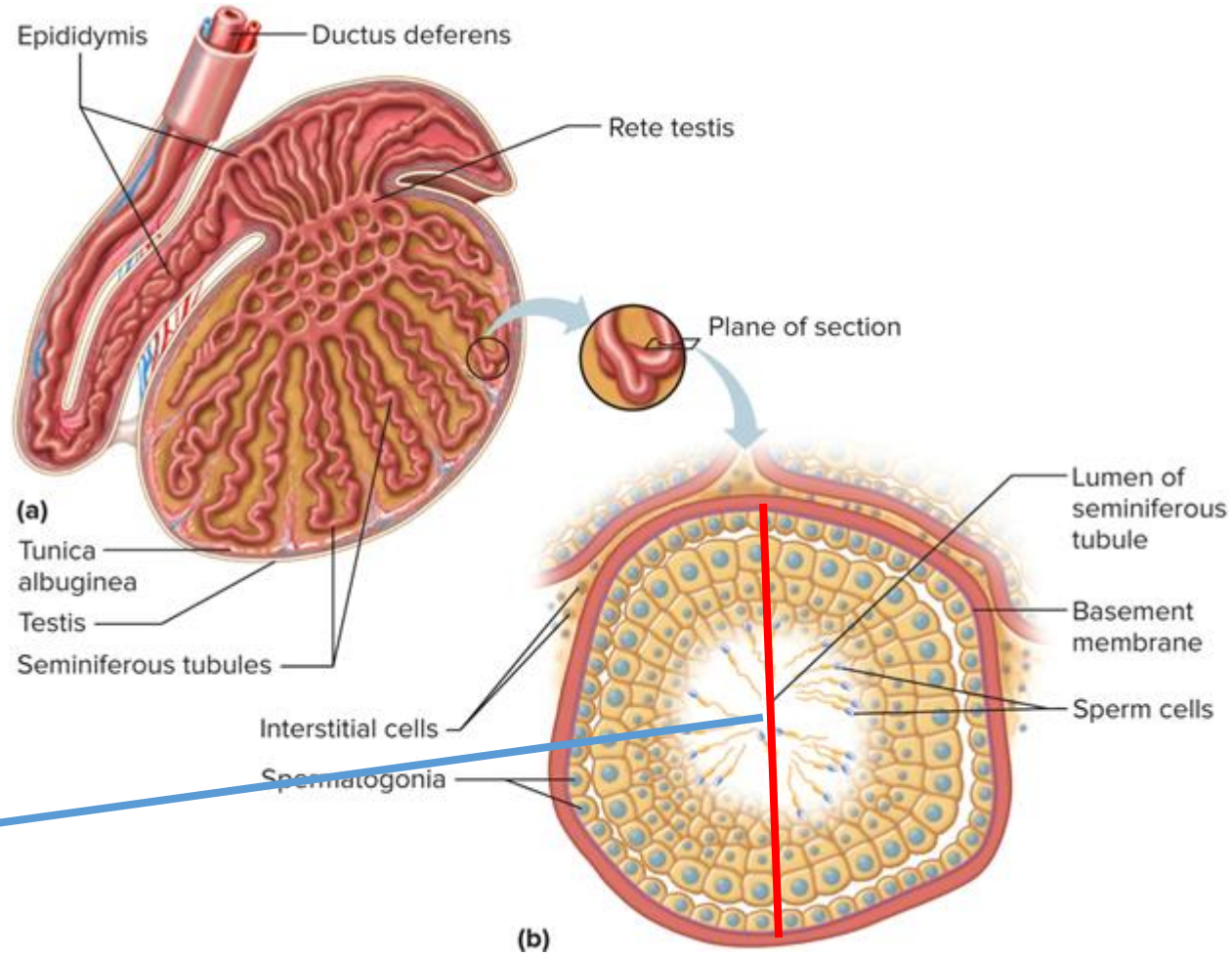
Stroma
Tunica albuginea
Septum
Mediastinum testis
Interstistium

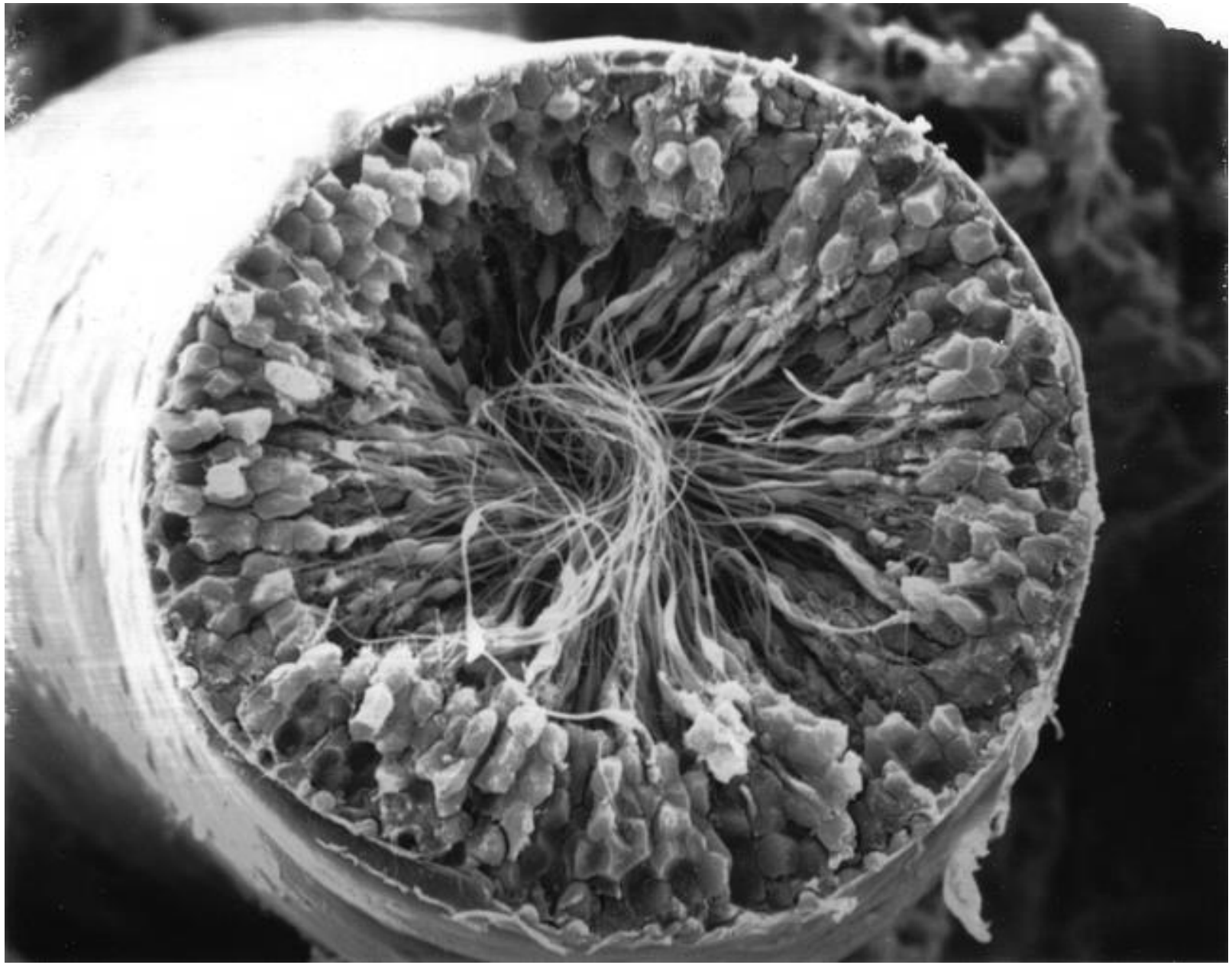
Paranchyme
Tubuli seminiferi contorti
(Seminiferous tubules)



Testicular lobules

- Septa from the mediastinum of the testis extend internally to divide it into approximately 250 lobules. The largest and longest lobules are found in the center of the testis with each lobule having one to four convoluted seminiferous tubules **(Tubuli seminiferi contorti)**. Tubules can reach more than 80 cm in length
- The collective length of the tubules in each testis has been estimated to be between 299 and 981 m, with an average of 540 m.
- The average tubule diameter in young adults is 180 µm (± 30).

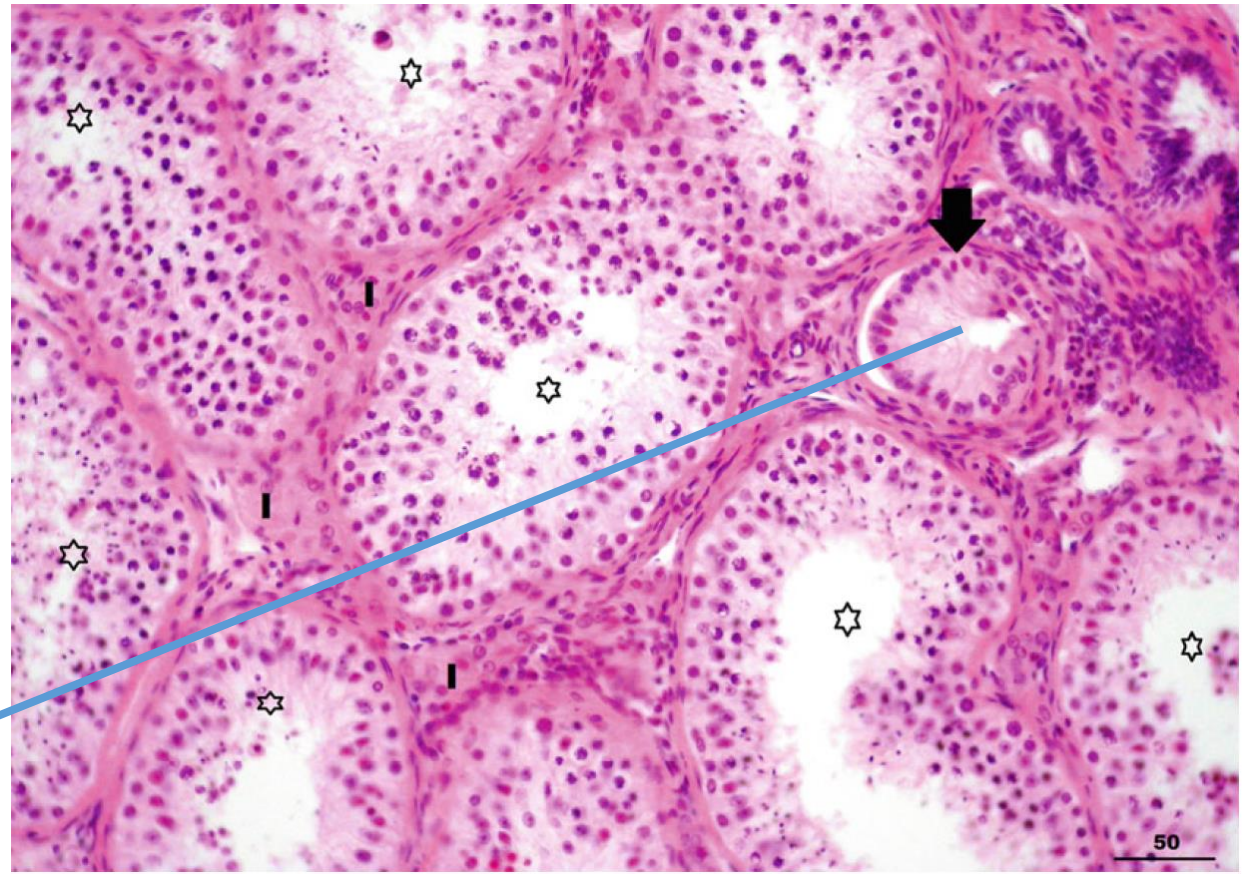




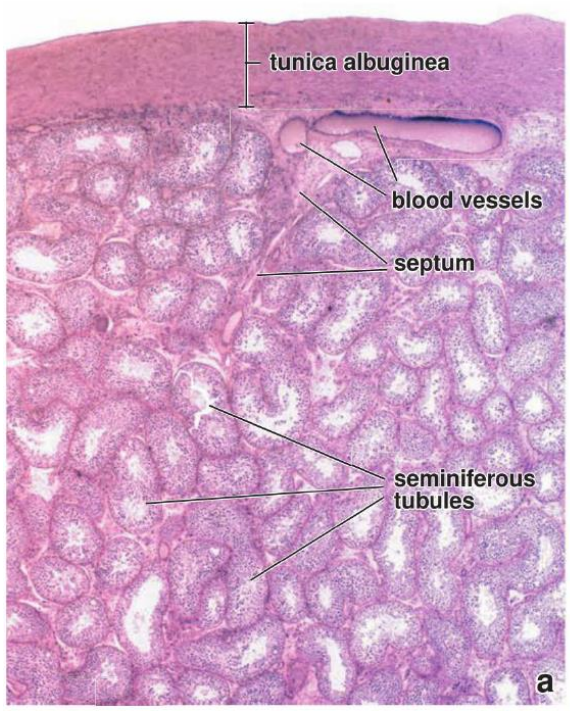
Seminiferous tubules

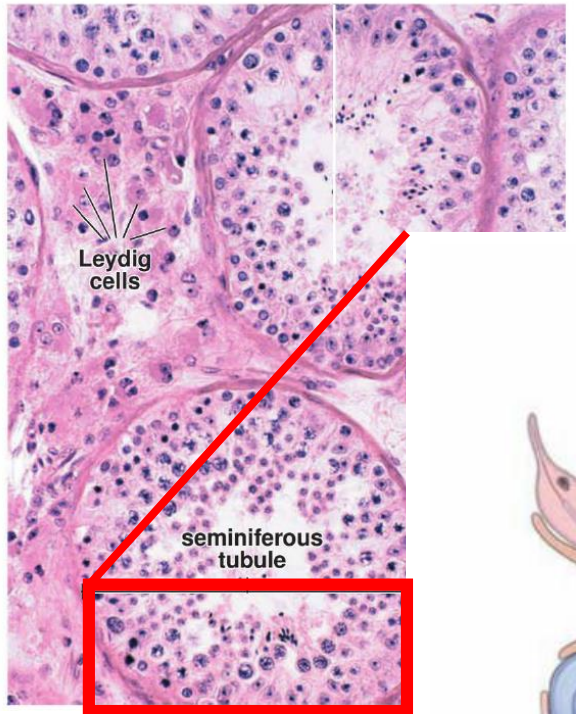
Seminiferous tubule
Tubulus rectus (straight tubules)
Rete testis
Ductuli efferentes
Epididymis (D. epididymis)
Head (Caput)
Body (Corpus)
Tail (Cauda)
Ductus deferens (vas deferens)

- The seminiferous tubules are lined with seminiferous epithelium and are encircled by lamina propria.
- The lamina propria is composed of five to seven layers of flattened peritubular (myoid) cells that occasionally contract (human).
- **The seminiferous epithelium consists of supporting Sertoli cells and spermatogenic cells: spermatogonia, primary and secondary spermatocytes, and early and late spermatids.**
- When early spermatids are released into the tubular lumen (stars), they are considered mature spermatozoa.
- The seminiferous tubules end in a system of narrow straight ducts called *tubuli recti (Tubuli seminiferi recti).*
- These straight ducts are devoid of spermatogenic cells and empty into flattened spaces called the *rete testis*.
- The rete testis is located in the thickening of the tunica albuginea, called the *mediastinum*.

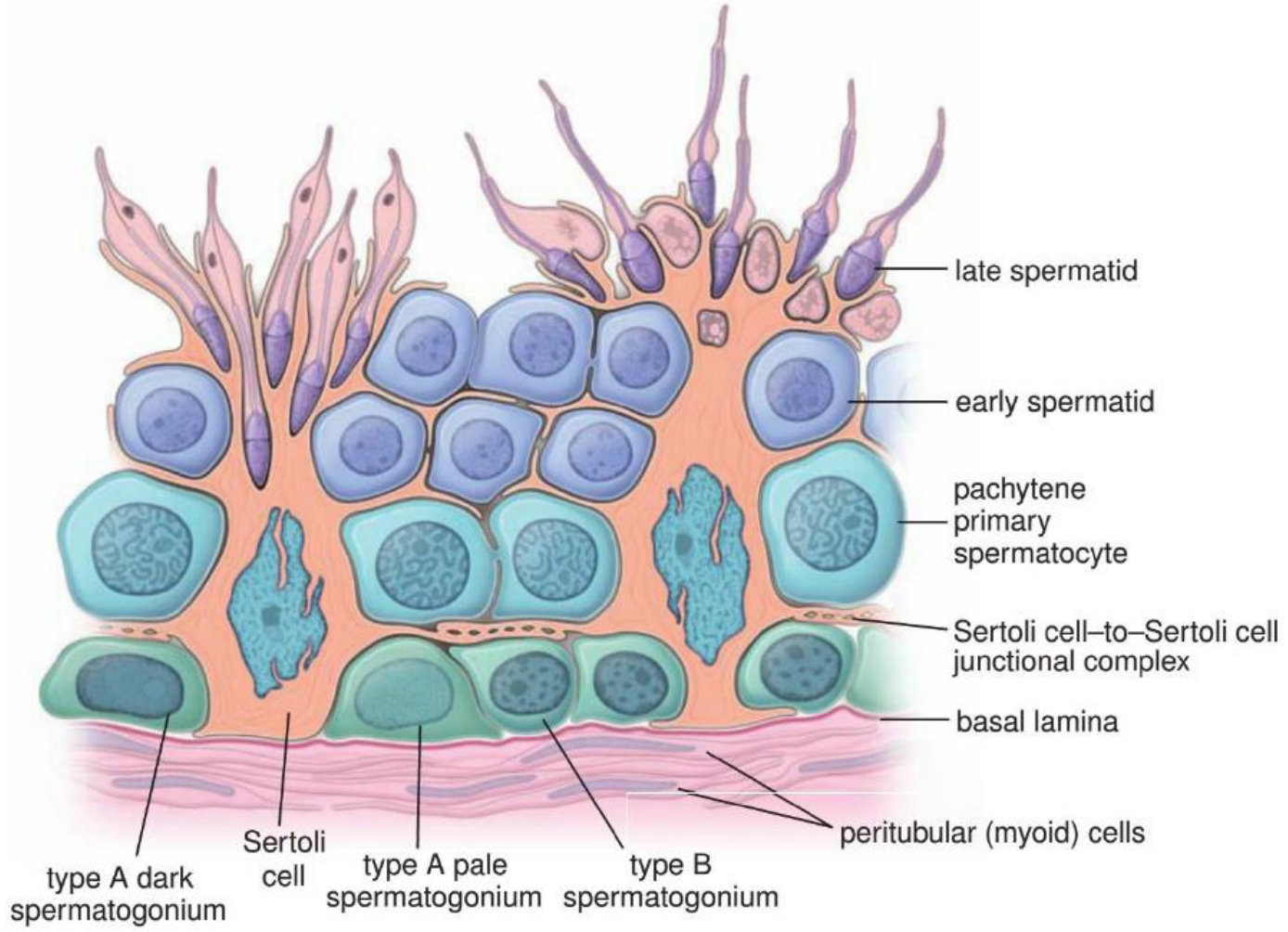


I: **interstitium**, where the Leydig cells are present





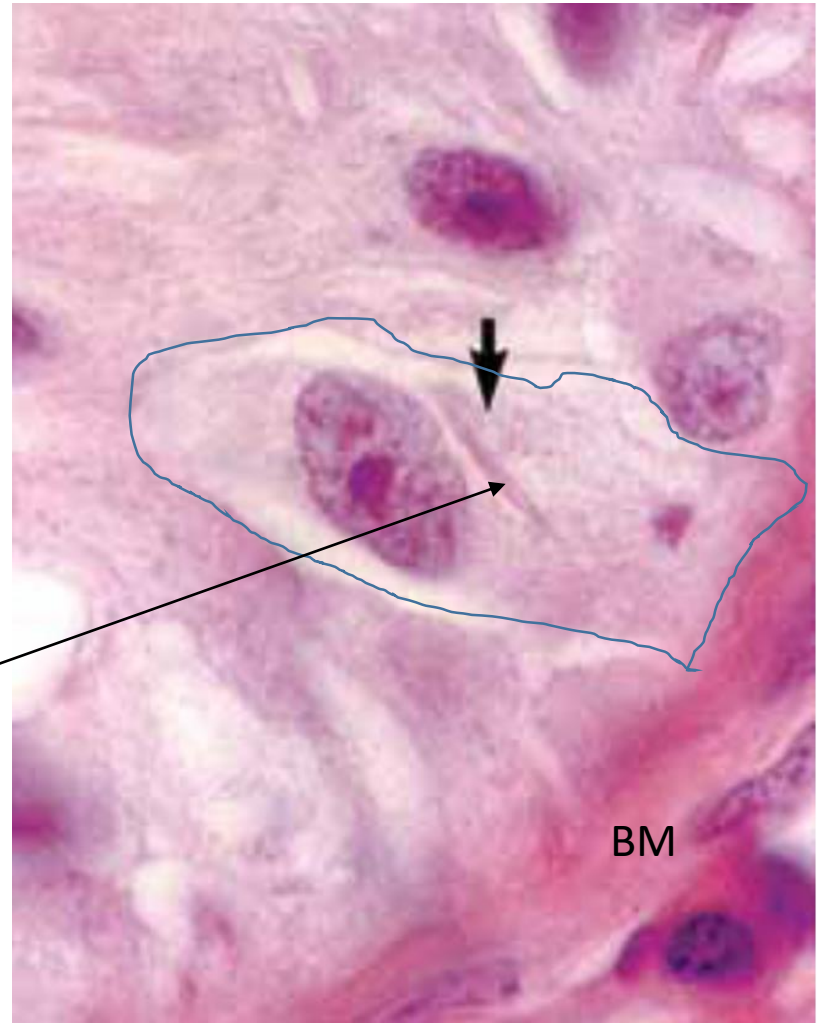
- Basement lamina
- flattened peritubular (myoid)
- Sertoli cells
- spermatogenic cells:
  - spermatogonia,
  - primary spermatocytes
  - secondary spermatocytes
  - early and late spermatids.



Sertoli cells

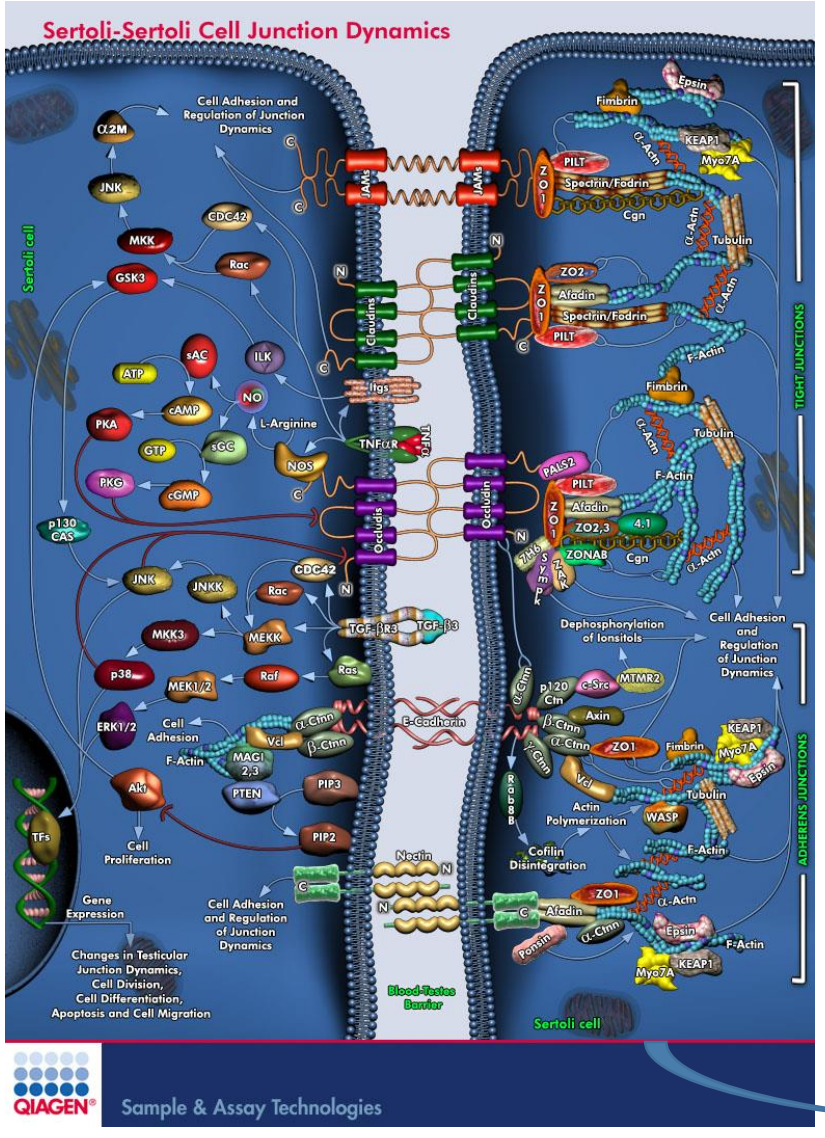
Enrico Sertoli
Italian physiologist

- Tall, columnar, epithelial cells *(supporting,* or *sustentacular, cells.)*
- These cells do not replicate after puberty.
- Sertoli cells are columnar cells with extensive apical and lateral processes that surround the adjacent spermatogenic cells and occupy the spaces between them.
- Hardly seen distinctly in routine hematoxylin and eosin (H&E) preparations.
- Sertoli cells give structural organization to the tubules as they extend through the full thickness of the seminiferous epithelium.
- Sertoli cells contain an extensive sER, a well-developed rER, and stacks of annulate lamellae.
- They have numerous spherical and elongated mitochondria, a well-developed Golgi apparatus, and varying numbers of lysosomes, lipid droplets, vesicles, and glycogen granules.
- The cytoskeleton of the Sertoli cell contains:
  - **microtubules** that are abundant and predominately oriented parallel to the long axis of the cell. are responsible for repositioning of the embedded elongated spermatids in the Sertoli cell cytoplasm.
  - **intermediate filaments** that are a major component of the Sertoli cell cytoskeleton and consist mainly of **vimentin** (class III of intermediate filament proteins).
  - **actin filaments** that are concentrated beneath the plasma membrane near the intercellular junctions.
- In man, characteristic **inclusion bodies of Charcot-Bóttcher** are found in the basal cytoplasm. recent studies detected an accumulation of lipoprotein receptor (CLA-1) proteins. It might be involved in lipid transport and their utilization by the Sertoli cells.



The Sertoli cell-to-Sertoli cell junctional complex consists of a structurally unique combination of membrane and cytoplasmic specializations → Blood-testis barrier

- **Immunological**
  - The barrier isolates the developing germ cells from circulating antibodies in plasma
  - The immune system of the organism does not «see» the haploid, cossingover-experienced spermatozoal
- **Toxicological**
- **Endocrinological**
- **Nutritional**



zonula occludens protein

claudin

Tight junction

Occludin

E-cadherin

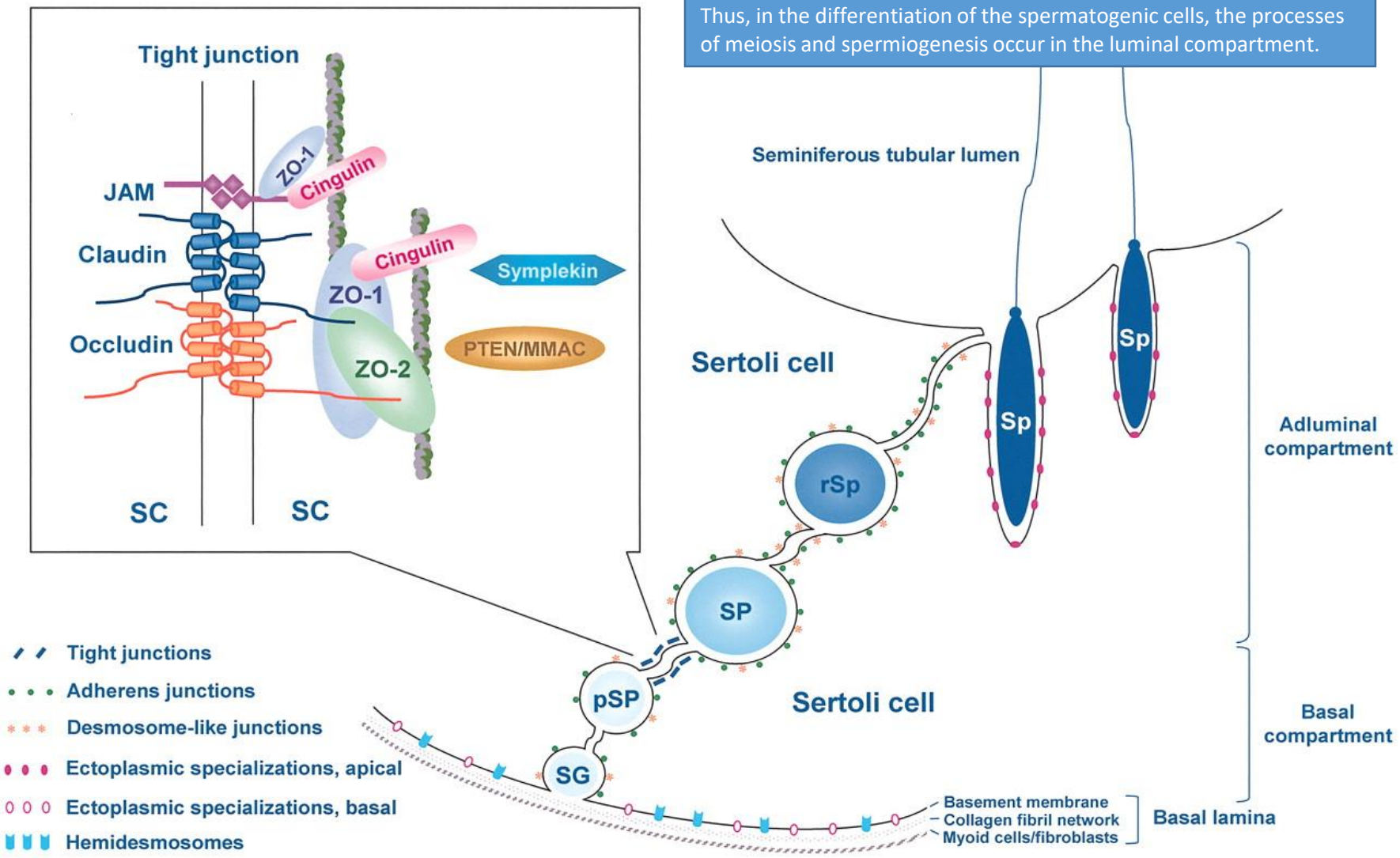
nectin

Gap junctions and desmosomes

hemidesmosomes

- The blood-testis barrier isolates the spermatogenic cells and the mature spermatozoa from blood. Differentiating spermatozoal nestle in pockets, in the peripheral cytoplasm of these cells.
- Sertoli cells help to translocate the differentiating spermatogenic cells to the lumen and phagocytose the degenerating or failed-to-mature germ cells.
- They also remove the surplus cytoplasm remaining after the process of spermiogenesis

Movement of germ cells along the seminiferous epithelium occurs via the formation of a new junctional complex between Sertoli cell processes that extend beneath the newly formed spermatocytes, followed by the breakdown of the junction above them.
Thus, in the differentiation of the spermatogenic cells, the processes of meiosis and spermiogenesis occur in the luminal compartment.

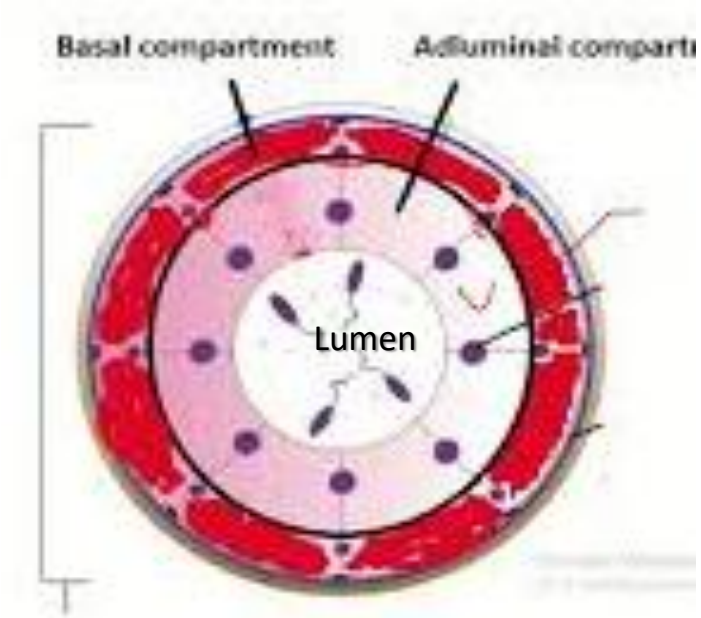


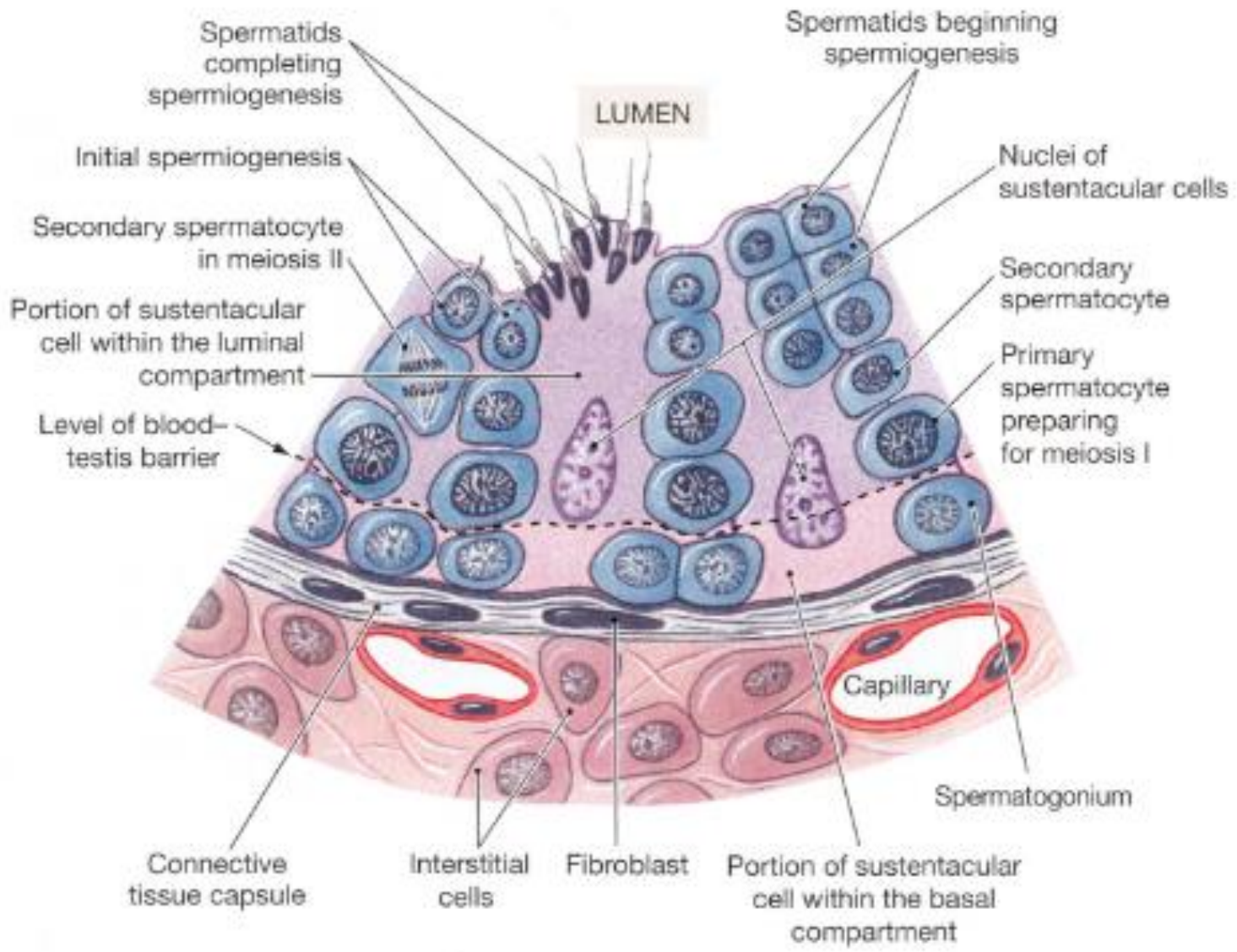
Biol Reprod, Volume 68, Issue 4, 1 April 2003, Pages 1087–1097, https://doi.org/10.1095/biolreprod.102.010371

BLOOD-TESTIS BARRIER

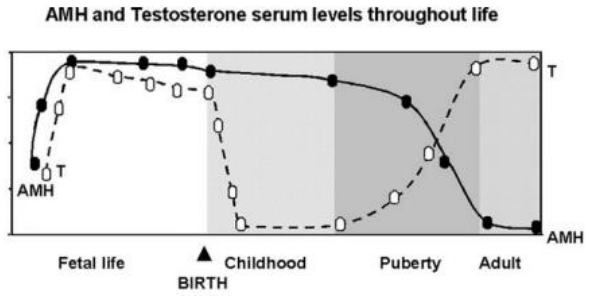
The occluding junctions formed **blood testis barrier** between adjacent Sertoli cells subdivide the lumen of the seminiferous tub

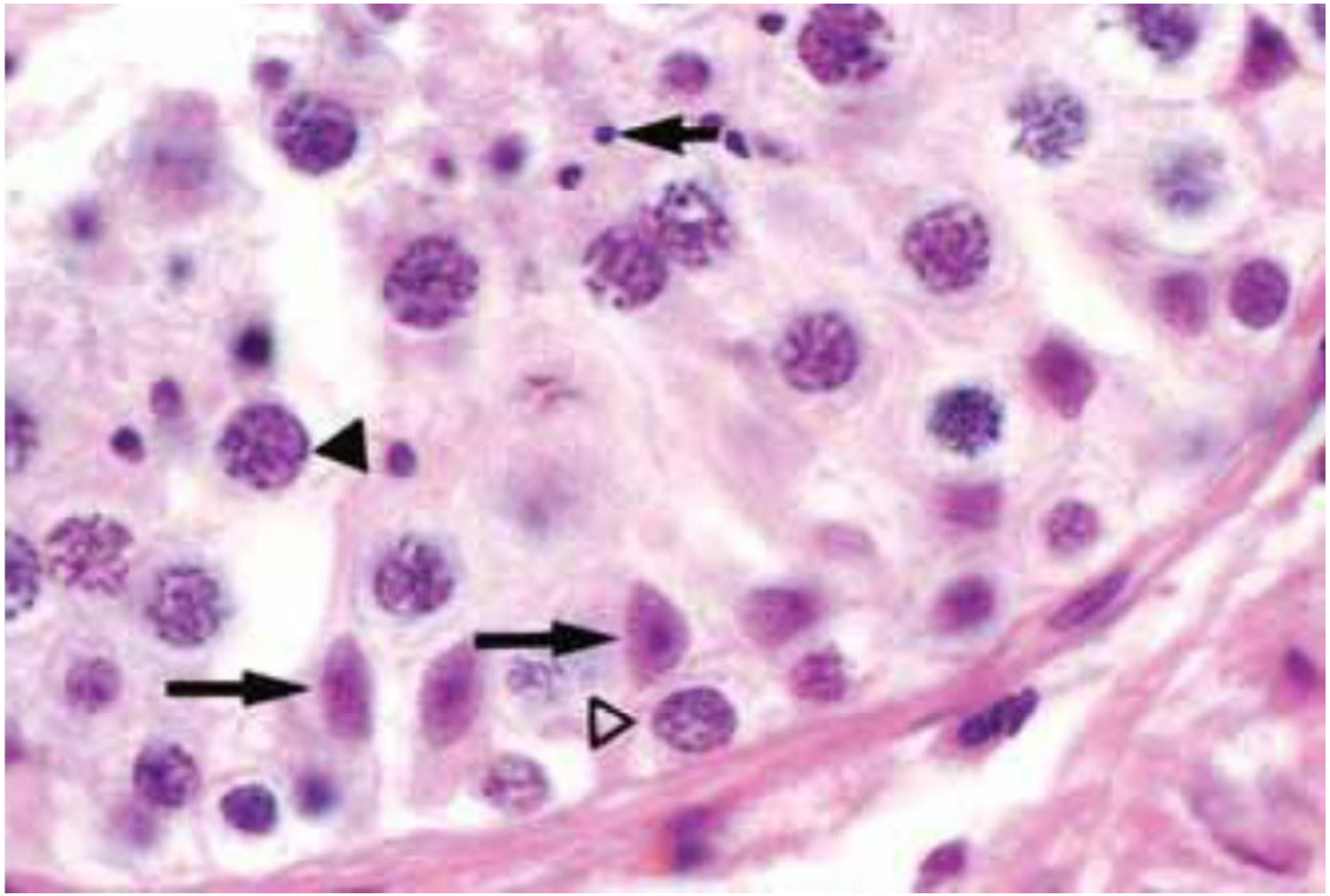
- A **basal compartment,**
- An **adluminal compartment,**





Sertoli cells

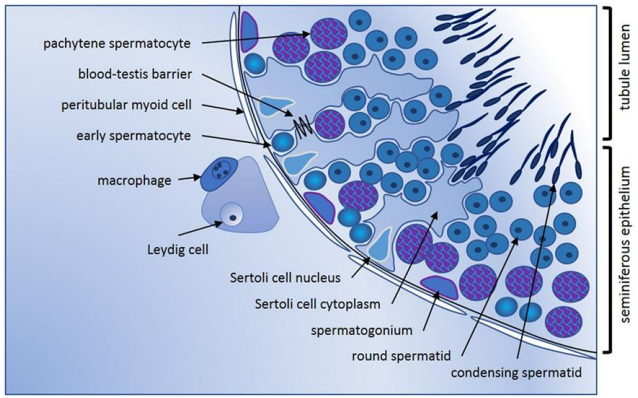




- Exocrine secretory products of the Sertoli cells (**androgen-binding protein [ABP],** highly concentrates testosterone in the luminal compartment of the seminiferous tubule, essential for normal maturation of the developing sperm.
- The blood-testis barrier isolates the genetically different and therefore antigenic haploid germ cells (secondary spermatocytes, spermatids, and sperm) from the immune system
- FSH and testosterone receptors are present on Sertoli cells;
- Sertoli cells secrete several endocrine substances, such as **inhibin,** involved in the feedback loop that inhibits FSH release from the anterior pituitary gland.
- Sertoli cells synthesize **plasminogen activator,** which converts plasminogen to the active proteolytic hormone plasmin,
- **transferrin** (an iron-transporting protein),
- **ceruloplasmin** (a copper-transporting protein).
- Müllerian-inhibiting factor (MIF), stem cell factor (SCF), and glial cell line-derived neurotrophic factor (GDNF).

Myoid cells

- Contractions of the peritubular myoid cells are responsible for moving the luminal fluid and spermatozoa out of the seminiferous tubules through the rete and the efferent ducts into the epididymis.
- These cells contract in response to oxytocin, vasopressin, prostaglandin F2α, and endothelin. Several other substances (TGF beta, NO/cGMP) have been suggested to affect the contraction of the cell, though the mechanisms of the contraction are still unknown.
- Recent in vitro studies have demonstrated that the cells secrete a number of substances including extracellular matrix components (fibronectin, type I and IV collagens, proteoglycans) and growth factors (PModS, TGF beta, IGF-I, activin-A). Some of these substances are known to affect the Sertoli cell function.
- Furthermore, it has been reported that myoid cells contain androgen receptors and are involved in retinol processing.



Atlas on the human testis normal morphology and pathology

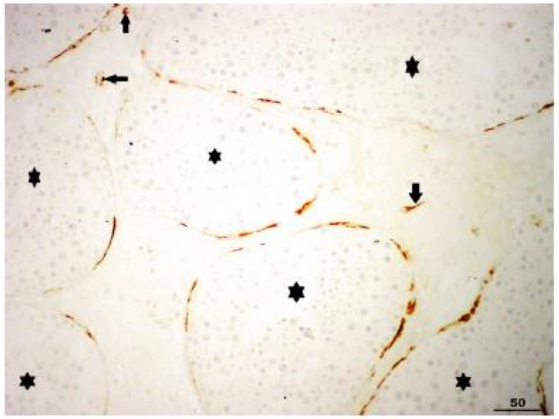
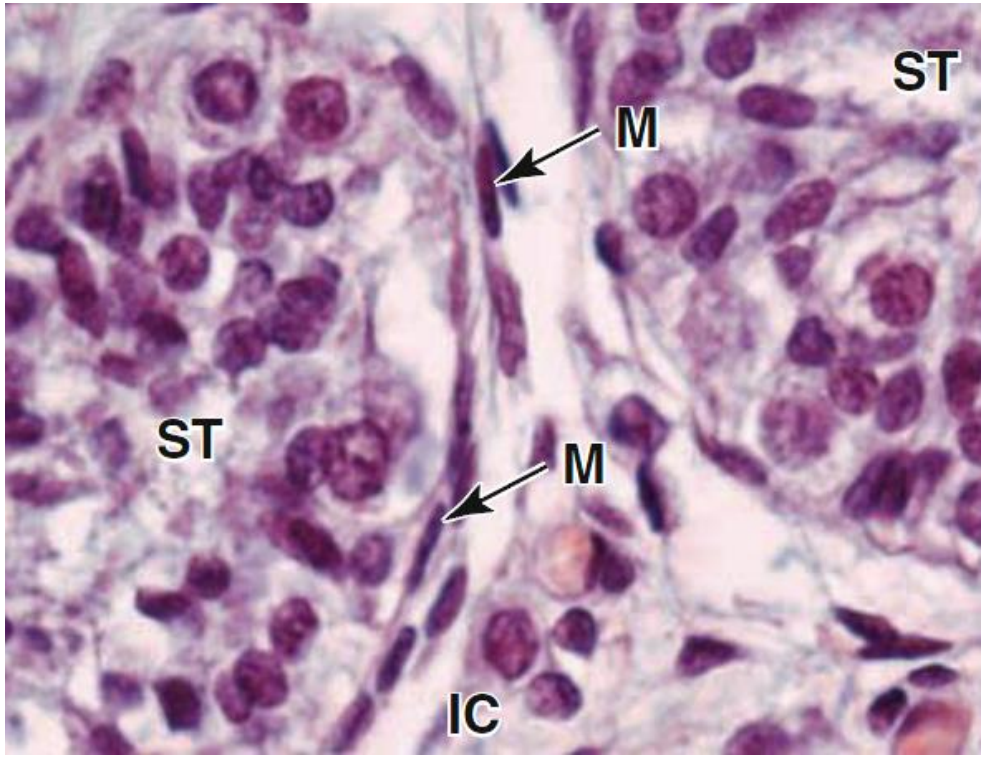


Fig. 7.8 Normal human testis: immunohistochemical (*IHC*) expression of α-smooth actin. Within the lamina propria of the seminiferous tubules (*asterisks*), peritubular (myoid) cells are positive. These cells have some of the properties of smooth muscle cells and, therefore, occasionally contract, enhancing the transport of spermatozoa toward the tubuli recti and rete testis. Smooth muscle cells of small blood vessels within the interstitium (*arrows*) also are positive (IHC stain [diaminobenzidine and hematoxylin counter-stain], ×200; *scale bar*, 50 μm)



Junqueira's Basic Histology Text and Atlas, 14th e

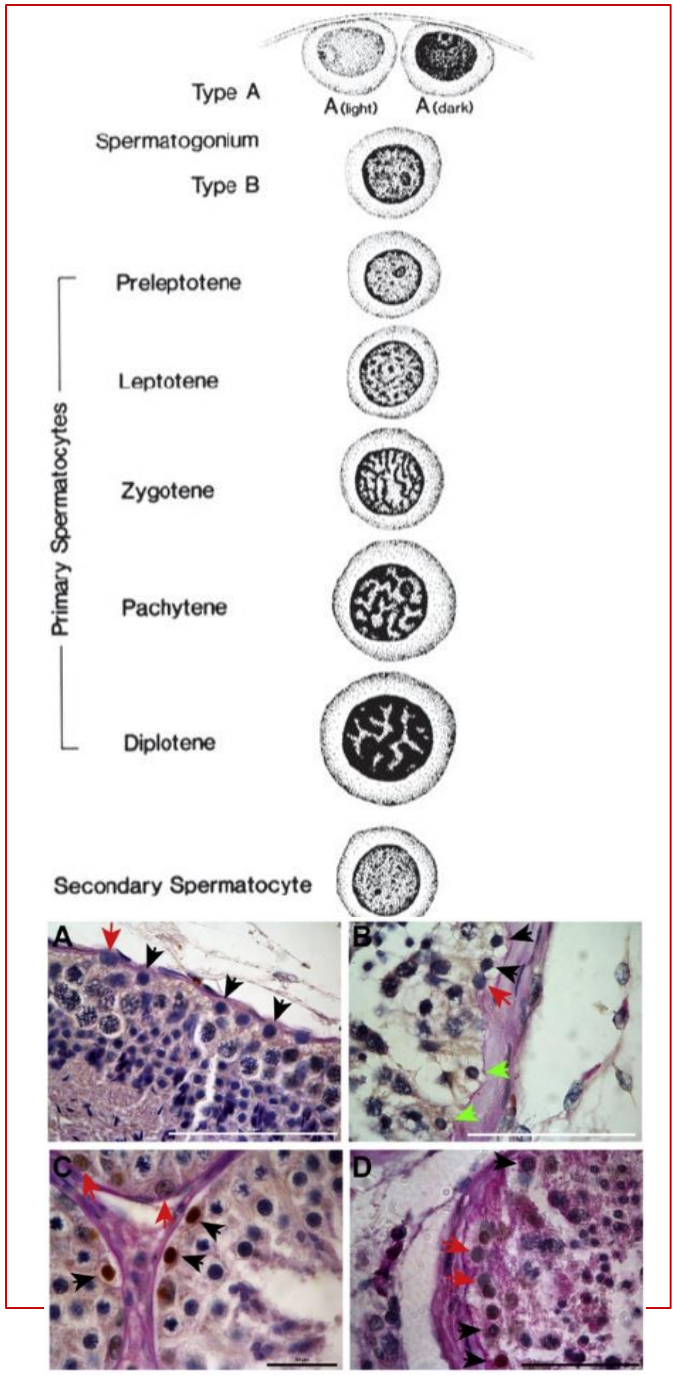
The peritubular myoid cells, intermingled with type 1 collagen fibrils and elastic fibers.
The outermost cells in this layer stain for vimentin, calponin, CD34, and actin, whereas the cells of the inner layer stain also for desmin, a staining pattern characteristic of fibromyocytes

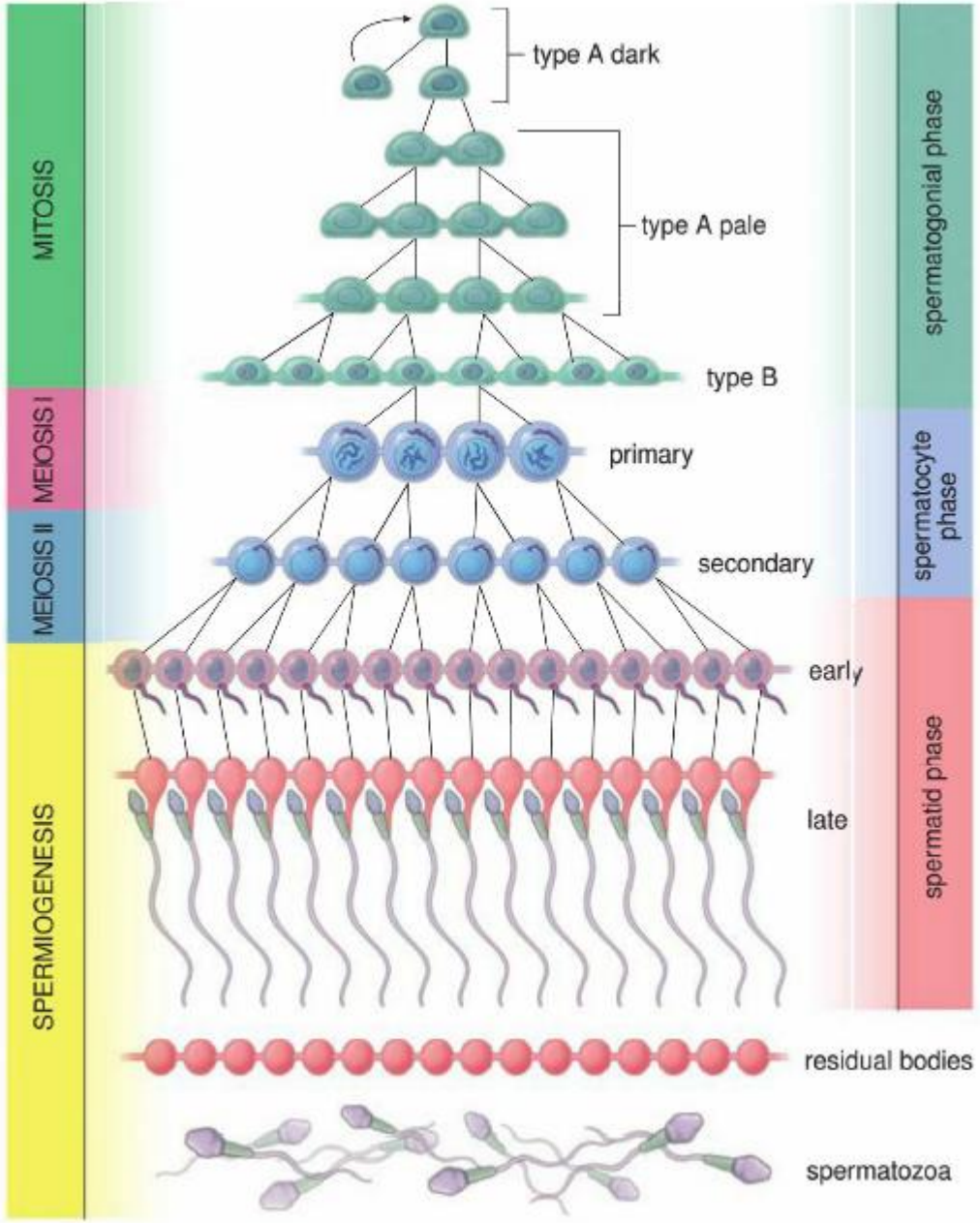
Spermatogenic cells and Spermatogenesis

- Spermatogenesis, the process by which sperm are produced, involves a complex and unique series of events.
- It begins shortly before puberty, under the influence of rising levels of pituitary gonadotropins, and continues throughout life.
- Spermatogenesis, including proliferation of committed spermatogonia, covers a period of 74 days
- The undifferentiated spermatogonia lie in the basal compartment of the adult testis.
- On the basis of their nuclear chromatin staining pattern, utilizing special fixatives such as Zenker-formol, spermatogonia have been divided into type A-dark and type A-pale cells. And a third type, type B.
- **Type A dark (Ad) spermatogonia** have ovoid nuclei with intensely basophilic, finely granular chromatin. These spermatogonia are thought to be the stem cells of the seminiferousn epithelium. They divide at irregular intervals to give rise to either a pair of type Ad spermatogonia that remain as **reserve stem cells** or to a pair of type Ap spermatogonia. Within the cytoplasm in a perinuclear location are the crystalloids of Lubarsch which can be seen by TEM
- The pattern of division of A-pale spermatogonia is still uncertain. Some of them proliferate to produce more type A-pale cells while others produce type B spermatogonia, which soon thereafter convert to the preleptotene form of primary spermatocytes.

- **Spermatogonial phase**, in which spermatogonia divide by mitosis to replace themselves as well as provide a population of committed spermatogonia that will eventually give rise to primary spermatocytes
- **Spermatocyte phase (meiosis)**, in which primary spermatocytes undergo two meiotic divisions to reduce both the chromosome number and amount of DNA to produce haploid cells called spermatids
- **Spermatid phase (spermiogenesis)**, in which spermatids differentiate into mature sperm cells

- **Type A pale (Ap) spermatogonia** have ovoid nuclei with lightly staining, finely granular chromatin. Ap spermatogonia are committed to the differentiation process that produces the sperm. They undergo several successive mitotic divisions, thereby increasing their number.
- **Type B spermatogonia** have generally spherical nuclei with chromatin that is condensed into large clumps along the nuclear envelope and around a central nucleolus





- An unusual feature of the division of an Ad spermatogonium into two type Ap spermatogonia is that the daughter cells remain connected by a thin cytoplasmic bridge.
- This same phenomenon occurs through each subsequent mitotic and meiotic division of the progeny of the original pair of Ap spermatogonia
- Thus, all of the progeny of an initial pair of Ap spermatogonia are connected, much like a strand of pearls.
- These cytoplasmic connections remain intact to the last stages of spermatid maturation and are essential for the synchronous development of each clone from an original pair of Ap cells.

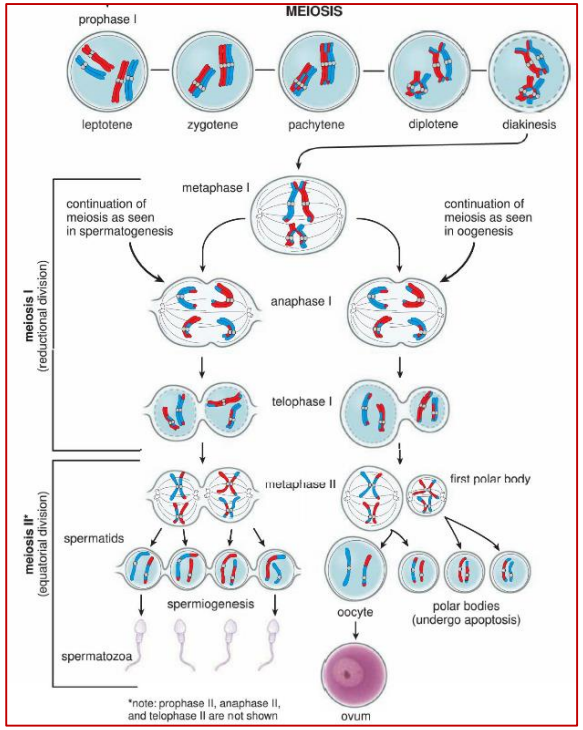
Spermatogenic cells and Spermatogenesis

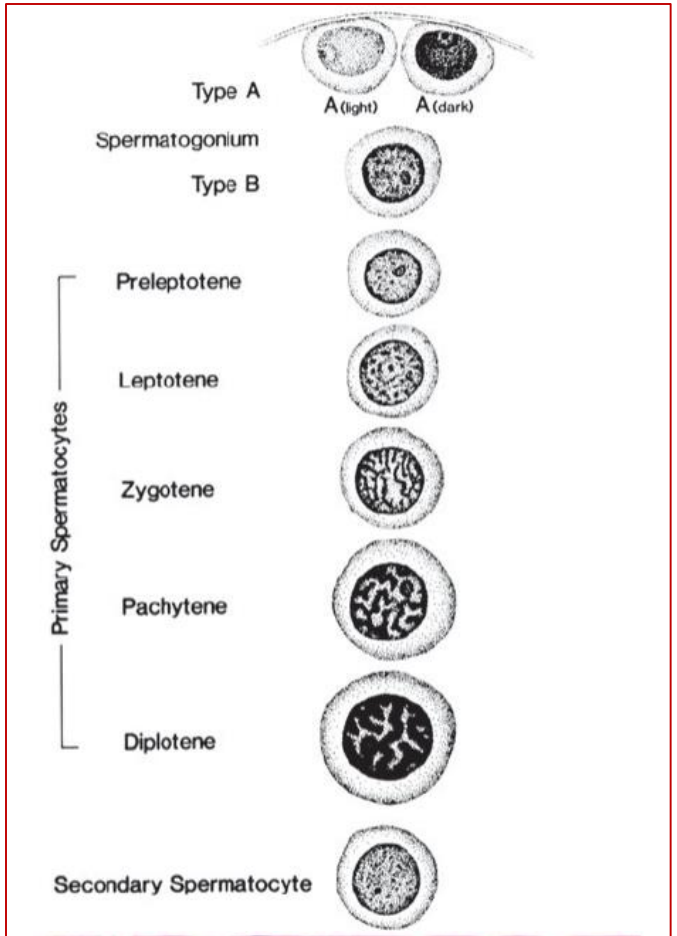
- In humans, it appears that preleptotene spermatocytes are produced per each original pair of Ap spermatogonia. The preleptotene spermatocytes then move into the adluminal compartment and start the process of the first meiotic division.
- The mitotic division of type B spermatogonia produces primary spermatocytes. They replicate their DNA shortly after they form and before meiosis begins, so that each primary spermatocyte contains the normal chromosomal number (2n) and double the amount of DNA (4d). Each chromosome consists of two sister chromatids; hence, 4d amount of DNA.
- **Meiosis I** results in reduction of both the number of chromosomes (from 2n to 1n) and the amount of DNA to the haploid condition (from 4d to 2d); thus, secondary spermatocyte is characterized by haploid number of chromosomes (1n) and 2d amount of DNA. Because no DNA replication precedes **meiosis II,** after this division, each spermatid has the haploid (1n) number of chromosomes, each containing a single chromatid (1d).

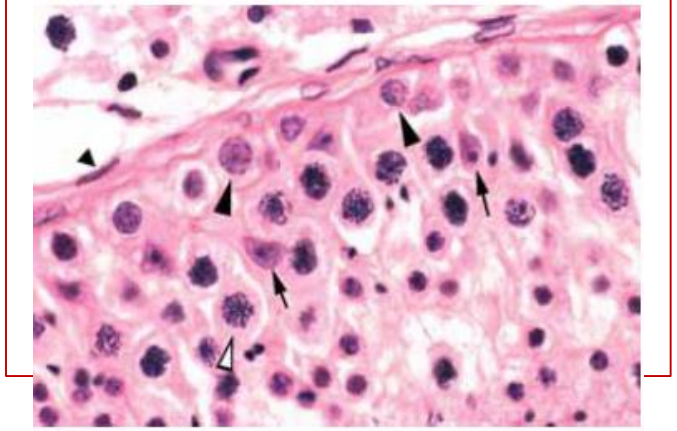
- The classication of primary spermatocytes is based on the alterations of the nuclear chromatin pattern.
- The leptotene primary spermatocytes are characterized by a change in the chromatin pattern to a filamentous structure with a fine-beaded arrangement.
- Zygotene spermatocytes have an even coarser granularity of the chromatin laments, with a tendency for the chromatin to gather eccentrically in the nucleus.
- Pachytene and diplotene spermatocytes are the most easily recognized of the primary spermatocytes because of their large size and their prominent nucleus, containing thick, short chromatin filaments

- **Spermatogonial phase**, in which spermatogonia divide by mitosis to replace themselves as well as provide a population of committed spermatogonia that will eventually give rise to primary spermatocytes
- **Spermatocyte phase (meiosis)**, in which primary spermatocytes undergo two meiotic divisions to reduce both the chromosome number and amount of DNA to produce haploid cells called spermatids
- **Spermatid phase (spermiogenesis)**, in which spermatids differentiate into mature sperm cells

The primary spermatocyte phase occupies a period of 24 days



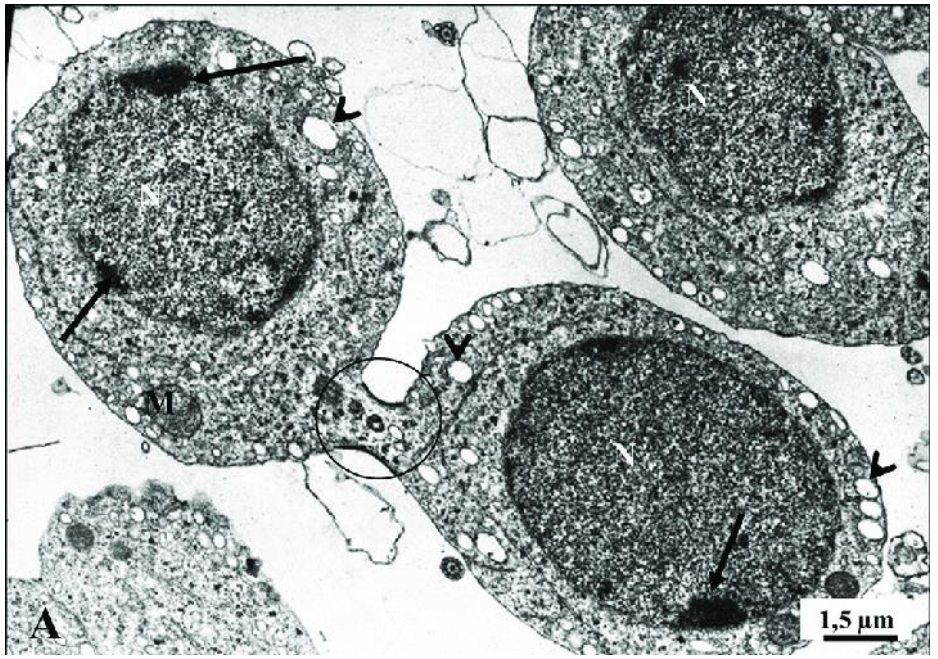


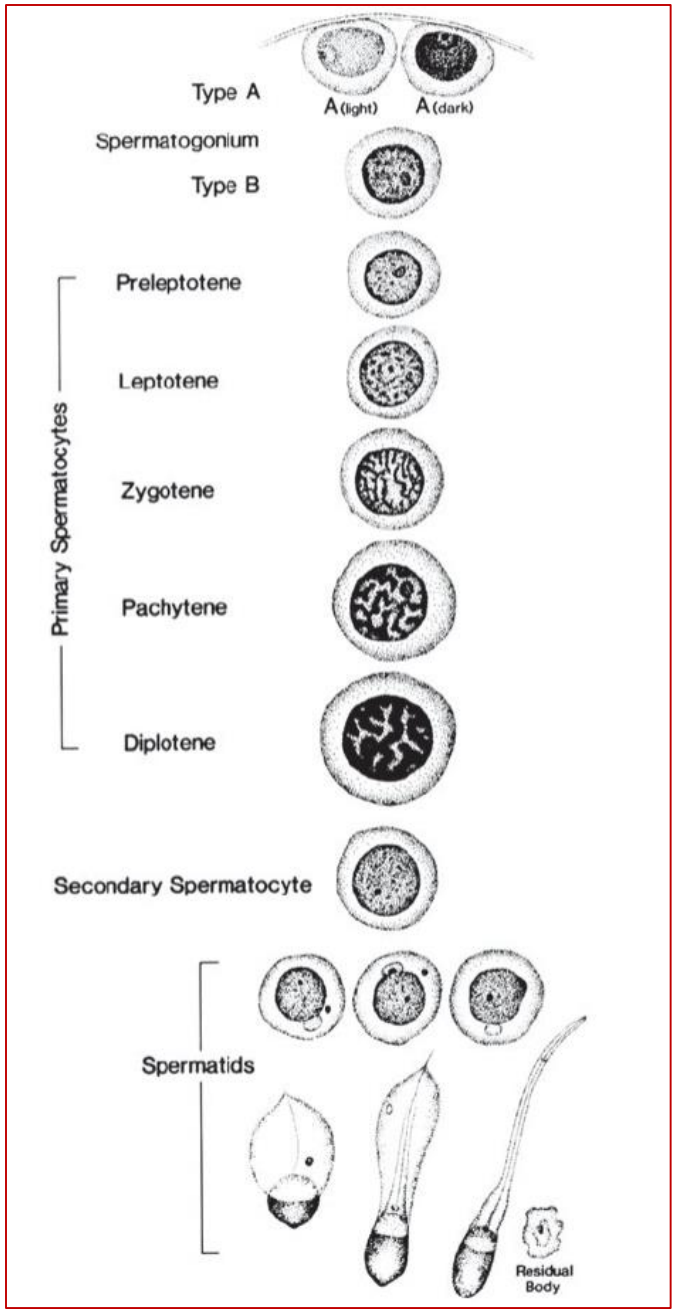


Spermatogenic cells and Spermatogenesis

- **Secondary spermatocytes**, having an extremely short half-life and make up only a small minority of the cells seen in a cross section of the tubule. Their nuclei, substantially smaller than those of the primary spermatocytes, have a finely granular chromatin pattern and a haploid number of chromosomes, but a diploid amount of chromatin because of the presence of the chromatid pairs. These cells, located near the tubule lumen, differ only slightly in appearance from the very early spermatids, with which they are closely associated
- These cells immediately enter the prophase of the second meiotic division *without synthesizing new DNA* (i.e., without passing through an S phase). The second meiotic division is short and lasts only several hours. Each secondary spermatocyte has a reduced number of chromosomes (1n), which is represented by 22 autosomes and an X or a Y chromosome. Each of these chromosomes consists of two sister chromatids. The secondary spermatocyte has the (2d) diploid amount of DNA. During metaphase of the second meiotic division, the chromosomes line up at the metaphase plate, and the sister chromatids separate and move to opposite poles of the spindle.
- As the second meiotic division is completed and the nuclear membranes re-form, two haploid spermatids, each containing 23 single-stranded chromosomes (1n) and the 1d amount of DNA, are formed from each secondary spermatocyte

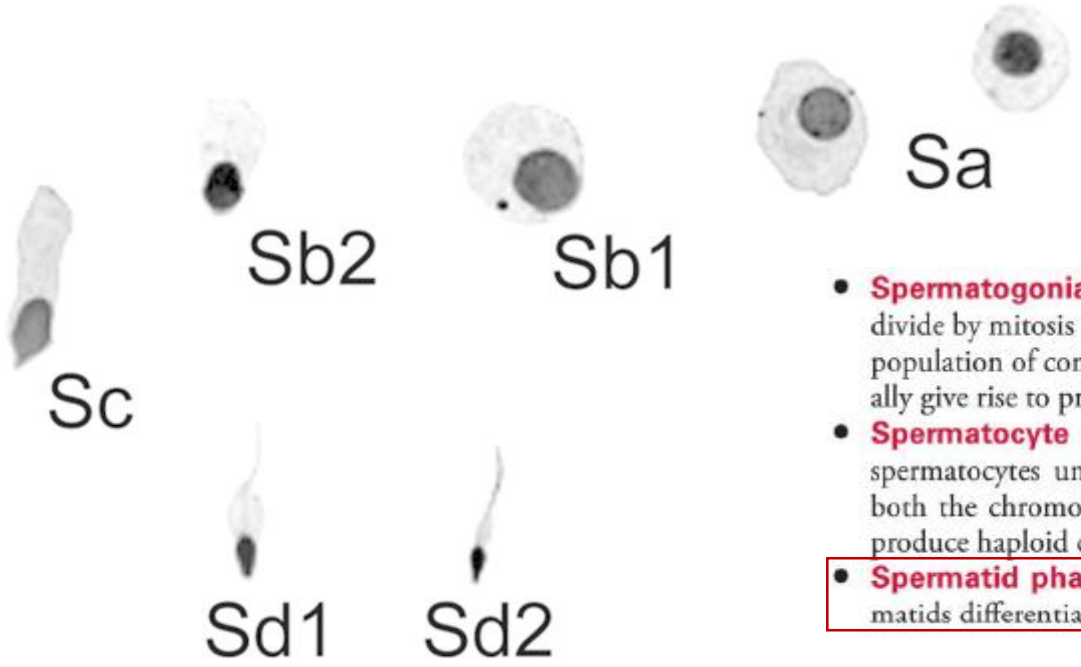
- **Spermatogonial phase**, in which spermatogonia divide by mitosis to replace themselves as well as provide a population of committed spermatogonia that will eventually give rise to primary spermatocytes
- **Spermatocyte phase (meiosis)**, in which primary spermatocytes undergo two meiotic divisions to reduce both the chromosome number and amount of DNA to produce haploid cells called spermatids
- **Spermatid phase (spermiogenesis)**, in which spermatids differentiate into mature sperm cells



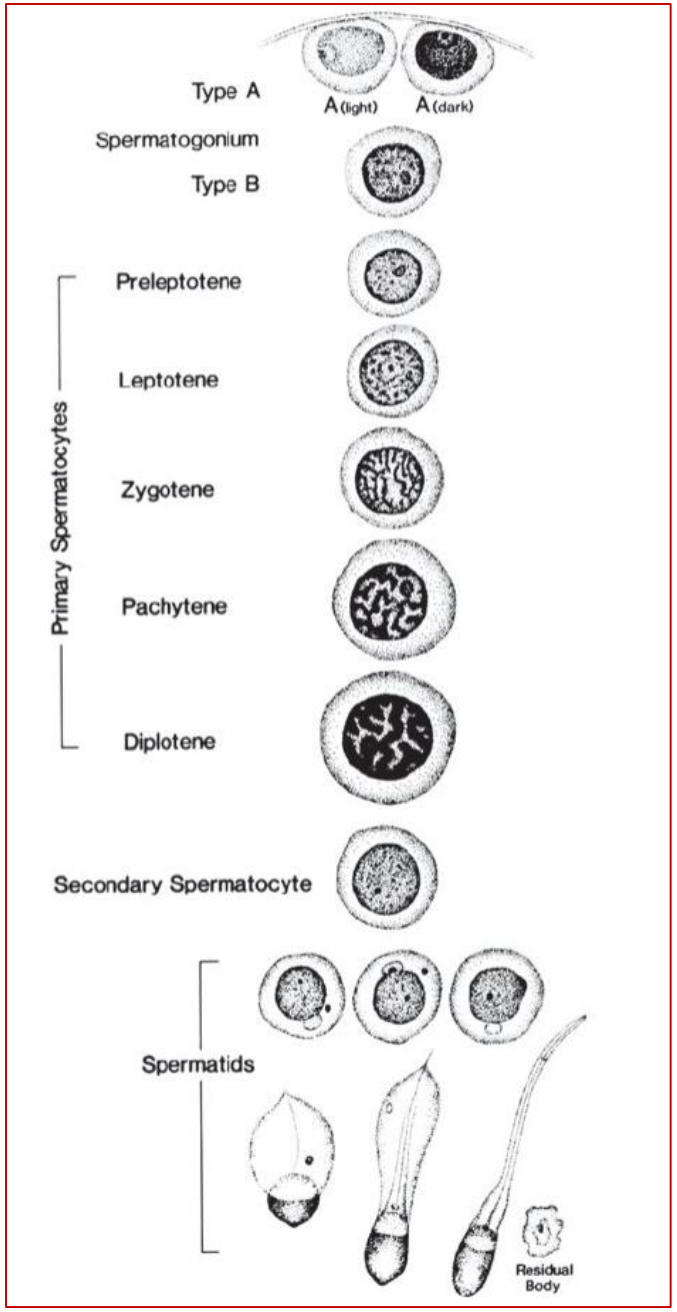


Spermatogenic cells and Spermatogenesis

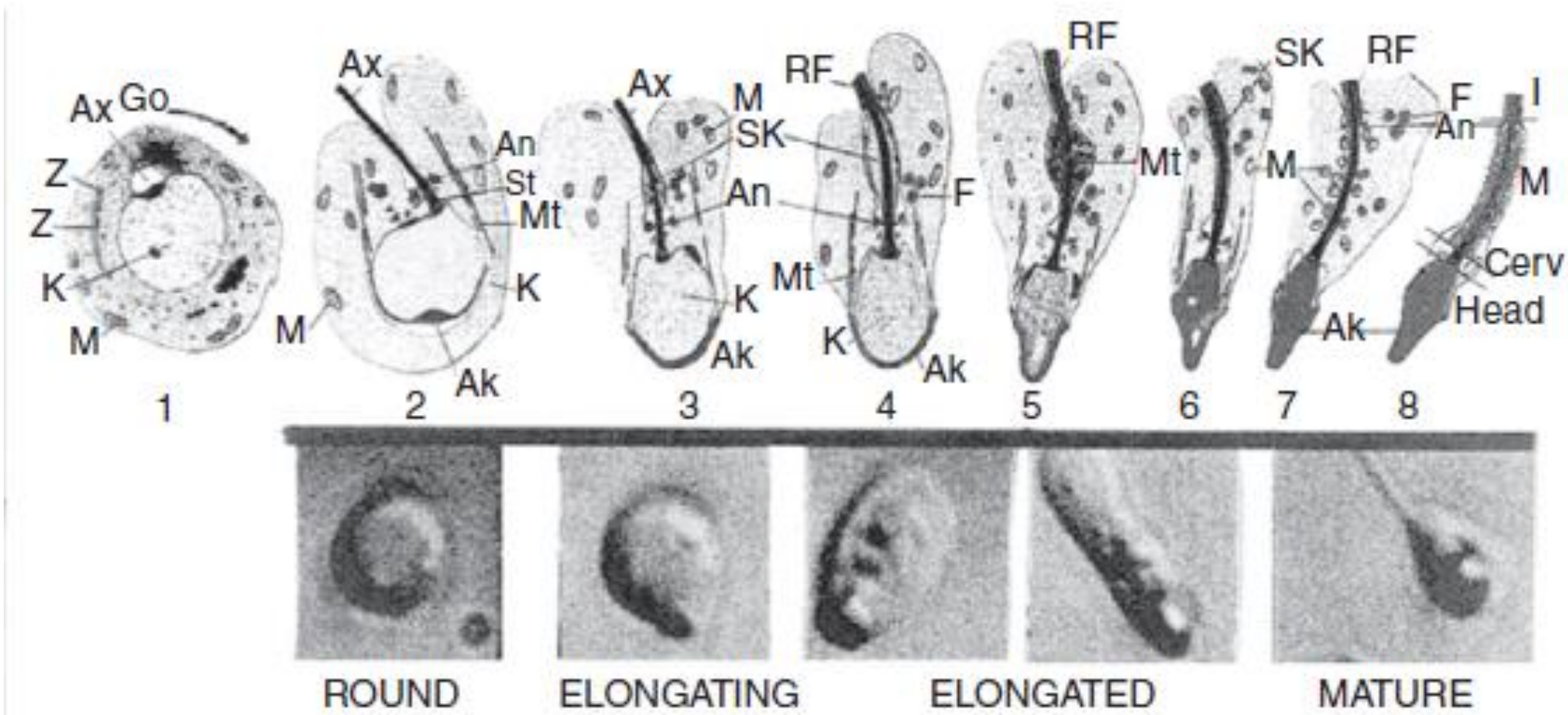
- Spermatids undergo extensive cell remodeling as they differentiate into mature sperm -> **Spermiogenesis**.
- Each spermatid that results from the second meiotic division is haploid in DNA content (1d) and chromosome number (1n) represented by 22 autosomes and an X or Y chromosome.
- No further division occurs. The haploid spermatids undergo a differentiation process that produces mature sperm, which are also haploid. The normal diploid condition is restored when a sperm fertilizes an oocyte.
- Spermatids are incapable of maintaining fertilization, although can be injected inside the oocyte and can provide live births after assisted oocyte activation. Further reading for round spermatid injection (ROSI) -> PMID: 33565426.
- The spermatids have been broken down into several types, based on their morphologic appearance and with particular emphasis on the nuclear and body shape and the development of the acrosome. The 6-type classication of Heller and Clermont, with designations of Sa, Sb1, Sb2, Sc, Sd1, and Sd2, is most commonly employed.



- **Spermatogonial phase**, in which spermatogonia divide by mitosis to replace themselves as well as provide a population of committed spermatogonia that will eventually give rise to primary spermatocytes
- **Spermatocyte phase (meiosis)**, in which primary spermatocytes undergo two meiotic divisions to reduce both the chromosome number and amount of DNA to produce haploid cells called spermatids
- **Spermatid phase (spermiogenesis)**, in which spermatids differentiate into mature sperm cells

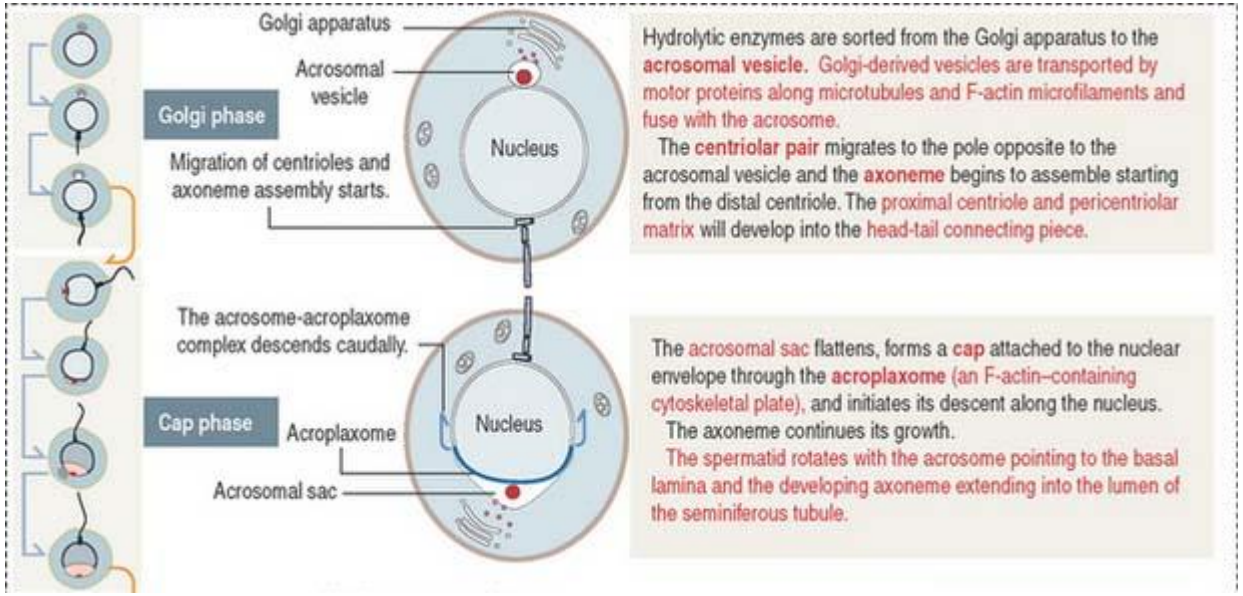


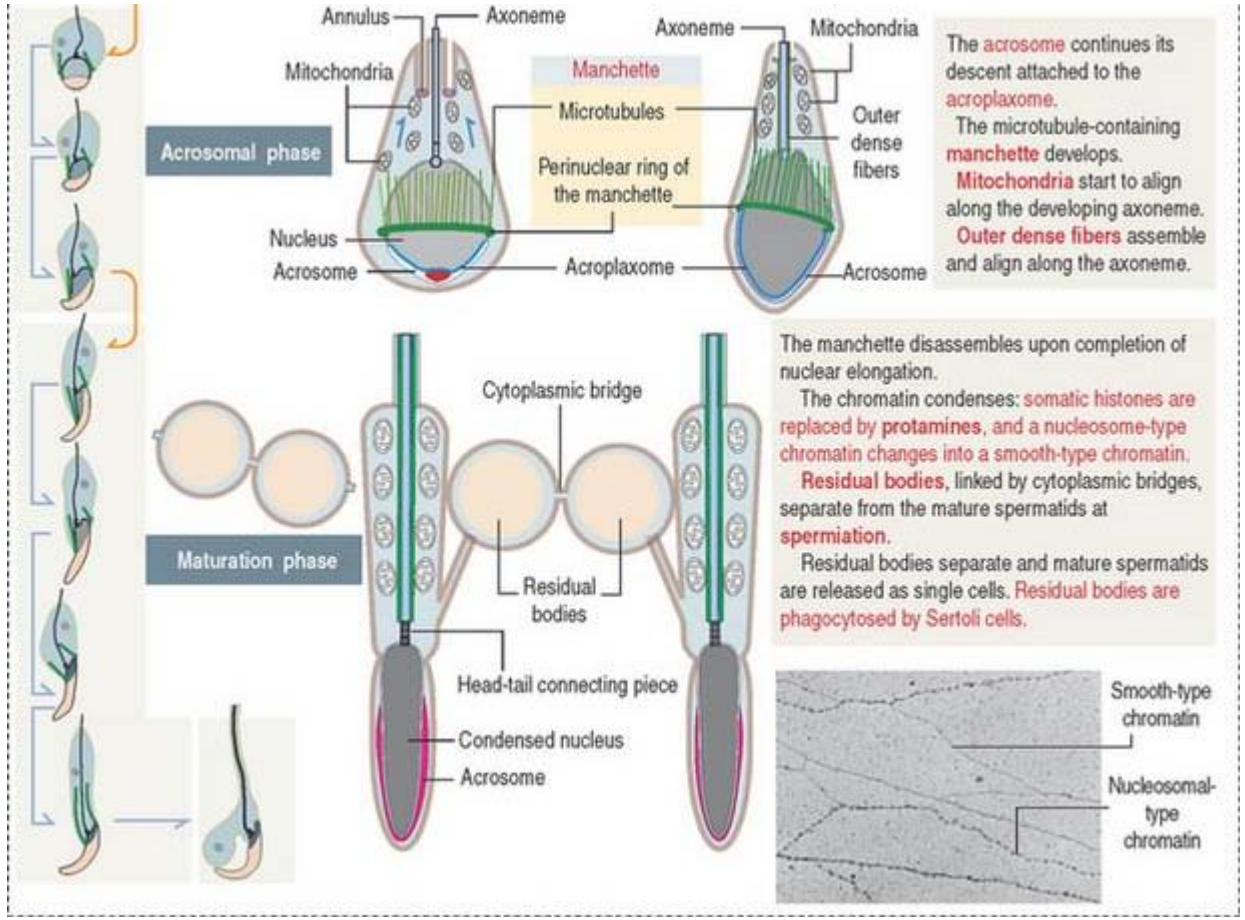
Sa Sb1-2 Sc Sd1 Sd2



From a spermatid to a mature sperm: Spermiogenesis

Maturation phase: This last phase of spermatid remodeling reduces excess cytoplasm from around the flagella to form mature spermatozoon. The Sertoli cells then phagocytose this excess cytoplasm, also termed the residual body. The intercellular bridges that have characterized the developing gametes since the pre-spermatocyte stages remain with the residual bodies. Spermatids are no longer attached to each other and are released from the Sertoli cells.



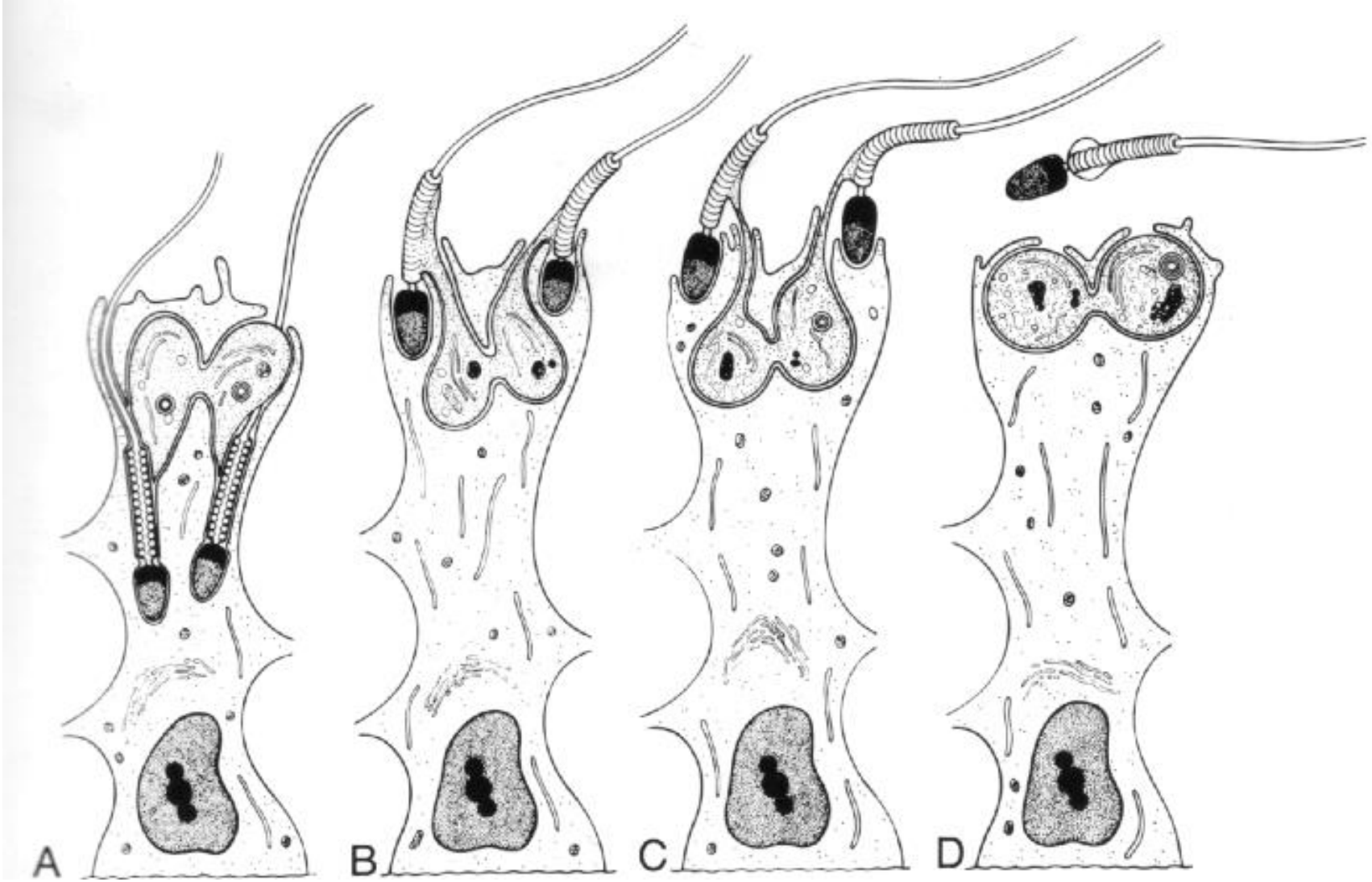


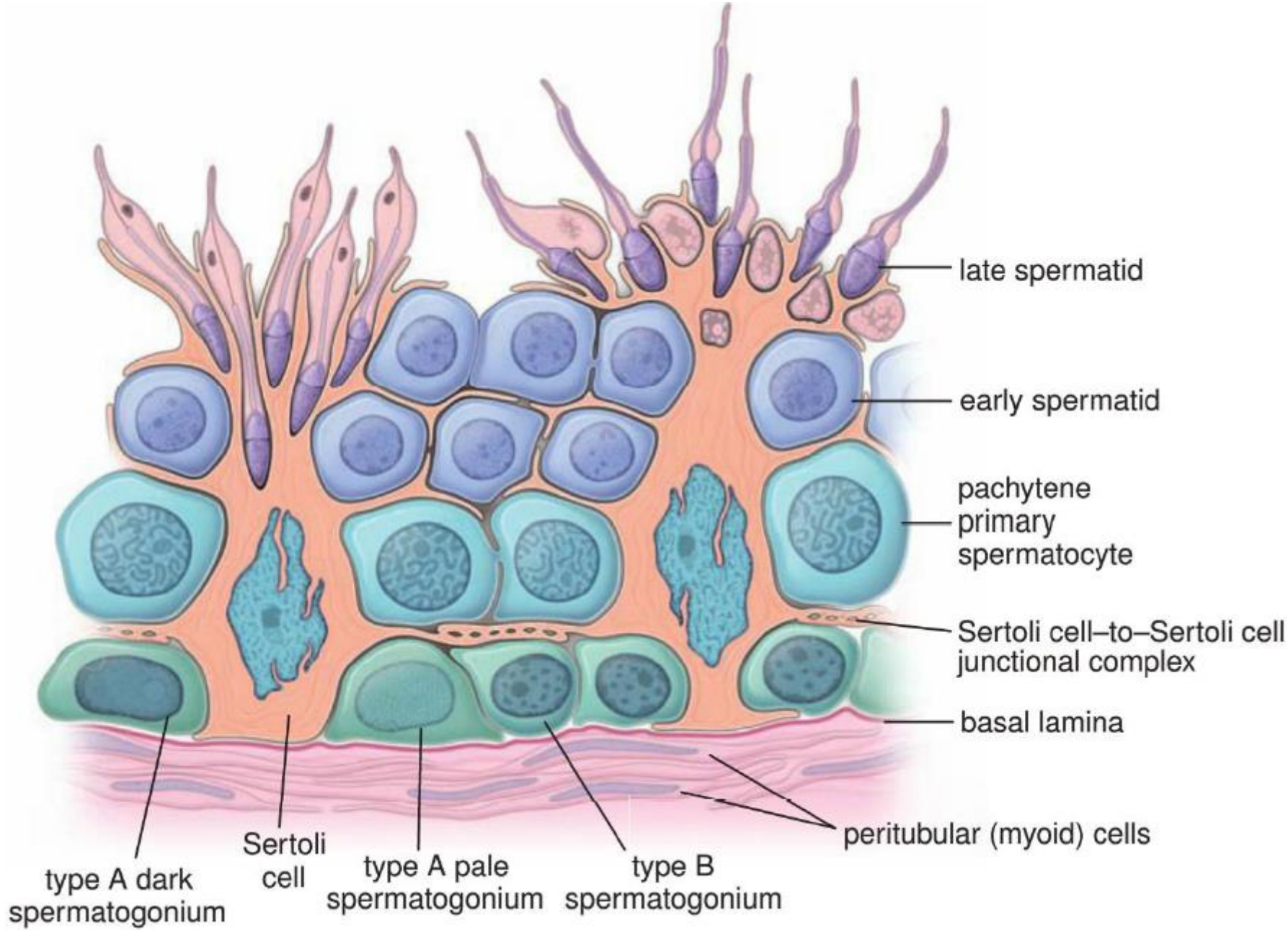
Golgi phase: Granules that accumulate in the multiple Golgi complexes of the spermatid: **acrosomal granules**. The centrioles migrate to the posterior pole of the spermatid, and initiates the assembly of the **axoneme** of the sperm tail.

Cap phase: In this phase, the acrosomal vesicle spreads over the anterior half of the nucleus: the acrosomal cap. The nuclear content condenses.

Acrosomal phase: The developing flagellum extends into the lumen of the seminiferous tubule. The condensed nucleus of the spermatid flattens and elongates, the cytoplasm is displaced posteriorly. The cytoplasmic microtubules become organized into a cylindrical sheath, the manchette, which extends from the posterior rim of the acrosome toward the posterior pole of the spermatid. Mitochondria start to get aligned.

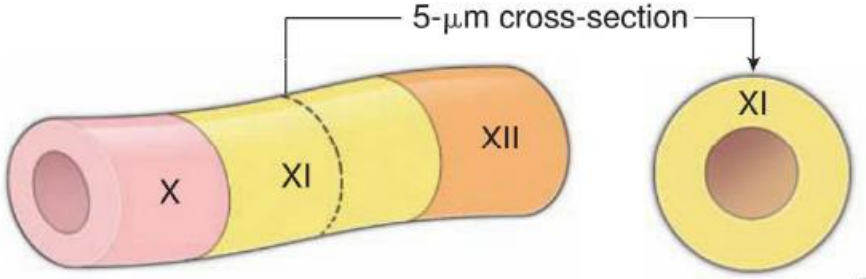
Spermiation



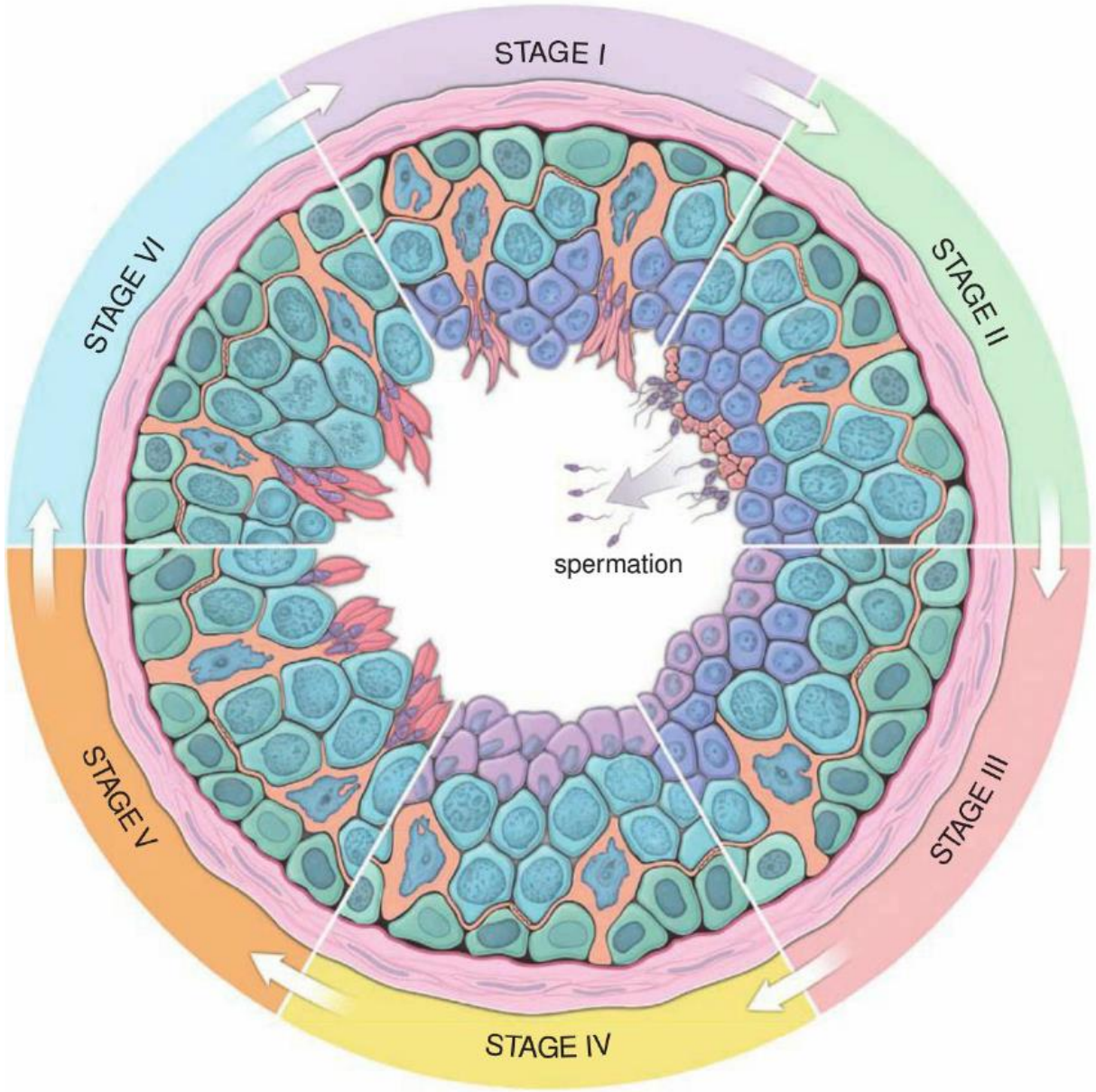

late spermatid
early spermatid
pachytene primary spermatocyte
Sertoli cell–to–Sertoli cell junctional complex
basal lamina
peritubular (myoid) cells
type A dark spermatogonium
Sertoli cell
type A pale spermatogonium
type B spermatogonium

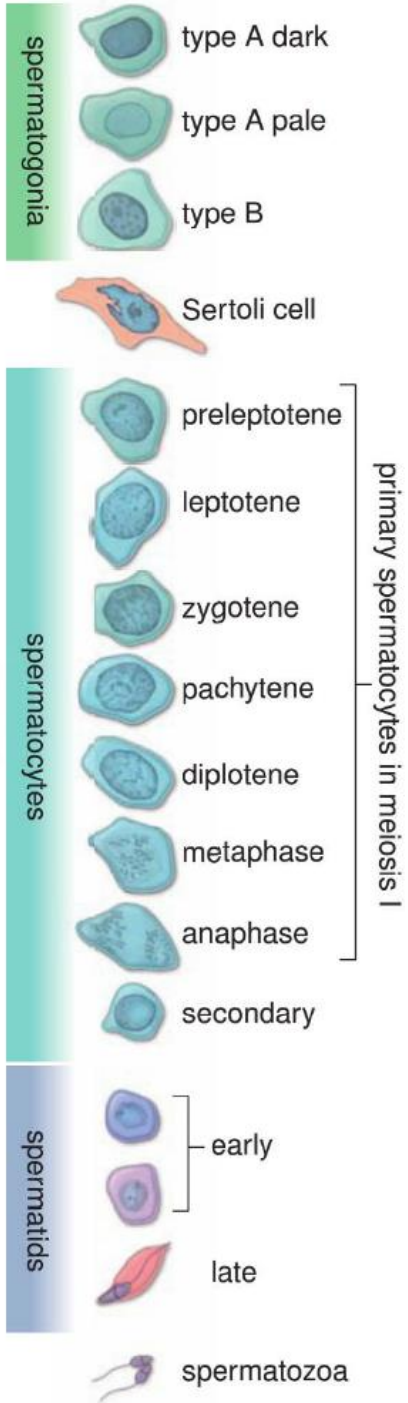
Cycle of Seminiferous Epithelium

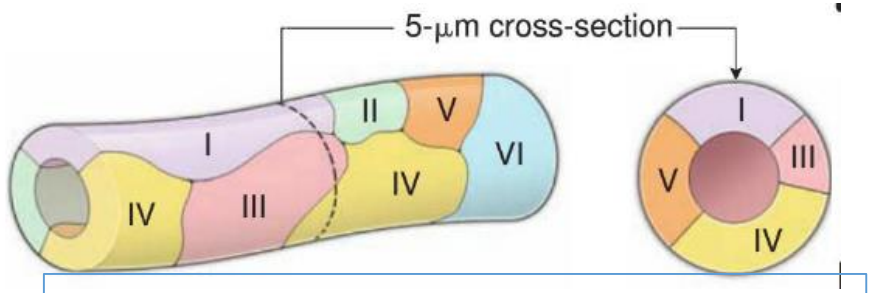
- The concept: Differentiating spermatogenic cells are not arranged at random in the seminiferous epithelium; specific cell types are grouped together. These groupings or associations occur because intercellular bridges are present between the progeny of each pair of type Ap spermatogonia and because the synchronized cells spend specific times in each stage of maturation.
- The cycle of the seminiferous epithelium has been most thoroughly studied in rodents, in which 14 successive stages occur in linear sequence along the tubule



- Approximately 300 million sperm cells are produced daily in the human testis.

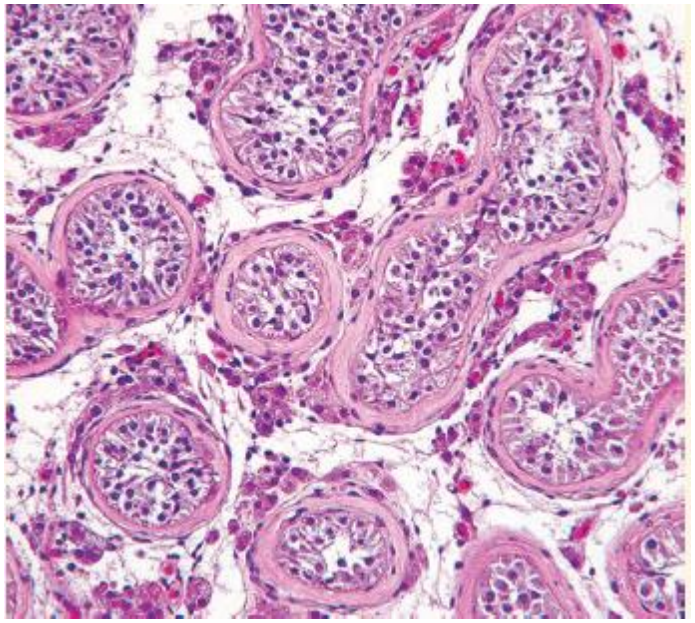






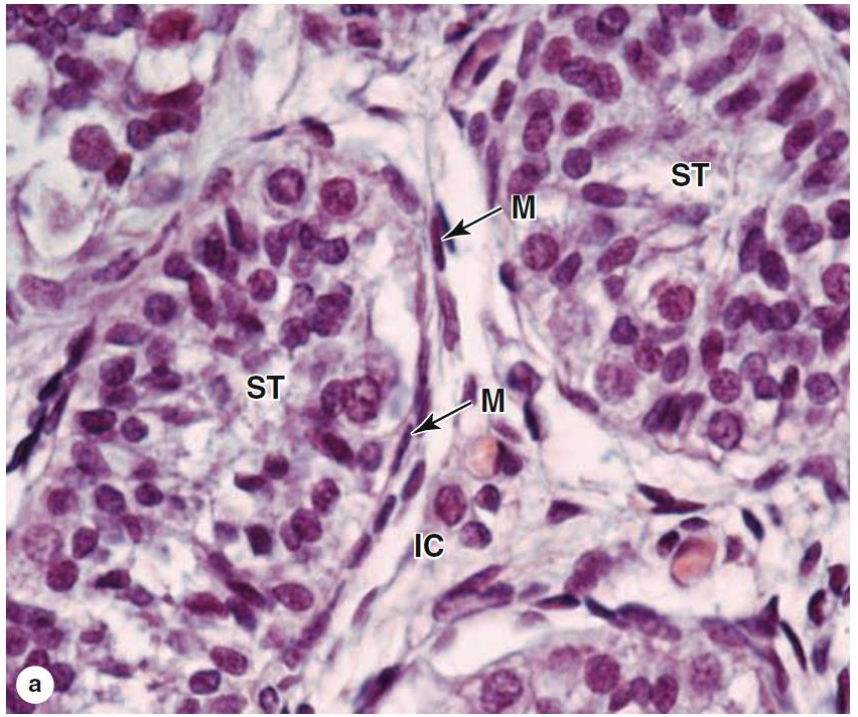
- In human, six stages or cell associations are defined in the cycle of the seminiferous epithelium. These stages are not as clearly delineated as those in rodents because in man the cellular associations occur in irregular patches that form a mosaic pattern.
- Several generations of developing cells may be present in the thickness of the seminiferous epithelium
- The duration of the cycle of the seminiferous epithelium is constant, lasting about 16 days in humans.
- In humans, it would require about 4.6 cycles (each 16 days long), or approximately 74 days to complete the process of spermatogenesis (+12 days for epididimal transit).

Interstitium of Testes



- The interstitium of the testis accounts for 25 to 30% of the testicular mass
- Within the interstitial region are **Leydig cells**, **blood vessels, lymphatics, nerves**, **mast cells**, and **macrophages**.

- Macrophages are often found in close association with the Leydig cells, where the two cells form complex cell–cell interactions.
- Cytokines (such as tumor necrosis factor alpha) and reactive oxygen species from macrophages are known to influence steroidogenesis of the Leydig cells and also likely play a role in the function of the peritubular myoid cells.
- Mast cells also are thought to have an influence on these structures

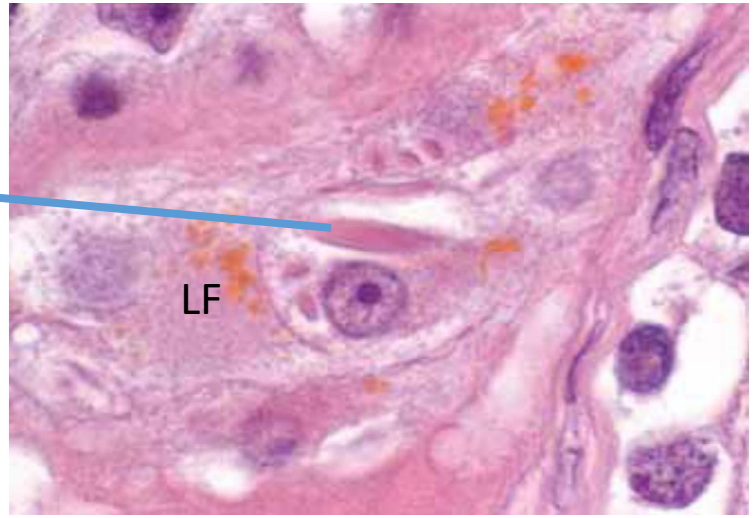


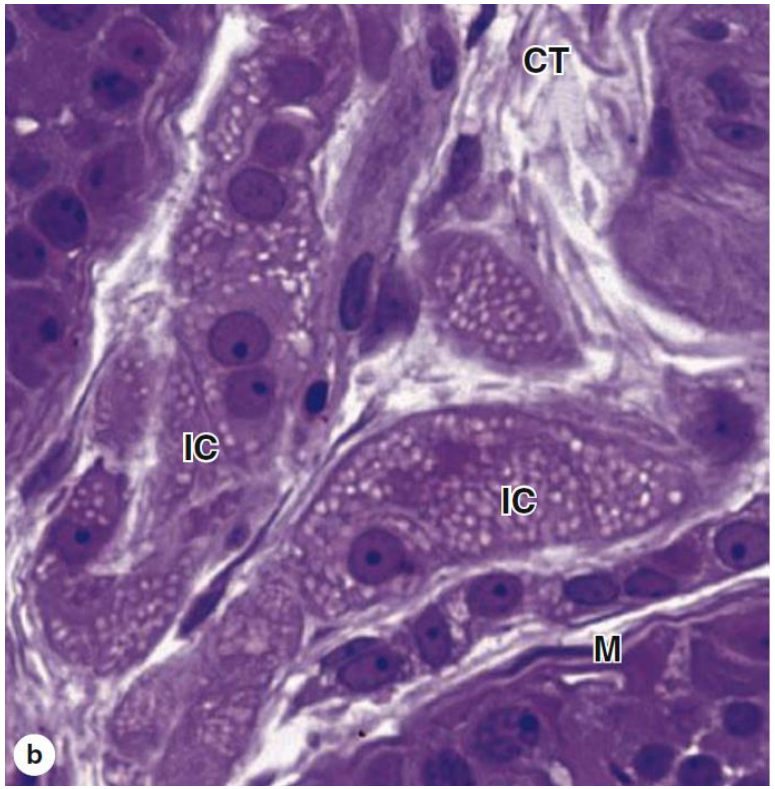
Leydig cells

Franz von Leydig

German zoologist and comparative anatomist

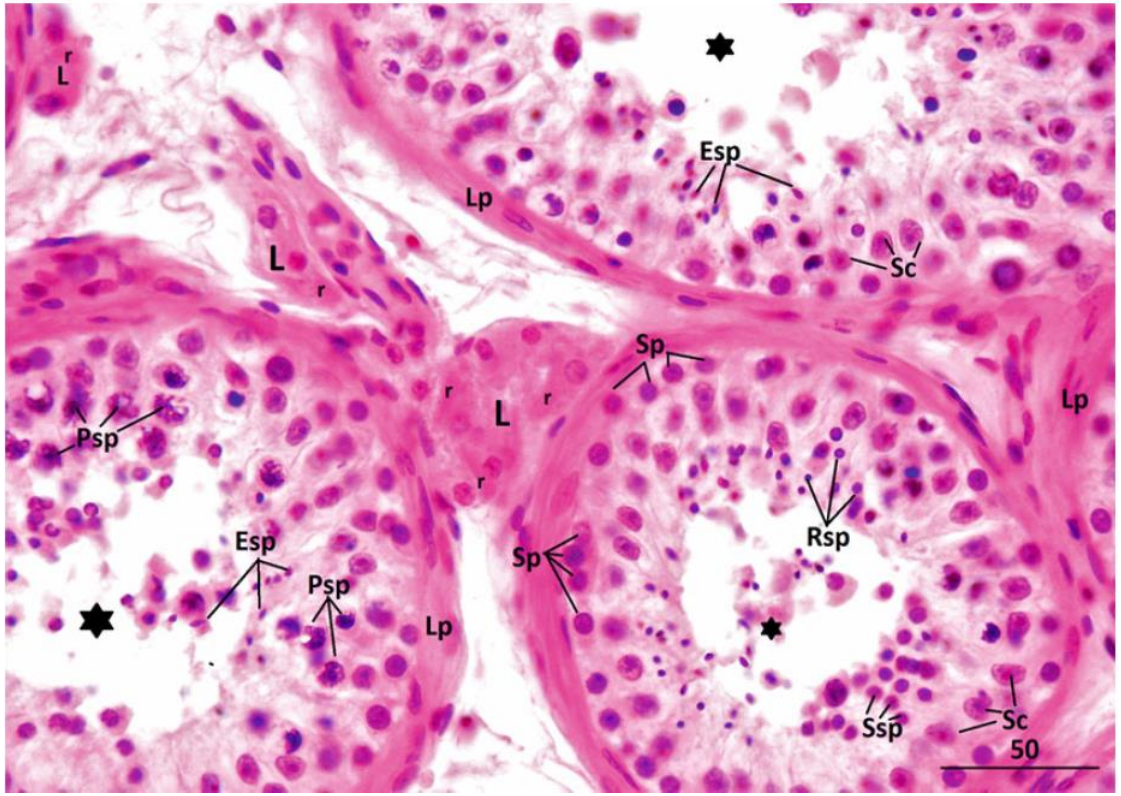
- Leydig cells (**interstitial cells**) are large, polygonal, eosinophilic cells that typically contain lipid droplets.
- Adult Leydig cells, **the source of testicular androgens** and **insulin-like factor 3 (INSL3)**, only rarely undergo mitotic division.
- They are found singly and in clusters within the interstitium of the testis, some lying immediately adjacent to capillaries and others being located next to the peritubular myoid cells.
- The single nucleus of the cell is round and vesicular, with one or two eccentrically located nucleoli. The cytoplasm is usually abundant and stains intensely with eosin. Lipid droplets and lipofuscin pigment are found in the cytoplasm, first appearing at the time of puberty and increasing in prominence in the aging testis.
- The characteristic rod-shaped Reinke crystalloids are present only in the postpubertal state. The nature of the material is unknown but is presumed to represent a protein product of the cell.



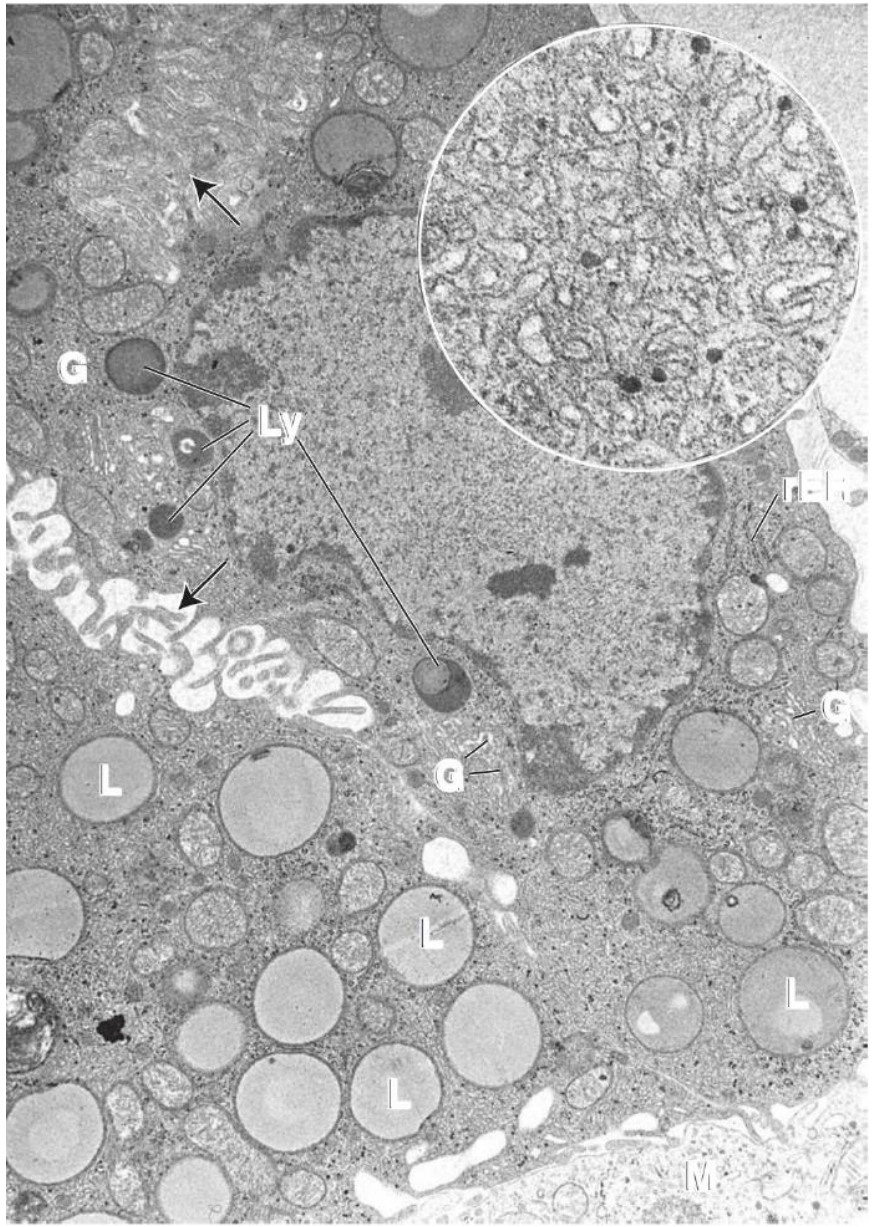


Leydig cells

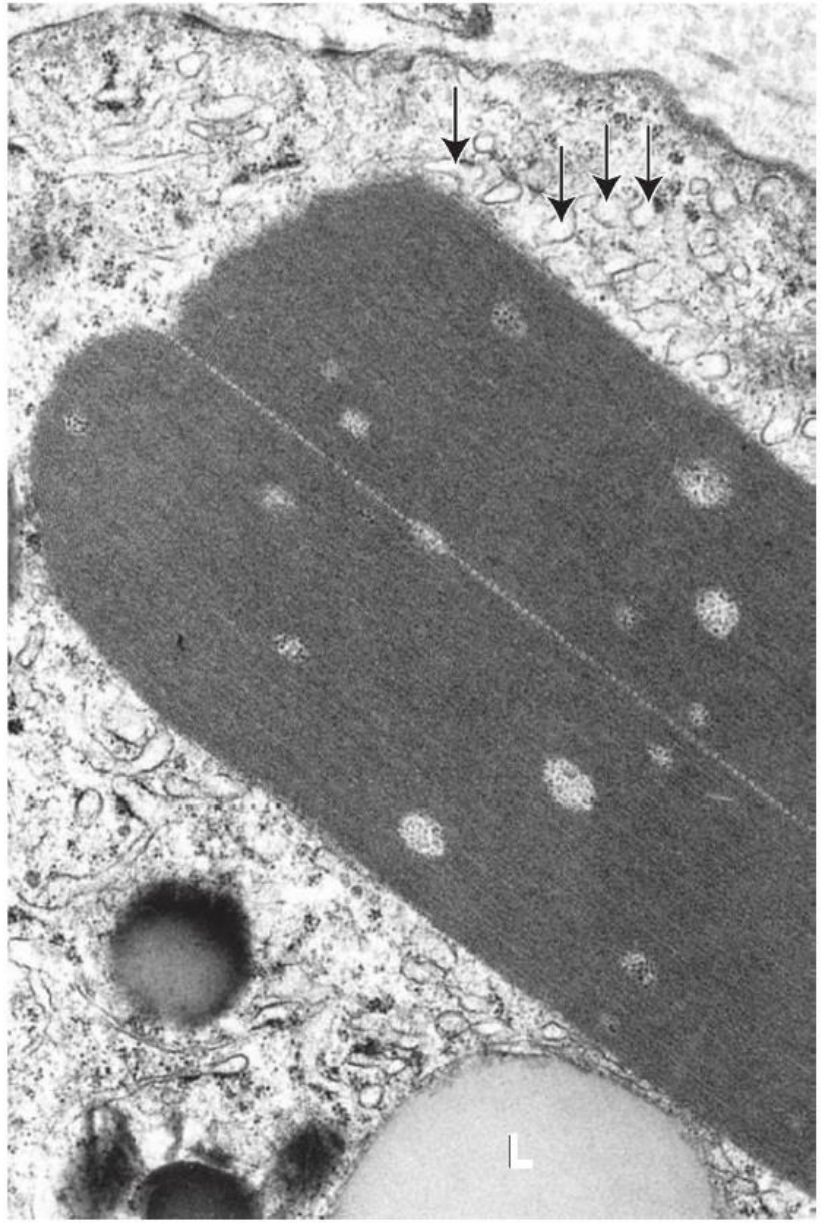
- Antibodies to inhibin α and calretinin stain Leydig cells intensely.
- **Insulin-like peptide 3 (INSL3) is a very specific marker for functioning fetal and adult types of Leydig cells.** Leydig cells also stain positively for S-100, glial fibrillary acidic protein, synaptophysin, chromogranin A and B, and neuronspecic enolase, supporting an important neuroendocrine function for these cells.



- **Like other steroid-secreting cells**, Leydig cells have an elaborate smooth endoplasmic reticulum (sER), a feature that accounts for their eosinophilia. The enzymes necessary for the synthesis of testosterone from cholesterol are associated with the sER. Mitochondria with tubulovesicular cristae, another characteristic of steroid-secreting cells, are also present in Leydig cells. Leydig cells differentiate and secrete testosterone during early fetal life. Secretion of testosterone is required during embryonic development, sexual maturation, and reproductive function.
- Measurement of INSL3 is utilized in clinical tests to establish the Leydig cell steroidogenetic capacity index. In addition to secretion of INSL3, Leydig cells produce and secrete oxytocin. Testosteron producion is induced by prolactin.



X 60,000



X 16,000.

Thank you…

Dr. Sinan Özkavukcu
Email: sinozk@gmail
Twitter: @SinanOzkavukcu