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MALE REPRODUCTIVE PHYSIOLOGY

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heading
OBJECTIVES

1) Know the Basic Structures of the Male Reproductive System

- a) Describe Testicular Anatomy
- b) Describe the Cell Types in the Testis
- c) Describe the Organs and Structures that Compose the Male Genitourinary System

2) Know the Differentiation and Development of the Male Genitourinary Organs and Tract

- a) Describe the steps involved in the Development of the Bipotential Gonad and the Sex Specific Pathways that Regulate Gonadal Differentiation into a Testis

i) Know the disorders of sexual determination (DSD)

- (1) Sex chromosome DSD
- (2) Disorders of ovarian development
- (3) Disorders Causing 46,XY DSD

b) Describe the Normal Development and the Congenital Anomalies of the Genitourinary Tract (Upper and Lower Tracts)

i) Know the hormonal controls of sexual differentiation of the genital tracts

- (1) Mechanisms underlying the sex specific establishment of the wolffian duct
- (2) Mechanisms underlying the sex specific establishment of the müllerian duct
- (3) The morphogenic factors involved in reproductive tract development

ii) Know the development of the external genitalia

- (1) Development of the genital tubercle and the endocrine control of this process
 - (a) Formation of the genital tubercle
 - (b) Formation of the urethra
- (2) Differentiation of the external genitalia
- (3) Descent of the testis during development

iii) Understand the birth defects of the genitourinary system and their importance to male infertility

3) Know the functions of the testis

- a) Describe the Function of the Sertoli Cell and Leydig Cell
- b) Describe the Regulation of Sertoli and Leydig Cell Function

4) Understand the Process of Spermatogenesis and Spermiogenesis

- a) Mitosis
- b) Meiosis
- c) Differentiation

5) Understand the Hormonal Control of Spermatogenesis

- a) Testicular Hormone Production
- b) The Hypothalamic-Pituitary-Testicular Axis

6) Know the structure and functions of the genital tract and accessory sexual organs

- a) Efferent Ducts
- b) Epididymis
- c) Vas Deferens
- d) Seminal Vesicles
- e) Prostate

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f) Penis

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g) Erection and Ejaculation

7) Know the Contributions of the Accessory Sex Glands to the Semen

8) Know the Diagnostic Categories of Male Infertility

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The Male Reproductive System

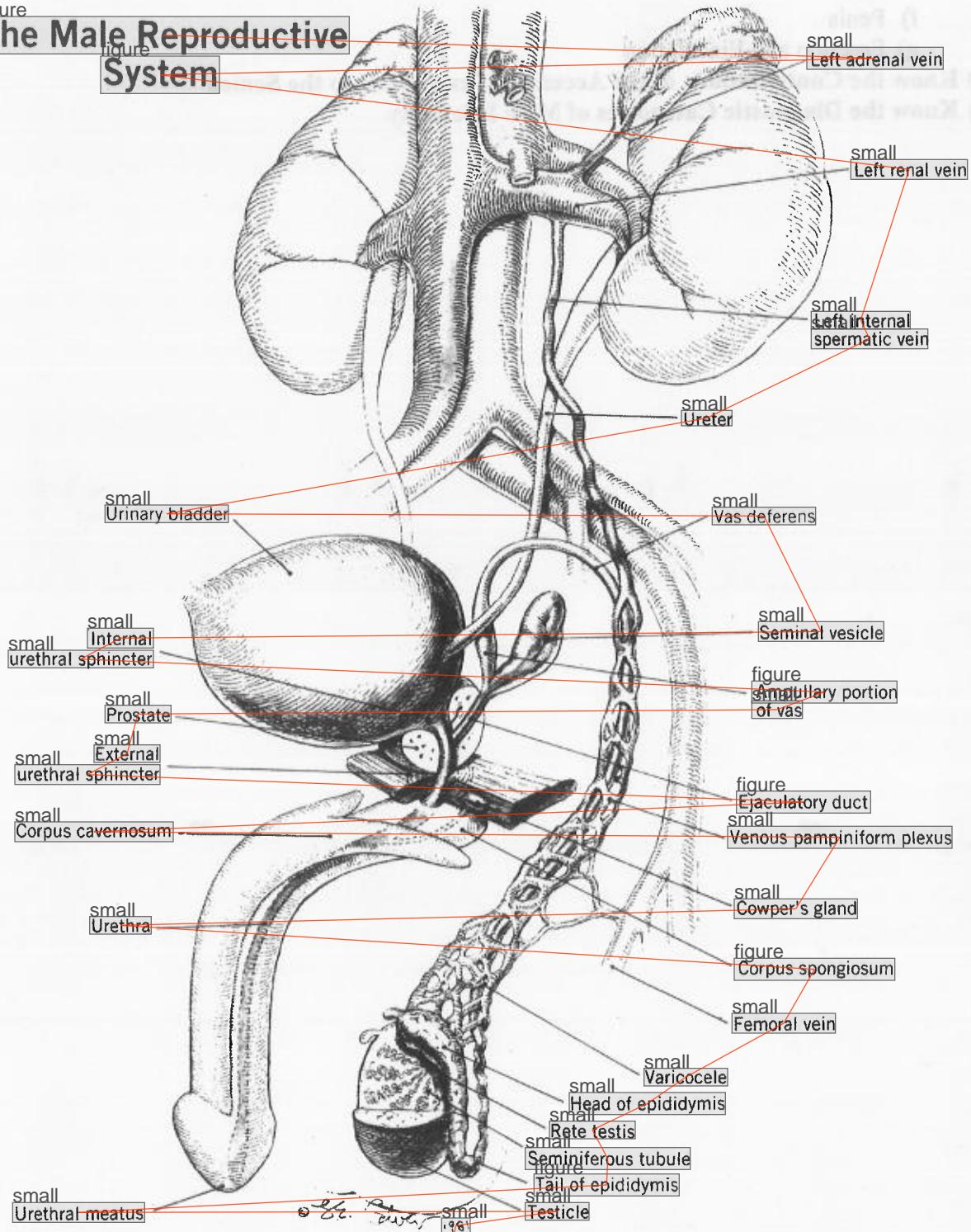


Image Description

Figure 1. Anatomy of the male reproductive system. From L. Glasser, Diagnostic Medicine July/August 1981.

Content TESTICULAR ANATOMY (Figure 1)

- a) **The Organization of the Testes:** The testes are paired ovoid organs located in the scrotum of the male. The average testicular volume is 20cc in healthy young men and decreases in

elderly men. Normal longitudinal length of the testis is approximately 4.5-5.1 cm. This extra-abdominal location maintains the testis at a temperature about 2°C-3°C lower than normal body temperature and this is required for normal spermatogenesis. The testis is surrounded by the tunica albuginea, a thick protective covering of the testis. It is suspended by the spermatic cord, which also contains the vas deferens, spermatic artery, and venous and lymphatic plexus. This tunica is thickened to form the mediastinum where the rete testis is found. The testis itself is composed of a series of lobules (in humans approximately 300 lobules) divided by fibrous septa from the mediastinum. The testis contains seminiferous tubules and interstitial cells. The tubules are segregated into regions by connective tissue septa and occupy approximately 80% of the testicular volume. The tubules are long, V-shaped tubules, the ends of which terminate in the rete testis (see Figure 1).

i) **Function of the Tunica:** This capsule contains blood vessels, smooth muscle fibers and nerve fibers sensitive to pressure. The functional role of the testicular capsule is unknown but may relate to movement of fluid out through the rete testis or control of blood flow to the testis. In humans, it creates a partition between groups of seminiferous tubules, which are present within these lobules. The tough, fibrous tunica may also serve a protective function because of the position of the testes external to the pelvis. There are three layers that comprise the tunica—the tunica vasculosa, tunica albuginea, and tunica vaginalis.

ii) **The lobules** are composed of one to four seminiferous tubules, which are long looping structures that open at both ends into the rete testis. Within these lobules are the seminiferous tubules and the interstitial tissue that includes the blood and lymphatic vessels, nerves, Leydig cells, and macrophages.

iii) **Seminiferous Tubules** are long tubes lined with stratified epithelium about 150-250 µm in diameter and 30-70 cm long. The combined length of the seminiferous tubules in a testis is approximately 250 m! The tubuli recti or straight tubules connect these seminiferous tubules to the rete testis, a complex series of channels that connect to the epididymis by the ductuli efferentes.

iv) **Mediastinum** supports the blood vessels, lymphatic system, and the ducts within the testis that transport the sperm and connect to the rete testis.

v) **Rete Testis/Efferent Ducts (Ductuli efferentes):** The rete testis receives drainage from the central, superior, and posterior regions of the testicular seminiferous tubules. The rete coalesces in the superior portion of the testis to form efferent ducts, which leave the testis, entering the head or caput of the epididymis. The sperm move through the tubuli recti (straight tubules lined by simple cuboidal epithelium) to the rete testis (anastomosing channels in the mediastinum of the testis) to the efferent ducts (lined by columnar epithelium) that connect the testis to the initial segment of the epididymal duct. In the human, there are about 10-20 efferent ducts that have cilia that beat in the direction of the epididymis. This region plays an important role in the absorption of fluids secreted by the seminiferous epithelium. This region is surrounded by large lymphatic channels and blood vessels associated with large clusters of Leydig cells. The efferent ducts coalesce into a variable pattern within the caput to form a single epididymal tubule.

Content

vi) **The artery to the testis** is specialized in that it is highly coiled and intimately associated with a network of anastomotic veins that form the pampiniform plexus (Figure 1). This vascular arrangement facilitates the exchange of heat and small molecules, including testosterone. The counter-current exchange of heat in the spermatic cord provides blood to the testis that is 2°C-4° C lower than rectal temperature in the normal individual.

Headline

b) **Genitourinary Tract and Accessory Gland Anatomy**

Content

i) **An Overview of the Major Organs and Tracts In the Male Genitourinary System (Figure 1):** The genitourinary system of both males and females includes two kidneys, each with a ureter leading from the kidney to the urinary bladder, and one urethra. In both genders, the reproductive organs are closely aligned and included in this body system. In males the reproductive organs and tract include two testes, two epididymites, two ductus deferens, one prostate gland, and two seminal vesicles, as well as the two ampullas and ejaculatory ducts leading from the ductus deferens to the prostate gland, and a single urethra through which both urine and semen flow. The urethra leads from the urinary bladder through the prostate gland through the penis to end at the urethral meatus or opening. The bulbourethral gland or Cowper's gland sits at the base of the prostate. The penile structures include the corpora cavernosa, corpora spongiosum, the penile shaft, glans penis, and the prepuce or foreskin.

Headline

ii) **Each of These Organs and Tracts Will Be Described in More Detail Below**

Content

2) THE DEVELOPMENT OF THE MALE REPRODUCTIVE TRACT: SEX DETERMINATION AND SEX DIFFERENTIATION: There are two processes that occur during development of the gonads and the reproductive tract, its organs, and external genitalia-these processes are termed sex determination followed by sex differentiation

a) **Sex determination:** During early embryogenesis for the first 6 weeks, there are no observable sexual differences between XX and XY fetuses apart from their chromosomes. A urogenital ridge (the precursor of the adrenals, urinary, and genital systems) forms on the ventral side of the mesonephros and appears as a paired thickening of intermediate mesoderm, which will ultimately be composed of somatic and germ cells. For the genital ridge to form, there must be sufficient expression of two proteins, Wilms Tumor 1 (WT1) and SF1, an orphan nuclear receptor. SF1 is a dosage sensitive gene, and loss of a copy can induce sex reversal in XY individuals. The primordial germ cells, cells derived from the proximal epiblast, migrate through the primitive streak into the extra-embryonic region at the base of the yolk sac by the 4th week of gestation. This migration is driven by the kit ligand signaling system (KITL, also known as stem cell factor, steel factor, or mast cell growth factor) expressed in the gonadal ridge and hindgut along the pathway of migration.

b) **Testis Determination:** In the 1940s a fascinating series of experiments by Dr. Alfred Jost showed that the presence of a testis during development drives the development of the internal and external genitalia along the male pathway. In the absence of any gonad, the internal reproductive tract and external genitalia develop along the female pathway.

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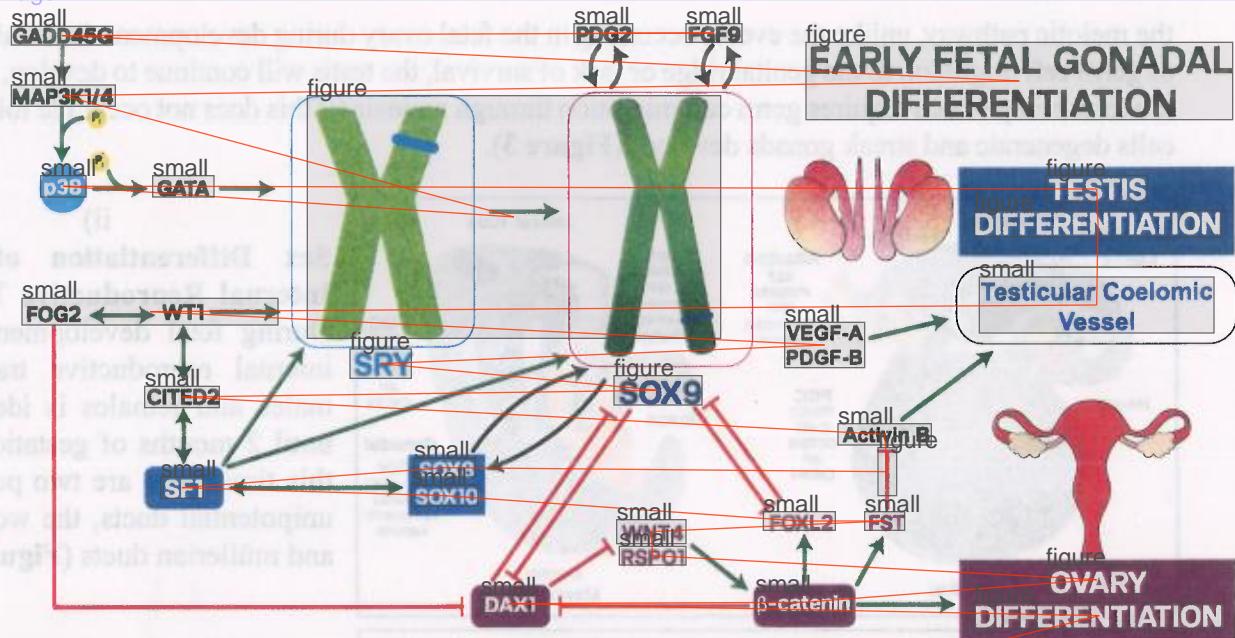


Image Description

Figure 2. Molecular Controls of Testicular or Ovarian Differentiation: Black arrows indicate a positive regulation; double arrows indicate a positive feedback loop; red lines indicate a negative regulation; double red lines indicate a mutual antagonism. Adapted from Rey et al., 2000.

Content

i) **Male Sexual Determination: The Importance of the sex-determining region on the Y chromosome (*SRY*), but sex determination is more complex than just one gene:** *SRY* is the testis-determining factor because it upregulates *SOX9* gene expression and the transcription factor *SOX9* is now considered by many to be the master testis determining factor. Thus, *SRY*, which tilts the balance between testis and ovarian directing gene expression, is necessary but not sufficient for testis determination, and both the timing of expression and the level of expression are critical factors. *SOX9* either succeeds in determining Sertoli cell differentiation or is silenced by other genes that enact ovarian differentiation—it is a true battle of the sexes! It is important to be aware that there are a number of genes that must be expressed during early fetal gonadal sexual differentiation to effectively elicit the development of a functional testis or ovary (Figure 2). **For the purposes of this course the take home message is that both *SRY* and *SOX9* actions are required for testis differentiation.**

(1) **Sertoli cell differentiation:** requires the actions of not only *SRY*, but also fibroblast growth factor 9 (FGF9), and cord formation is dependent on the basal lamina deposition between the Sertoli and peritubular myoid cells—these cords will form the seminiferous tubules.

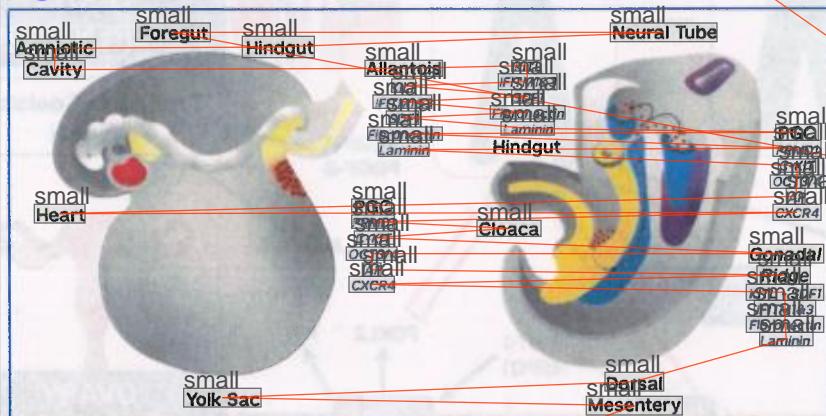
(2) **Leydig cell differentiation:** the origin of the fetal Leydig cells is not clearly understood, but they are present at around 8 weeks of gestation and begin to produce testosterone, which is needed for the maintenance of the wolffian ducts and masculinization of the external genitalia. At this time the Leydig cell is stimulated by placental hCG (first and second trimesters) and later by fetal pituitary LH. The Leydig cells also secrete insulin-like growth factor 3 (INSL3) that is responsible for the first, transabdominal phase, of testicular descent.

(3) **Germ cell differentiation:** By the end of the 5th week of gestation, the germ cells have arrived at the genital ridge and proliferate. These germ cells are encompassed by the cells forming the seminiferous cords and differentiate into spermatogonial precursors but do not enter

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the meiotic pathway, unlike the events occurring in the fetal ovary during development. In the absence of germ cell migration to the genital ridge or lack of survival, the testis will continue to develop, unlike the fetal ovary which requires germ cell migration through meiosis (if this does not occur the follicular cells degenerate and streak gonads develop) (Figure 3).

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ii) **Male Sex Differentiation of the Internal Reproductive Tract:** During fetal development, the internal reproductive tract of males and females is identical until 2 months of gestation. At this time there are two pairs of unipotential ducts, the wolffian and müllerian ducts (Figure 4).

Figure

Figure 3 Early Development of the Gonads and the Molecular Controls of This Process

(1) **The wolffian ducts** are derived from the intermediate mesoderm and ultimately give rise to the kidney and the proximal male genital tract. As a result, when kidney development is abnormal it is likely that there are other malformations of the urinary and/or reproductive systems.

(2) **The müllerian ducts** are derived from the coelomic epithelium and will later form to develop the Fallopian tubes, the ducts in the pelvic region fuse to give rise to the uterovaginal canal. In the female, the wolffian duct begins to regress at about 2 months of gestation.

(3) **Regression of müllerian ducts and differentiation of the wolffian duct into the male accessory organs** is a key element of male differentiation of the internal reproductive tract organs: The initial indication of male differentiation of the genital tract occurs in about 55-60 day old embryos. The müllerian duct first undergoes epithelial to mesenchymal transformation and a wave of apoptosis spreads along the müllerian duct. The connections between the mesonephric tubules and gonadal primordium are established by week 6 of gestation and give rise to the rete testis. The wolffian duct survives and the upper part gives rise to the epididymis and, below that, the vas deferens. The seminal vesicle emerges from a dilation of the terminal portion of the vas deferens in the male fetus at 3 months gestation.

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iii) **Testicular Descent** (Figure 5): The upper pole of the testis is

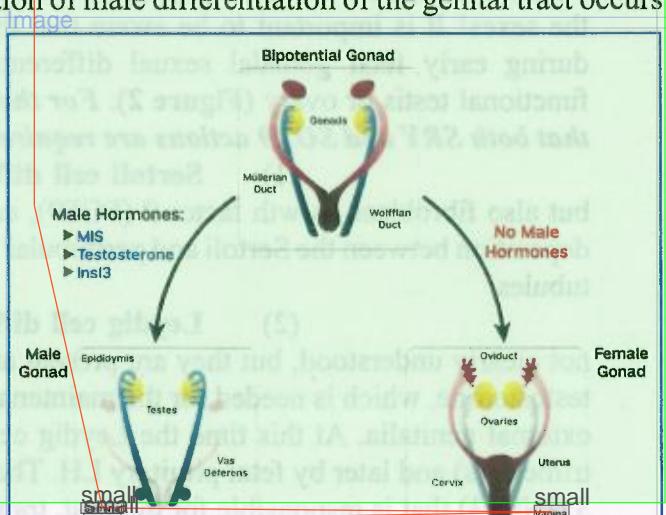
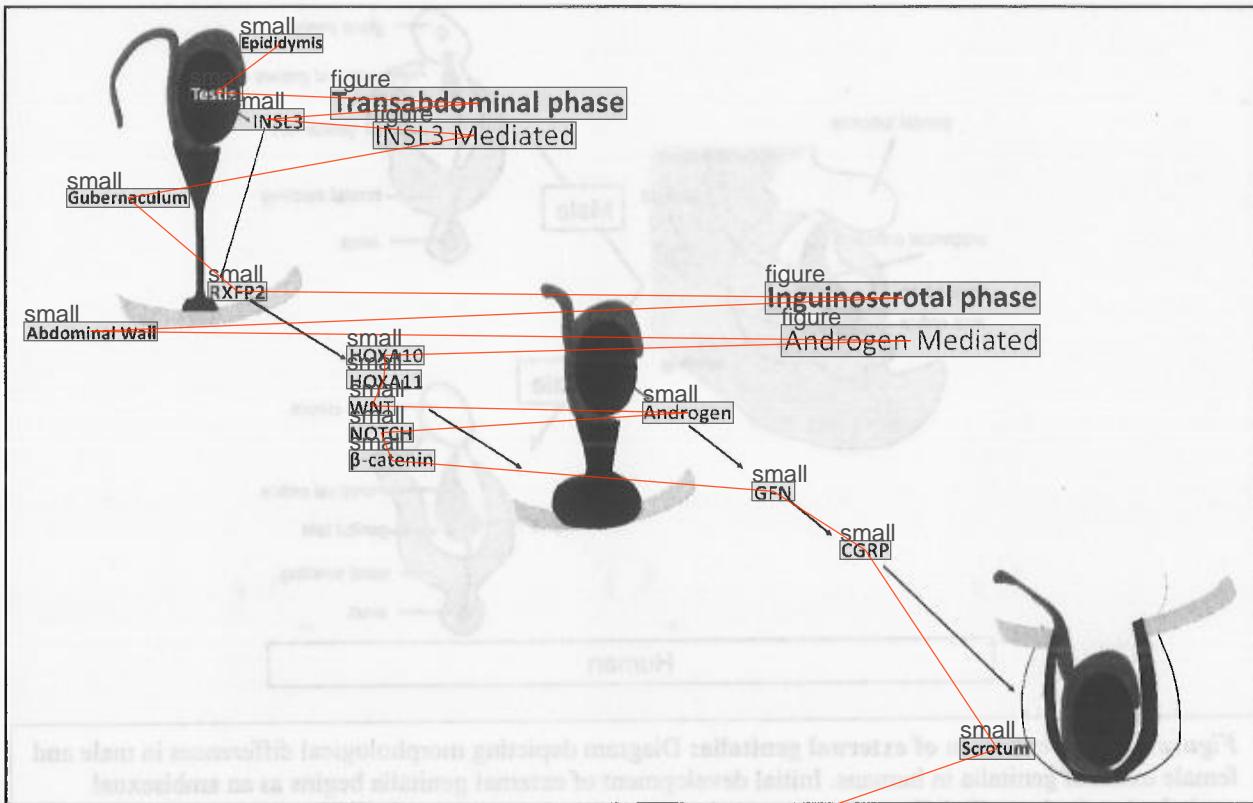


Figure 4. Sex Determination of the Bipotential Gonad and Sexual Differentiation of the Genital Tract.

Image



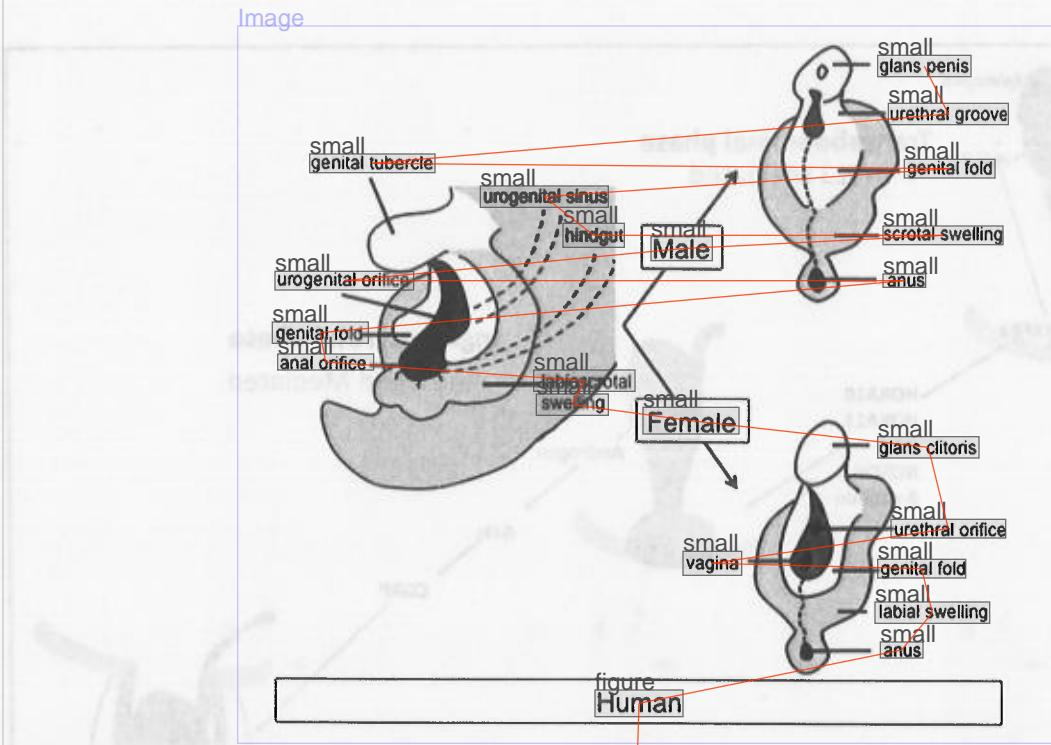
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Figure 5. Molecular Controls of Testicular Descent During Development: The first transabdominal phase of testicular descent depends upon insulin-like growth factor 3 (INSL3) working through its receptor, LGR8. The second phase of testicular descent is largely androgen mediated and occurs between 27-35 weeks of gestation.

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connected to the posterior abdominal wall by the cranial suspensory ligament. A primitive gubernaculum extends from the caudal pole to the inner inguinal ring, so essentially the testis, epididymis, and vas deferens are supported by the cranial suspensory ligament above and the gubernaculum below. At three months of gestation, the cranial suspensory ligament dissolves and then swells. This process begins to move the testis down towards the inguinal ring. At 25 weeks, the first phase (transabdominal) of testicular descent is completed when the gubernaculum bulges beyond the inguinal ring and the process vaginalis allows the external inguinal ring to open. The second phase of testicular descent from the inguinal ring into the scrotum is largely androgen controlled and occurs between 27-35 weeks of gestation.

iv) **Prostate Development and the Urogenital Sinus:** Prostatic buds develop at about 10 weeks at the site of the müllerian tubercle, and solid branching cords form. A prostatic utricle accompanies the development of the prostate. Sinoutricular bulbs then develop from the urogenital sinus. This serves to close the opening of the wolffian ducts and fuse with the medial Müllerian tubercle to form the sinoutricular cord within the prostate gland. This structure canalizes at 18 weeks to form the prostatic utricle. This male structure is considered to be analogous to the female vagina. The urogenital sinus also develops into the urethra of both sexes and the urinary bladder.



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Figure 6. Differentiation of external genitalia: Diagram depicting morphological differences in male and female external genitalia in humans. Initial development of external genitalia begins as an ambisexual genital tubercle that will differentiate into male or female genitalia in response to molecular and hormonal signals. Yellow signifies mesenchymal structures and pink signifies epithelial structures.

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v) **External genitalia (Figure 6):** The genital tubercle develops from the mesoderm and ectoderm surrounding the cloaca which also gives rise to the genital swellings and genital folds. The tubercle becomes the body and glans of the penis in males and the body and glans of the clitoris in females. The swellings become scrotal tissue in males and labia majora in females. The genital folds become the ventral aspect of the penis in males and the labia minora in females. The urethral plate gives rise to the male urethra after the urethral folds fuse ventrally and tubularization occurs. Urethral organogenesis is completed by 14 weeks of gestation. Penile and clitoral size is the same in fetuses until 14 weeks of gestation. Maximal phallic growth occurs during the third trimester of pregnancy and testosterone levels are declining.

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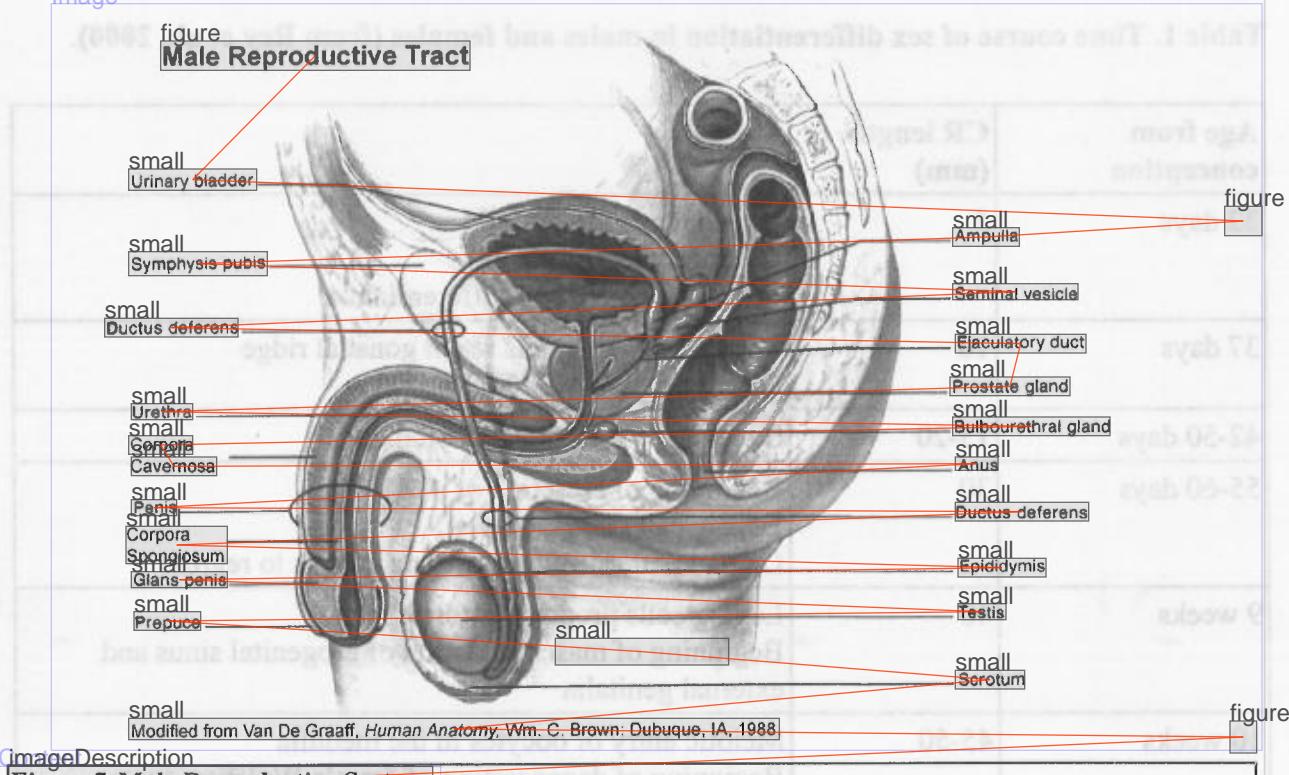
table

Table 1. Time course of sex differentiation in males and females (from Rey et al., 2000).

Image

Age from conception	CR length (mm)	Event
32 days	5	Gonadal primordia develop Growth of Wolffian ducts Primordial germ cell differentiation
37 days	10	Primordial germ cells reach gonadal ridge Differentiation of Müllerian ducts
42-50 days	15-20	Seminiferous cord differentiation
55-60 days	30	Beginning of secretion of AMH Leydig cell differentiation Cranial part of Müllerian ducts begins to regress
9 weeks	40	Leydig cells produce testosterone Beginning of masculinization of urogenital sinus and external genitalia
10 weeks	45-50	Meiotic entry of oocytes in the medulla Beginning of degeneration of female Wolffian ducts Male Müllerian ducts have disappeared Prostatic buds appear
12 weeks	55-60	The vaginal cord is formed Primordial follicles appear Seminal vesicles develop Testis at internal inguinal ring
14 weeks	70	Completion of male urethral organogenesis
16 weeks	100	Primary follicles appear
20 weeks	150	Testosterone serum level is low Formation of prostatic utricle
22 weeks	180	Vagina reaches perineum
24 weeks	200	Graafian follicles appear Beginning of penile growth
27-30 weeks	230-265	Inguino-scrotal descent of the testis
36 weeks	300	Secondary and tertiary follicles produce AM

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Figure 7. Male Reproductive System.

heading

1) THE TESTIS AND SPERMATOGENESIS IN THE ADULT

Content

a) Testicular Function

i) The testis serves three distinct but related roles in the male: an exocrine and an endocrine function, as well as a paracrine function.

(1) The **exocrine function** of the testis is involved in the production of mature sperm. The site of this function is localized in the seminiferous epithelium of the seminiferous tubules. The exocrine function of the testis involves the Sertoli cells, which serve as nurse cells and maintain the blood-testis barrier.

(2) The **endocrine function** of the testis involves the production and secretion of androgens from the Leydig cells in the interstitial compartment of the testis. The exocrine function of the testis is dependent upon the endocrine function.

(3) The **paracrine function** of the testis involves the local controls of spermatogenesis and intercompartmental signaling between the seminiferous tubules, the interstitial cells (Leydig cells, macrophages, and other cells), and the peritubular myoid cells. These paracrine factors include growth factors, cytokines, and factors affecting the spermatogonial stem cell niche.

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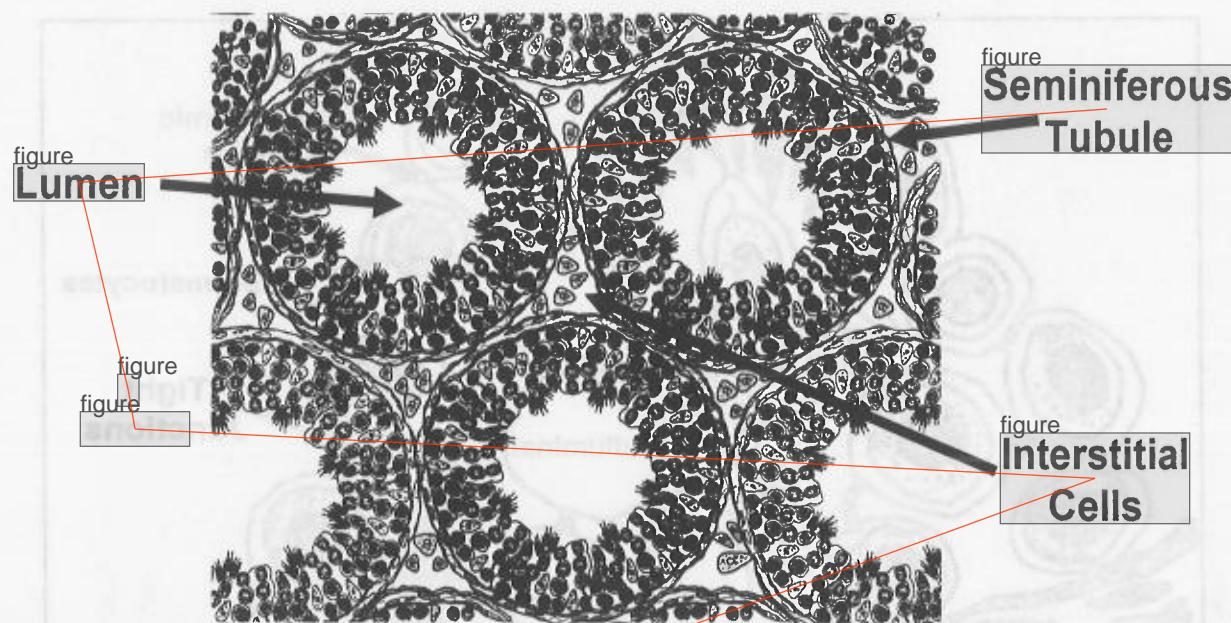


Figure 8.

Figure 8. Diagram illustrating a transverse section of the seminiferous tubules (Keel 2006).

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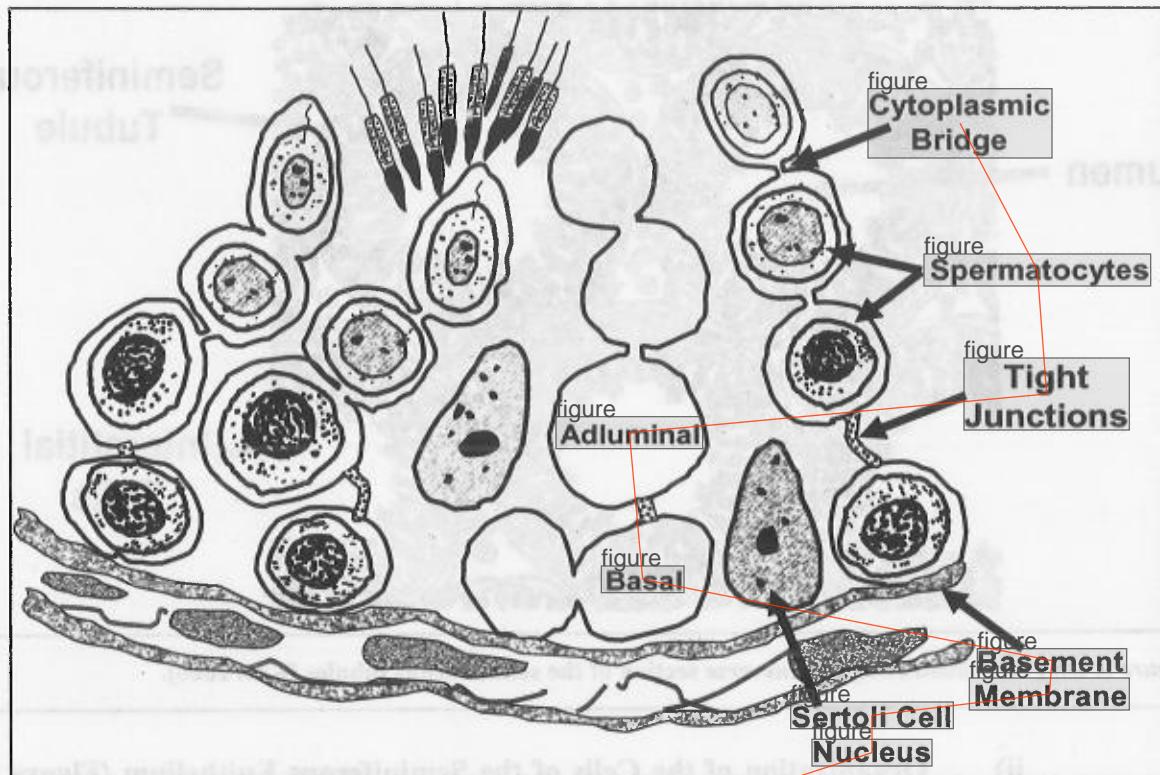
ii) Organization of the Cells of the Seminiferous Epithelium (Figure 8):

The wall of the seminiferous tubule is surrounded by fibroblasts and peritubular myoid cells. The myoid cells are flattened and have the characteristics of smooth muscle. These cells are separated from the seminiferous tubule by the basement membrane.

b) Function of the Seminiferous Tubules: The seminiferous tubules provide a unique environment for the production of germ cells. Production of germ cells involve the germinal elements—the spermatogonia—and supporting cells, the Sertoli cells, and peritubular cells of the basement membrane. Each cell type is described below. The process of meiosis is described afterwards.

(1) The Sertoli cells (Figure 9) are the only non-germinal cell within the seminiferous epithelium. A large voluminous cytoplasm envelops the developing germ cells while the base of the cell adheres to the basal lamina. It is usually difficult to distinguish the outlines of the Sertoli cell by bright light microscopy. The cells have abundant smooth endoplasmic reticulum, and some rough ER, a well-developed Golgi complex, mitochondria, and lysosomes. The nucleus is elongated and has numerous invaginations of the membrane, a prominent nucleolus and little heterochromatin. The spermatogonia are located in the basal compartment (outside of the blood-testis barrier) surrounded by the Sertoli cell with the basal lamina below. The spermatocytes and early spermatids are found in adluminal niches between adjacent Sertoli cells (protected by the blood-testis barrier—formed by tight or occluding junctions). The elongating spermatids are in crypts at the luminal side of the Sertoli cell. The tight junctions serve to prevent proteins and antibodies from reaching the spermatogenic cells and eliciting an immune response. The Sertoli cells do not divide after puberty. The Sertoli cells form niches between adjacent cells for the spermatocytes and spermatids. The late spermatids are in crypts at the luminal surface of the Sertoli cells. After puberty the Sertoli cells are terminally differentiated and no longer undergo mitosis. The seminiferous tubules also produce an

Image



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Figure 9. Illustration of the Sertoli cell. The adluminal and basal compartments, separated by tight junctions which comprise the blood-testis barrier, are shown (Keel 2006).

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environment known as the blood-testis barrier. Since the differentiating germ cells (with 1N haploid DNA) are potentially antigenic, and recognizable as foreign, the barrier sequesters these cells from the blood environment. The blood-testis barrier is maintained by the Sertoli cells.

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c) Factors Controlling Sertoli Cell Function

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i) Follicle-Stimulating Hormone (FSH): The Sertoli cell has the receptors for FSH secreted by the pituitary gland, and this hormone stimulates the release of inhibin (alpha and beta subunits) by the Sertoli cell that feeds back to inhibit GnRH release, FSH release, and activin (an alpha-alpha or beta-beta homodimer of the inhibin subunits that stimulates the release of FSH).

ii) Testosterone: Androgens are absolutely required for normal spermatogenesis, and the androgen receptors are located in the Sertoli cells. There are no receptors in the developing germ cells, and all actions of androgen are on the Sertoli cells.

Growth Factors and Cytokines, Small Peptides and RNAs provide the local controls of Sertoli cell function and spermatogenesis (for a review see Wu et al., 2019).

d) Functions of the Sertoli Cell:

Content

i) Supportive, protective and nourishing for the developing germ cells: The cell acts as a supporting matrix for the developing germ cells without having a permanent attachment to the germ cells. Sertoli cells also provide the germ cells with nutrients and may act as a “bridge” to bring substances from the capillaries to the germ cells. The hormones FSH and testosterone act directly on the Sertoli cells working through their cognate receptors to alter Sertoli cell function and impact the process of spermatogenesis.

ii) Phagocytosis of residual bodies of excess cell portions during spermiogenesis (spermatid differentiation): Sertoli cells are capable of ingesting degenerating germ cells and residual bodies. The phagocytic activity becomes more pronounced following germinal epithelium damage and massive degeneration of the germ cells.

iii) Spermiation
(The release of the mature spermatids into the lumen of the tubule.)

Content

iv) The number of Sertoli cells ultimately determines the spermatogenic potential of the testis in a normal man: Sertoli cell proliferation during the pre-pubertal phase is influenced by FSH and activin as well as thyroxin.

v) The blood-testis barrier, like the blood-brain barrier, serves to separate the testes from the normal circulation of blood and other body fluids throughout the body. Proteins, which are abundant in blood plasma and testicular lymph, are present in very low concentrations in the tubule fluid, but only proteins secreted by the Sertoli cell enter the lumen of the tubule. Specialized junctional complexes (tight junctions) formed by neighboring Sertoli cells (see Figure 9) create an effective blood-testis barrier, which accounts for the differences in

Table 2. Organ, Cell Type, and Receptor for Major Hormones

Organ	Cell Type	Receptor	Major Hormone(s) Produced
Hypothalamus	(GnRH) Producing Neurons	Androgen receptor (AR) Estrogen Receptor (ESR1)	Gonadotropin Releasing Hormone (GnRH)
Hypothalamus, Pre-optic nucleus	(GnRH) Producing Neurons	GnRH	FSH LH
Pituitary	Gonadotrophs	Follicle stimulating hormone receptor (FSHR) Androgen Receptor (AR) Estrogen receptor (ESR1), thyroid hormone receptor, Relaxin receptor	Alpha Inhibin
Testis	Sertoli Cell	Luteinizing Hormone Receptor Growth Factor Receptor: Insulin and Insulin-like Growth Factor Receptors Fibroblast Growth Factor Receptors (FGFR) Platelet derived growth factor Pdgfra (fetal)	Mullerian Inhibiting Substance (MIS) Testosterone Insulin-like Growth Factor 3 (IGF3)
	Leydig cell		

Content

chemical composition of the tubule fluid and the blood plasma or lymph. This barrier protects the sperm from the immune system and ensures that the fluid balance within the seminiferous tubule is conducive to sperm development. **These complexes between Sertoli cells divide the epithelium into two compartments:**

(1) **Basal compartment** between the Sertoli junctions and the basal lamina containing the spermatogonia

(2) **Adluminal compartment** above the Sertoli cell junctions containing the more advanced germ cells (Figure 9). The movement of leptotene spermatocytes from the basal to the adluminal compartment involves the blood-testis barrier. The formation of the blood-testis barrier might be required to establish an appropriate environment for the completion of meiosis.

vi) **Secretion of proteins and ions into the lumen:** Tubule Fluid – The seminiferous tubules contain fluid which has a different composition from that of blood plasma or lymph. Sertoli cells probably are responsible for the secretion of this fluid. Its function is to transport spermatozoa to the epididymis and provide substrates for sperm survival.

(1) **Inhibin** – Sertoli cells produce this protein hormone, which specifically inhibits the release of FSH from the pituitary. Severe damage to the germinal epithelium results in decreased production of inhibin and subsequent increases in FSH secretion. The human male produces primarily inhibin B (see below).

(2) **Secretion of müllerian-inhibiting substance (MIS)**, also called anti-müllerian hormone (AMH). MIS/AMH inhibits the growth and causes regression of the müllerian ducts during fetal development and, thus, plays an important role during sexual differentiation.

Local factors: There is evidence for strong local control via growth factors and their receptors of spermatogenesis

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1) THE LEYDIG CELL AND TESTICULAR STEROIDOGENESIS

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Leydig Cells: The Leydig cells are clusters of cells that occur in the interstitial tissue between the seminiferous tubules (see Figure 8). These cells comprise only about 5% of the total testicular volume. The Leydig cell synthesizes androgens from cholesterol (Figure 10 a, b). Androgens secreted from the Leydig cell regulate the development and function of the male reproductive tract and secondary sexual characteristics as well as promote spermatogenesis. The major androgen secreted is testosterone. Its synthesis and release is stimulated by pituitary LH. Leydig cells can synthesize cholesterol from acetate or take up cholesterol from lipoproteins for steroidogenesis. The rate limiting step for steroid biosynthesis is the mobilization of cholesterol from the intracellular stores to the inner mitochondrial membrane where it is converted to the first steroid formed, pregnenolone. Although several proteins have been implicated in this process of cholesterol transport to the mitochondria, acute steroidogenic regulatory protein (StAR) plays a major role in regulated steroid production. A second protein (translocator protein

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or TSPO) has been implicated as a possible regulator as well. From pregnenolone, the Leydig cell produces testosterone via metabolism through the $\Delta 4$ steroidogenic pathway shown in

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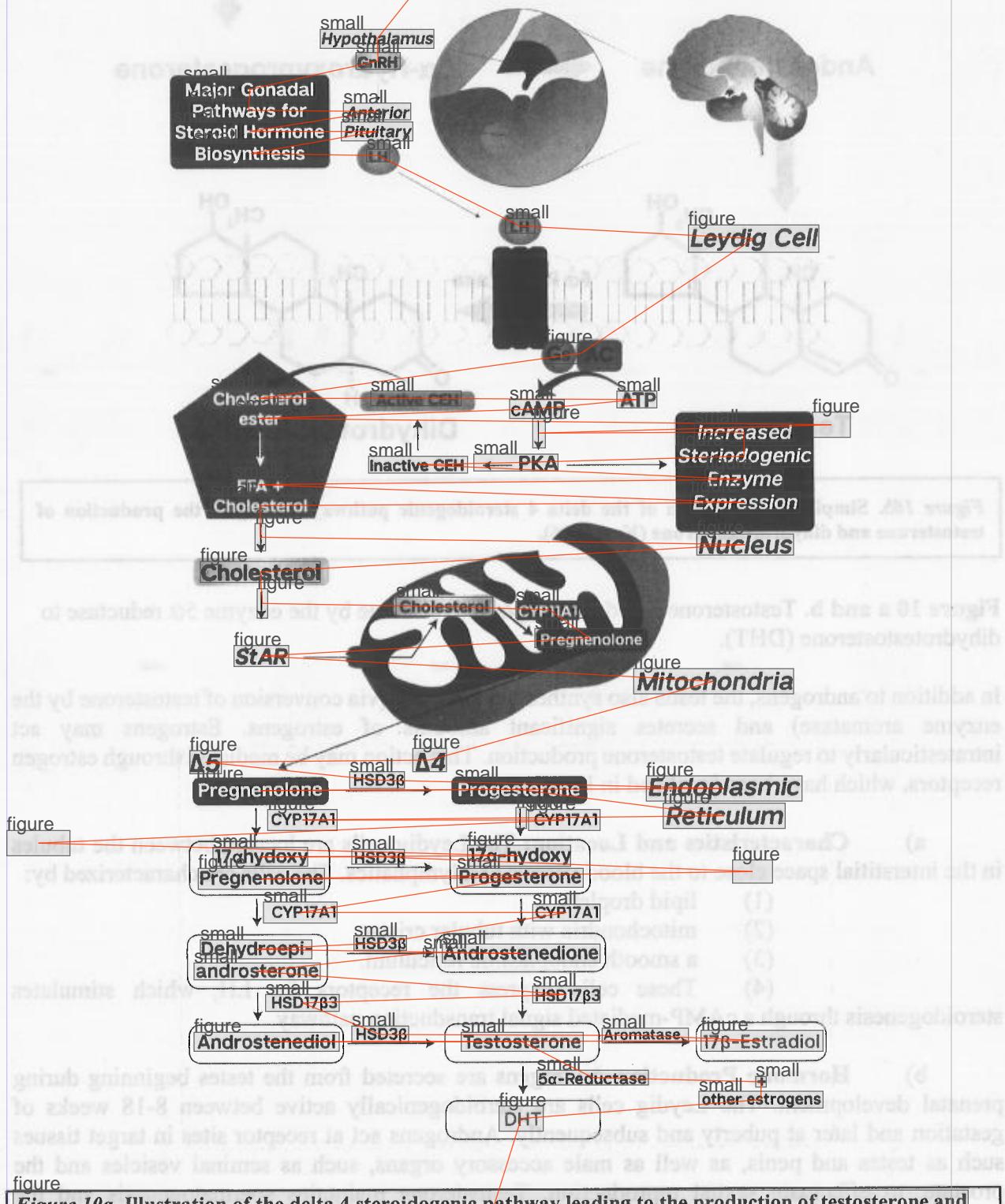
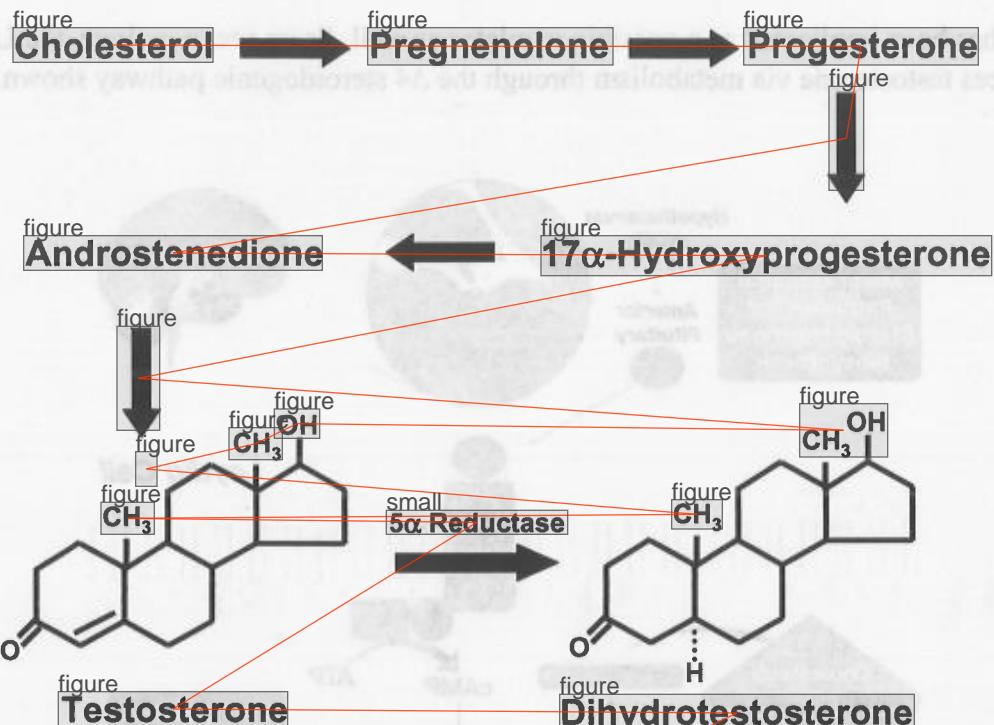


Figure 10a. Illustration of the delta 4 steroidogenic pathway leading to the production of testosterone and dihydروtestosterone. (Adapted from Ayaz & Howlett, 2015.)

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Figure 10b. Simplified illustration of the delta 4 steroidogenic pathway leading to the production of testosterone and dihydrotestosterone (Keel 2006).

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Figure 10 a and b. Testosterone is reduced in peripheral tissue by the enzyme 5α reductase to dihydrotestosterone (DHT).

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In addition to androgens, the testis also synthesizes estradiol (via conversion of testosterone by the enzyme aromatase) and secretes significant amounts of estrogens. Estrogens may act intratesticularly to regulate testosterone production. This action may be mediated through estrogen receptors, which have been localized in Leydig cells.

a) **Characteristics and Location:** The Leydig cells are located between the tubules in the interstitial space close to the blood vessels and lymphatics. The cells are characterized by:

- (1) lipid droplets
- (2) mitochondria with tubular cristae
- (3) a smooth endoplasmic reticulum.

(4) These cells express the receptors for LH, which stimulates steroidogenesis through a cAMP-mediated signal transduction pathway.

b) **Hormone Production** Androgens are secreted from the testes beginning during prenatal development. The Leydig cells are steroidogenically active between 8-18 weeks of gestation and later at puberty and subsequently. Androgens act at receptor sites in target tissues such as testes and penis, as well as male accessory organs, such as seminal vesicles and the prostate, to effectuate sexual reproduction. Testosterone maintains spermatogenesis and the function of the male accessory glands. Androgens regulate central nervous system functions to

influence libido and sexual behavior. Androgens also stimulate metabolism and protein synthesis and influence muscle growth, as well as the additional secondary sex characteristics (male pattern body hair and balding, deepening of the voice, increased bone density, calcium retention, increased red blood cells, and increased body water due to increased renal absorption of water). The functions of the Leydig cells are regulated by:

(1) LH that stimulates testosterone biosynthesis

(2) Prolactin that induces the expression of the LH receptor

2) **The Germ Cells:** The germinal elements comprise a population of cells, which include a slowly dividing primitive stem cell population, the rapidly proliferating spermatogonia, spermatocytes undergoing meiosis and the metamorphosing spermatids.

a) **Mitosis in the Testis:** The spermatogonia in the testis have the highest rate of proliferation in the body. They proliferate to ensure the relatively constant production of sperm by the testis.

i) **Spermatogonial stem cells** were first postulated to exist based upon subtle morphological characteristics and the realization that in some instances after prolonged periods of secondary infertility, after exposure to gonadotoxins, rejuvenation of spermatogenesis might occur years later. The spermatogonial stem cells are largely quiescent but have the capacity to regenerate spermatogenesis after a toxic insult. The cells are characterized by their ability to undergo self-renewal throughout the life of males. The cells reside in a niche or specialized microenvironment on the basal side of the blood-testis barrier. Regulation of self-renewal is under investigation, but growth factors such as GDNF and FGF are critical regulators of spermatogonial stem cell renewal. Spermatogonial stem cell transplantation techniques developed in the mid-1990s definitively showed the regenerative potential of these cells to restore spermatogenesis to an otherwise Sertoli cell-only testis. Interestingly, more recent studies in mouse models and in human spermatogenesis show that these cells are also pluripotent with the ability to form multi-potent embryonic stem cell-like lines that can differentiate into somatic cells.

ii) **Type A spermatogonia:** These are the least mature germ cells and are located directly along the basal lamina. The primitive spermatogonium is about 12 µm in diameter, and on a hematoxylin and eosin stained slide, they appear to have a lighter halo around the nucleus. The cells are connected by small cytoplasmic bridges. There are two type A spermatogonia, type A pale and A dark. The A dark spermatogonia are the putative stem cells. Type B spermatogonia are more differentiated. Retinoic acid is usually metabolized by the testis from retinol in circulation. Retinoic acid acts directly on the spermatogonia to stimulate their entry into the meiotic pathway and differentiate into type B spermatogonia. Retinoic acid also acts on the Sertoli cells to regulate the cyclic functions of this cell in spermatogenesis. The clock appears to be set by retinoic acid but the germ cells can influence this cyclic activity of the Sertoli cell as well (O'Donnell, Stanton, & de Kretser, 2000).

b) In a routine pathological examination, the types of spermatogonia are not routinely assessed. **Spermatogonia** are the diploid spermatogenic cells located along the basal lamina of the

basal compartment of the seminiferous epithelium. They are outside of the blood-testis barrier (below the tight junctions between adjacent Sertoli cells). A spermatogonial stem cell undergoes successive rounds of mitosis at puberty. This mitosis is very inefficient, and many cells undergo apoptosis. *This stage is known as the proliferative stage of spermatogenesis.* After exposure to toxic agents or radiation, the stem cells have the potential to repopulate the testis with spermatogenic cells and re-establish the spermatogenic process.

3) **Meiosis:** involves the steps that follow the entry of the type B spermatogonia into the meiotic pathway. This is a process where the germ cells undergo a series of DNA replication resulting in a tetraploid gamete, followed by meiotic recombination with double-strand breaks, crossing over and DNA repair followed by two successive reductive divisions to yield the haploid spermatid (O'Donnell et al., 2000).

a) **Primary Spermatocytes:** The type B spermatogonia are the progenitor cells that differentiate into the primary spermatocytes. The spermatocytes are large cells with twice the normal amount of DNA per cell and a 4C chromosome value. The spermatocytes are located in the adluminal compartment of the seminiferous epithelium (inside of the blood-testis barrier). The **primary spermatocyte** undergoes the first or reductional meiotic division to produce two secondary spermatocytes (2C DNA content). Prophase is divided into 4 stages—leptotene zygotene, pachytene, and diplotene. This is the longest stage, taking about 22 days in humans, so most spermatocytes seen in a section will be in this phase. The cells reach diakinesis (crossing over of genes of the chromosomes occurs). The cells then progress to metaphase, the chromosomes move to the poles at anaphase. The cells are the largest spermatogenic cells and are characterized by chromosomes in various stages of coiling.

i) **First Meiotic Division**

1. **Leptotene:** Each homologous chromosome is two sister chromatids (maternal and paternal) that attach to the inner membrane of the nuclear envelope.

2. **Zygotene:** Synapsis of the homologous chromosomes begins. A synaptonemal complex develops between homologous chromosomes.

3. **Pachytene:** Synapsis is complete when homologous chromosomes become entirely linked. Stretches of paternal and maternal DNA are coordinated in space and crossing over between non-sister chromatids starts (homologous recombination).

4. **Diplotene:** The chromosomes appear double. Disjunction takes place when crossing over ends. Chromosomes remain attached at specific points (chiasmata).

5. **Diakinesis:** Chromosomes detach from the nuclear membrane, shorten and become thicker. Synaptonemal complex disassembles, but a short piece remains in the chiasma region. A microtubule spindle begins to form.

ii) **Secondary Spermatocytes** are formed after completion of the first meiotic division. The secondary spermatocytes then undergo the second or equational division to form two spermatids with a haploid chromosome complement (1C DNA content). At the prophase these

cells are 46C (44+XY/X) with 4N of DNA. This division serves to reduce the number of chromosomes in half (22+X or 22+Y), and the DNA per cell is reduced from 4N to 2N. These cells are rarely identified in a section because they promptly undergo a second meiotic division to reduce the DNA in half again (2N to 1N) with 23 chromosomes forming haploid spermatids. There is no S phase (DNA synthesis) between the first and second meiotic divisions.

iii) **Second Meiotic Division:** After prolonged meiotic prophase, pairs of sister chromatids progress through metaphase, anaphase, and telophase and separate into daughter cells known as the secondary spermatocytes (2C DNA content).

iv) **Consequences of Meiosis**

1. Haploid chromosomal complement

2. Homologous recombination or random mixing of the paternal and maternal chromosomes

3. Crossing over increases genetic variation

b) Spermatids are the haploid germ cells within the seminiferous epithelium. This is the last phase of spermatogenesis. **Spermiogenesis** is the process of differentiation of the haploid spermatid into a mature spermatozoon. The process of spermiogenesis involves the differentiation of the spermatids. The spermatids are generated from the second meiotic division of the secondary spermatocytes. These cells are haploid with 1N DNA content. They are small in size (7-8 µm in diameter), with areas of condensed chromatin and juxtaluminal location within the seminiferous epithelium. The three phases of spermiogenesis are:

i) **Development of the Acrosome:** The acrosomal sac or cap is required for fertilization and consists of a storage area for hydrolytic enzymes. The development of the acrosome progresses through a Golgi stage, cap phase, acrosomal phase, and maturation phase.

ii) **Golgi Phase:** The cytoplasm contains a prominent Golgi complex, as well as mitochondria, a pair of centrioles, free ribosomes, and smooth ER. A small periodic acid-Schiff (PAS)-positive granule forms in the Golgi complex near the nucleus. These granules come together to form an acrosomal granule within an acrosomal vesicle. The centrioles move near the cell surface and opposite from the acrosome.

iii) **Acrosomal Phase:** The acrosomal vesicle spreads to cover the top half of the condensing nucleus to form the acrosome. This vesicle contains hydrolytic enzymes (hyaluronidase, neuraminidase, acid phosphatase, and a trypsin-like protease). These enzymes are needed by the mature sperm to transverse the cumulus complex and zona pellucida of the ova. The cell reverses orientation, and the acrosome is now juxtaposed to the basal region of the tubule. The nucleus undergoes extensive remodeling and condenses markedly. One of the centrioles differentiates to form the flagellum. The middle piece of the tail is a thickened region of the flagellum where sperm movement is generated. The mitochondria migrate along the developing axoneme.

Content

iv) **Development of the Flagellum:** The flagellum consists of an axoneme (9+2 microtubule doublets in a concentric arrangement) surrounded by a fibrous sheath and keratin-containing dense outer fibers. Mitochondria are in the mid-piece of the tail and provide energy.

v) **The Maturation Phase:** The spermatids continue to differentiate, condense, and elongate their nucleus; the residual cytoplasm is phagocytized by the Sertoli cell; and the spermatozoa are released into the lumen of the seminiferous tubule. The cytoplasmic bridges formed between the spermatogonia have been maintained and permit the exchange of information between cohorts of cells. Prior to spermiation, these bridges are lost with the residual cytoplasm that is extruded.

vi) **Condensation of the Nucleus:** The somatic chromatin histones are replaced by highly basic arginine and lysine rich protamines. The chromatin fibers associate and condense the nuclear material into a highly and tightly packaged structure. Transcriptional activity ceases (RNA synthesis).

vii) **Final Steps of Spermiogenesis:** The flagellum structure is key to future motility (9+2 microtubules surrounded by the outer dense fibers). The mitochondria align along the developing flagellum, and the manchette migrates caudally. The tail now has two segments: the mid piece (mitochondria are present) and the principal piece (tail is surrounded by the dense sheath). The residual body, excess cytoplasm extruded during spermiogenesis, is phagocytized by the Sertoli cell at the time of spermiation (release of the spermatozoa). At this time, nuclear condensation is complete, and histones are fully replaced by the protamines. The head of the sperm is covered by an intact acrosome, and these enzymes are released at the time of fertilization. The connecting piece links the head to the tail and contains the 2 centrioles. The distal centriole gives rise to the axoneme of the sperm tail. The mid-piece, principal piece, and end piece describe the tail.

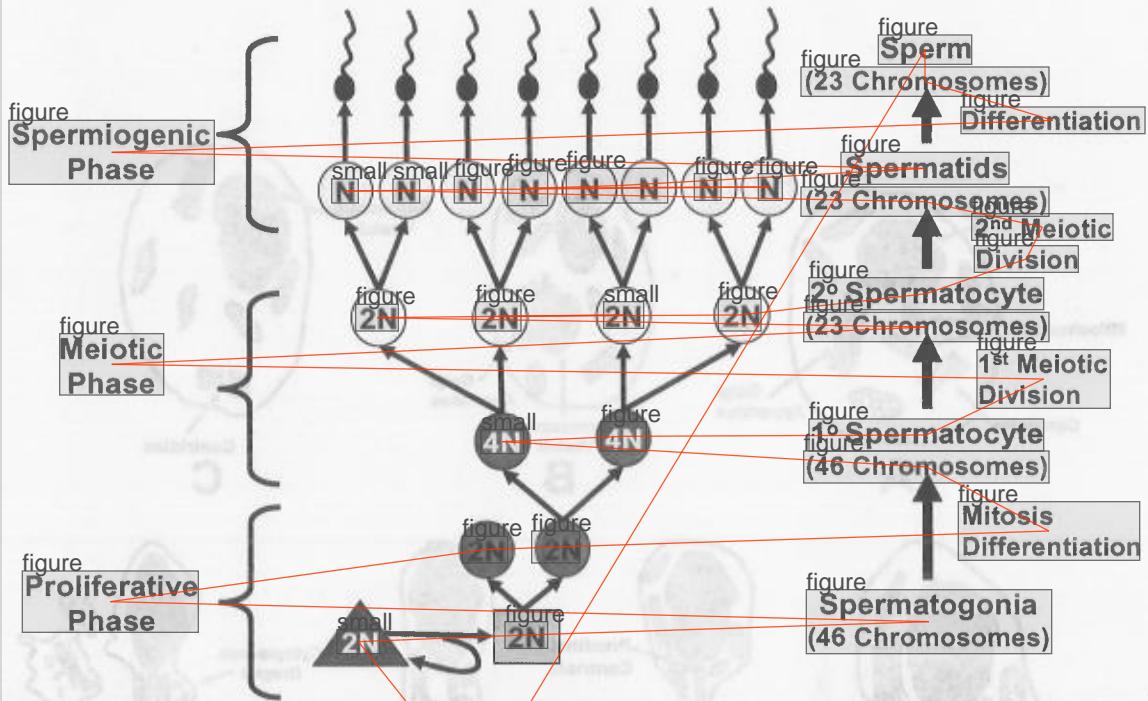
4) **Spermatogenesis:** Although the cell types were described above, the process of spermatogenesis will be the focus of the next section.

a) **Spermatogenesis, the process by which a spermatogonial stem cell gives rise to a spermatozoon, can be divided into three distinct phases (Figure 11):**

i) Spermatogonia proliferate to give rise to spermatocytes and simultaneously maintain their number by renewal.

ii) Spermatocytes prepare for and undergo the complex maturation divisions of meiosis that reduce the chromosome number of the germ cells by half.

iii) Spermatids, the product of the maturation divisions, undergo a remarkable metamorphosis, called spermiogenesis, which leads to the production of spermatozoa.



figure

Figure 11. Diagram illustrating the three phases of spermatogenesis. In the Proliferative Phase, the triangle refers to Type Ad spermatogonia, square refers to Type Ap spermatogonia and circle refers Type B spermatogonia. N refers to the amount of DNA present in the cell (Keel 2006).

Content

a) **Proliferative Phase:** Unlike the situation in the female, in which a full complement of oocytes is present in the ovary at birth, the production of generation after generation of meiotic spermatocytes in the male requires a means to replace the spermatogonia or stem cells.

- Several spermatogonial types have been described in man: Spermatogonial stem cells type Ad (dark) and type Ap (pale), and Type B spermatogonia. According to Clermont (1966), one member of a pair of type Ad spermatogonia divides to give rise to a pair of new type Ad cells, while the other member of the original pair of Ad divides to yield a pair of more differentiated type Ap spermatogonia. Thus, it is thought that the type Ad spermatogonia not only serve as a precursor for type Ap, but also eventually serve as the ancestor (i.e., stem cell) of a later generation of sperm.
- The type Ap spermatogonia divides by mitosis to give rise to two type B spermatogonia, a subset of which further divide to produce the preleptotene spermatocytes that enter meiosis.

heading

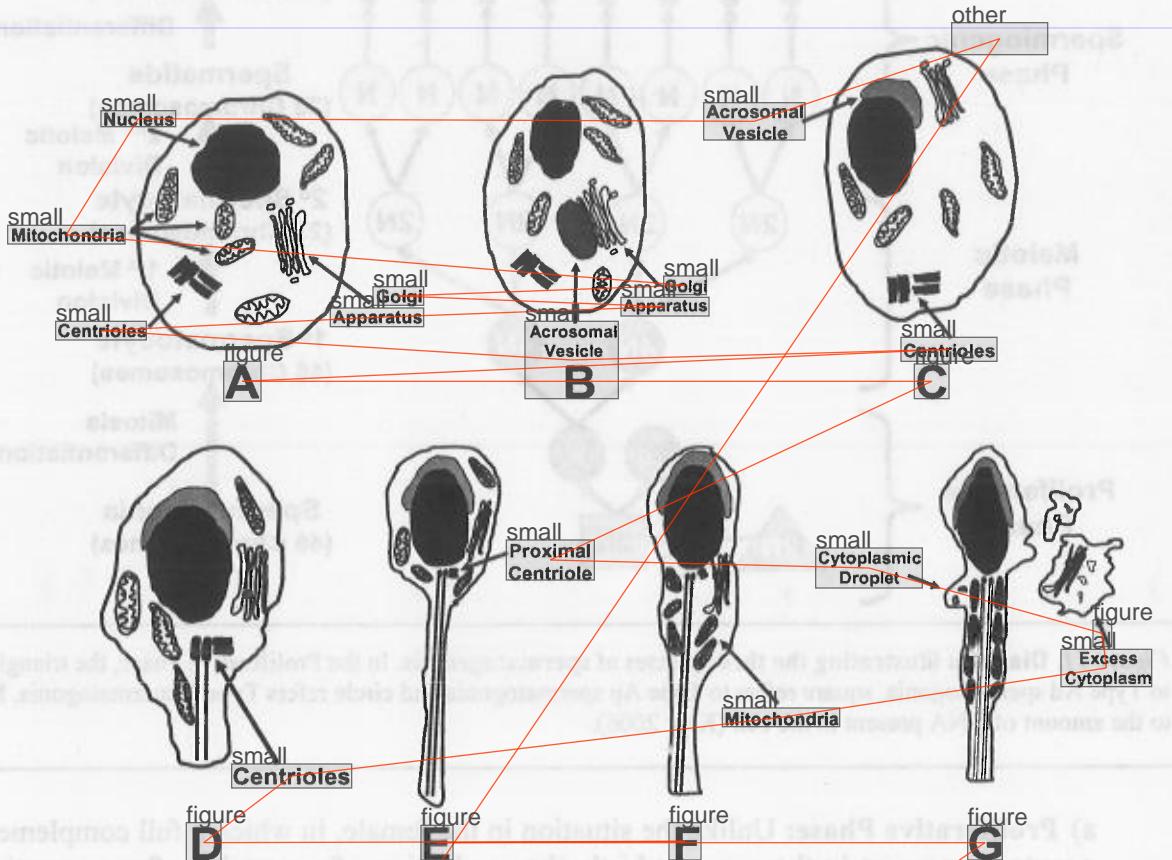
b) Meiotic Phase (Summarized here)

Content

- The diploid type B spermatogonia, which are also diploid (i.e., 2N) in terms of DNA content and chromosome number, divide by mitosis to give rise to a new generation of cells: the primary spermatocytes.

other

Image



figure

Figure 12. Illustration of the various stages of spermatogenesis (Keel 2006).

Content

- ii) The primary spermatocytes initially have double the amount of DNA (i.e., tetraploid or $4N$) but remain diploid in terms of chromosome number (see **Figure 11**).
- iii) The primary spermatocytes then go through the preleptotene, leptotene, zygotene, and pachytene steps of the long prophase of the first maturation division of meiosis.
- iv) Following a short diplotene phase, the primary spermatocytes complete the first maturation division through metaphase, anaphase, and telophase to give rise to **secondary spermatocytes** (which are haploid, but contain $2N$ amount of DNA since they are double-stranded chromosomes).
- v) The secondary spermatocytes then quickly proceed through the second maturation division of meiosis to yield **haploid spermatids** containing $1N$ amount of DNA.

other

Content

7) Spermiogenesis is the process of differentiation of the round spermatid to undergo morphological changes to develop an acrosome and flagella and to undergo nuclear condensation and extrusion of the cytoplasm.

a) **Round Spermatids:** As the spermatid matures it elongates, develops a tail or flagellum, and assumes a configuration similar to that of the mature spermatozoon. Very few spermatozoa are present in histological sections of the testis because as soon as they mature, the sperm are released into the seminiferous tubular lumen and rapidly flow out to the rete testis. The spermatid contains a prominent round nucleus, a Golgi apparatus, a set of centrioles, and numerous mitochondria (Figure 12). These organelles, with the aid of the Sertoli cell, will undergo architectural changes that will transform the spermatid into the mature spermatozoon

Image

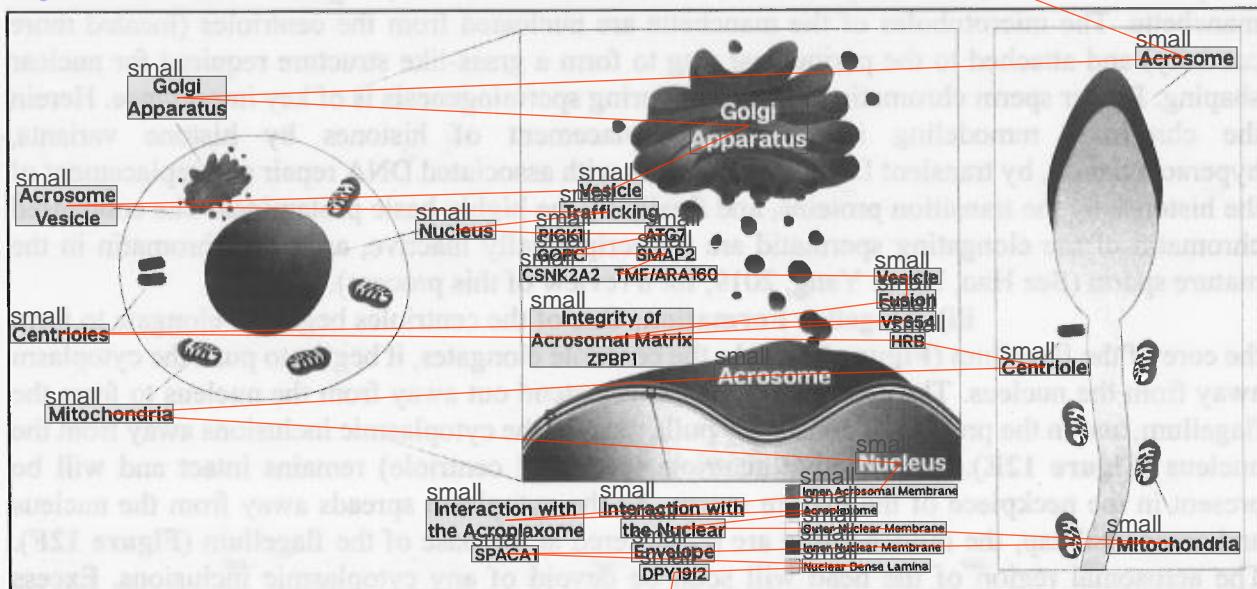


Image Description

Figure 13. A Review of Acrosome Biogenesis and the Proteins That Play Key Roles in This Process. During the biogenesis of the acrosome, the endoplasmic reticulum processes some of the proteins needed, and there is vesicle trafficking from the Golgi apparatus. These vesicles fuse to form the precursor of the acrosome. The inner acrosomal membrane interacts with the acroplaxome. The acroplaxome interacts with the outer and inner nuclear membranes. Proteins required for these steps are shown above, and when absent or non-functional lead to globozoospermia. The absence of SPACA1, which interacts with the acroplaxome, and DYP19L2, which interacts with the nuclear membrane, result in the absence of the nuclear dense lamina. The genes involved and their abbreviations are: protein interacting with PRKCA 1 (PICK1); golgi-associated PDZ and coiled-coil motif containing (GOPC); casein kinase 2, alpha prime polypeptide (CSNK2a2); autophagy related 7 (ATG7); small AGAP 2 (SMAP2); TATA element modulatory factor 1 (TMF1 or ARA160); zona pellucida binding protein (ZPBP or ZPBP1); vacuolar protein sorting 54 (VSP54); ArfGAP with FG repeats 1 (HRB), sperm acrosome associated 1 (SPACA1); heat shock protein 90 kDa beta 1 (HSP90b1); glucosidase, beta (bile acid) 2 (GBA2).

Content

i) During the first stage of spermiogenesis, large acrosomal vesicles are elaborated by the Golgi apparatus (Figure 12A). Other than the nucleus, the acrosomal vesicle soon becomes the most prominent cytoplasmic inclusion within the spermatid. The acrosomal vesicle migrates to one pole of the nucleus, and the centrioles move to the opposite end of the nucleus (Figure 12C). The acrosomal vesicle will eventually become the acrosomal cap of the sperm. The molecular controls of this process involve the proper functioning of a large number of different proteins at every stage of acrosome biosynthesis (Figure 13). When one of these proteins described

in Figure 13 are dysfunctional, teratozoospermia occurs, specifically round-headed sperm/globozoospermia due to the absence of the acrosome or acrosome atrophy or displacement.

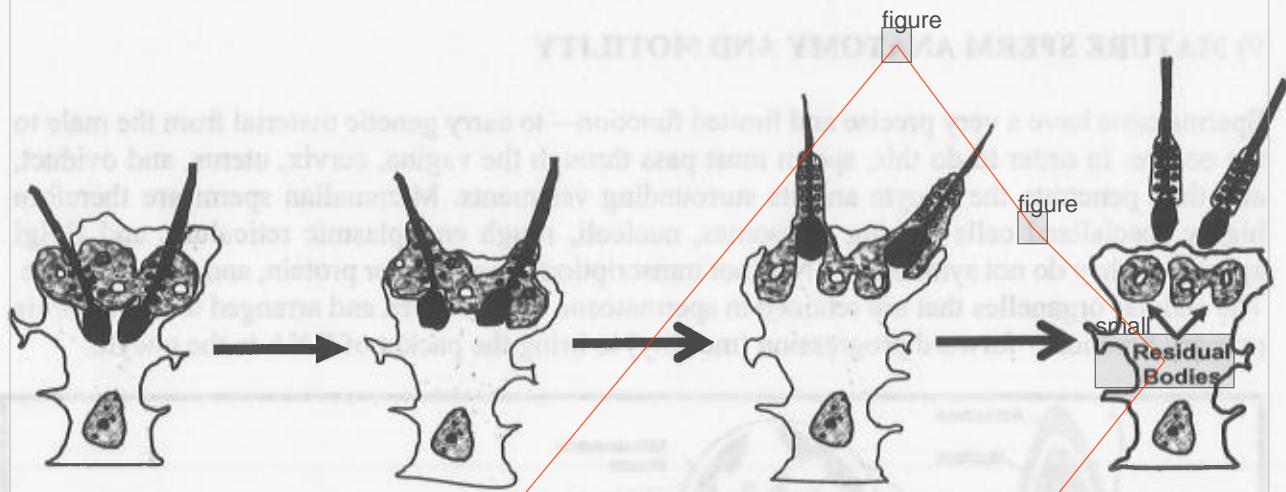
Headline

ii). Nuclear condensation: Surprisingly little research has been performed to fully understand the events required for the elongation and condensation of the spermatid nucleus. The acroplaxome, which consists of a bent plate and marginal ring encircling the spermatid nucleus, is key in this process. It serves to anchor the developing acrosome to the spermatid nucleus. The manchette also plays an important role in this process. The manchette surrounds the elongating spermatid head and is only present at the time of spermatid head shaping and tail formation. It is composed of a perinuclear ring and an attached fringe of microtubules. In humans it is proposed that the apical portion of the sperm head is driven by the actions of the acroplaxome and F-actin hoops located within the Sertoli cell, together with the transient manchette. The microtubules of the manchette are nucleated from the centrioles (located more caudally) and attached to the perinuclear ring to form a grass-like structure required for nuclear shaping. Proper sperm chromatin remodeling during spermiogenesis is of key importance. Herein the chromatin remodeling involves the replacement of histones by histone variants, hyperacetylation, by transient DNA strand breaks with associated DNA repair and replacement of the histones by the transition proteins, and finally by the highly basic protamines. The condensed chromatin of the elongating spermatid are transcriptionally inactive, as is the chromatin in the mature sperm (See Hao, Ni, & Yang, 2019, for a review of this process).

iii). Flagellar Formation: One of the centrioles begins to elongate to form the core of the flagellum (Figure 12A). As the centriole elongates, it begins to push the cytoplasm away from the nucleus. The centriole continues to extend out away from the nucleus to form the flagellum, and in the process, it constantly pulls most of the cytoplasmic inclusions away from the nucleus (Figure 12E). The inactive centriole (proximal centriole) remains intact and will be present in the neckpiece of the mature sperm. As the cytoplasm spreads away from the nucleus and acrosomal cap, the mitochondria are sequestered at the base of the flagellum (Figure 12F). The acrosomal region of the head will soon be devoid of any cytoplasmic inclusions. Excess cytoplasm, which now resides primarily in the area of the neckpiece, is cast off and phagocytized by the Sertoli cell. A remnant of the cytoplasm, the cytoplasmic droplet (Figure 12G), is sometimes seen on sperm during the semen analysis, and an excess of these droplets may indicate immature sperm in the ejaculate.

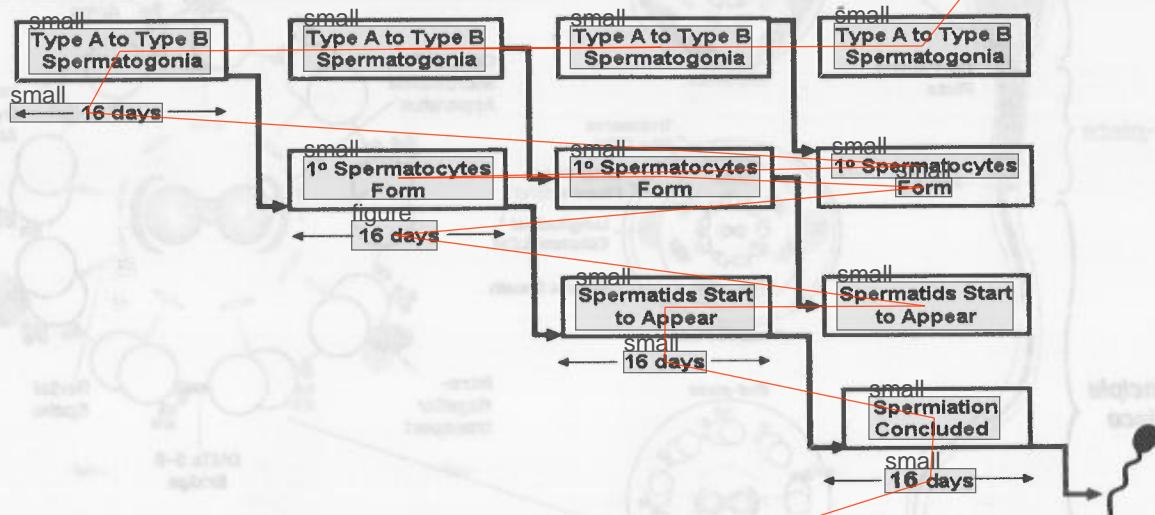
b) Spermiation: The last stage of sperm maturation and release is called **spermiation** (Figure 14) and is the process of non-motile spermatozoa leaving the Sertoli cell and being deposited into the lumen of the seminiferous tubules. It has been suggested that phagocytosis of residual bodies, representing the remnants of spermatid cytoplasm, by Sertoli cells may trigger the spermatogonia to initiate a new cycle of spermatogenesis.

c) The Cycle of Spermatogenesis: In man, the entire sequence of spermatogenesis from spermatogonia to spermatozoa takes about 64 days (Heller, 1963). The individual resting spermatogonia do not wait until one wave of spermatogenesis is complete before initiating a new sequence, nor do they initiate the process of spermatogenesis at random. The starting of a new generation of germ cells is connected in a definite manner with the development of the preceding generation.



figure

Figure 14. Illustration of the process of spermatogenesis. Keel 2006 after Kerr et al., 2006.



ImageDescription

Figure 15. Diagram illustrating the Cycle of the Seminiferous Epithelium in humans. Keel 2006 after Huckins, 1983.

Content

These groupings of cells are known as stages in the cycle of the seminiferous epithelium (Clermont, 1963). There are six stages in humans—stages I through VI constitute one cycle. Groups of adjacent resting spermatogonia initiate a new cycle about every 16 ± 1 days (Figure 15). When the primary spermatocytes of one cycle enter prophase, a second cycle is activated. A third cycle begins at about the time the spermatids from the first cycle appear. By the time these spermatids mature into spermatozoa, a fourth cycle begins. Around the circumference of any single seminiferous tubule, and throughout the testis, several of these cycles may be in the process simultaneously.

Approximately four cycles of the epithelium are required for a type Ap spermatogonia to mature to the spermatozoon. Thus, one cycle of seminiferous epithelium lasts 16 days, and the entire process of spermatogenesis is estimated at 64 days (4 cycles times 16 days each; Heller & Clermont, 1963).

heading

9) MATURE SPERM ANATOMY AND MOTILITY

Content

Spermatozoa have a very precise and limited function—to carry genetic material from the male to the oocyte. In order to do this, sperm must pass through the vagina, cervix, uterus, and oviduct, and then penetrate the oocyte and its surrounding vestments. Mammalian sperm are therefore highly specialized cells lacking ribosomes, nucleoli, rough endoplasmic reticulum, and Golgi apparatus; they do not synthesize RNA (not transcriptionally active) or protein, and do not secrete. The cellular organelles that are retained in spermatozoa are modified and arranged to allow for its primary function—forward progression (motility) to bring the packet of DNA to the oocyte.

Image

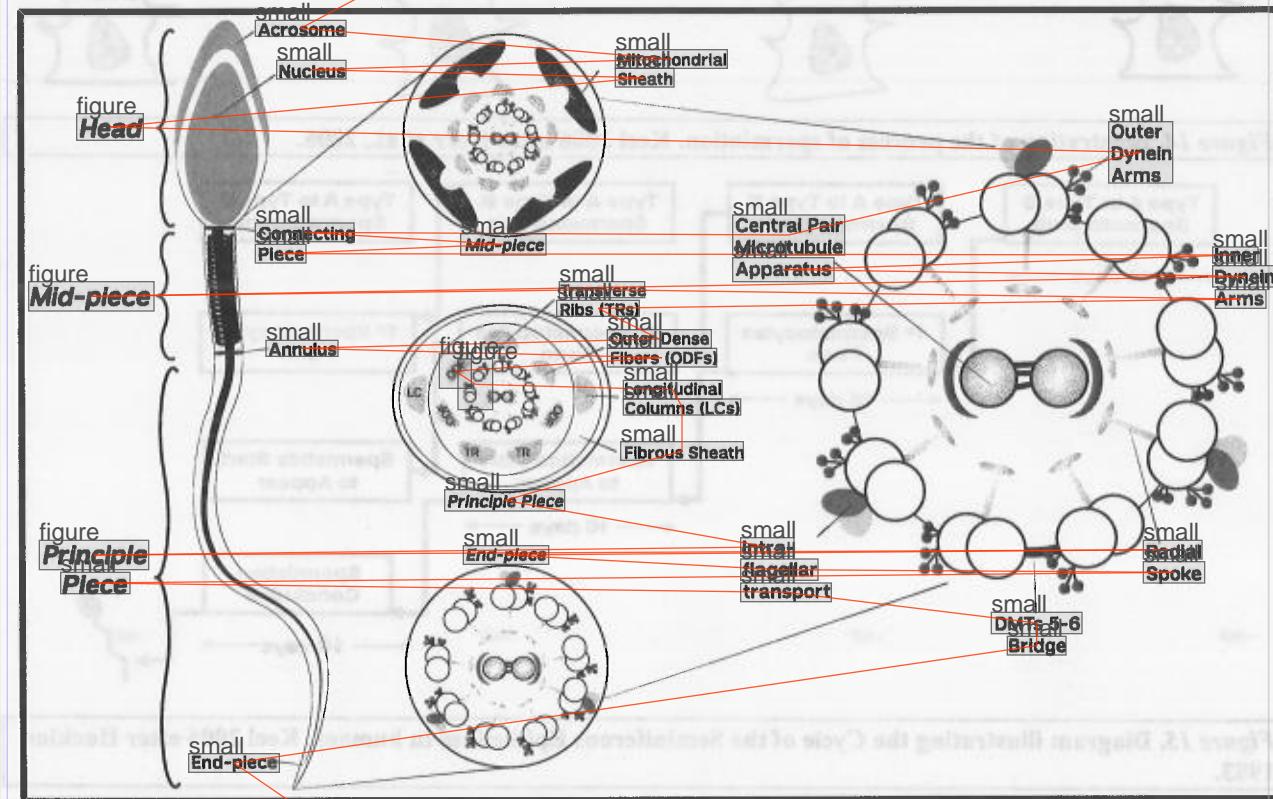


Image Description

Figure 16. Illustration of the Structure of the Mature Spermatozoa. Sperm flagellum is divided into a mid-piece, a principal piece, and an end-piece; the figure depicts the cross-section of each structure of the flagella. The annulus is a ring structure demarcating the mid-piece and the principal piece of the sperm tail. The axoneme is a highly evolutionarily conserved structure present in the whole flagellum. The view of the axoneme from a transverse view shows the general location of each component. The mid-piece features a helical mitochondrial sheath surrounding the axoneme. The midpiece is replaced by the fibrous sheath in the principal piece. The terminal piece of the flagella (end-piece) lacks any peri-axonemal structures. The approximate location of the key proteins known to be defective in some cases of sperm function deficiencies (See Chapter 15 on Reproductive Genetics) include the following proteins DNAH1, CFAP43, CFAP44, AK7, AKAP3, AKAP4, CEP135. Abbreviations: RSs: radial spokes; CPMA: central pair microtubule apparatus; IC/LC: intermediate chain/light chain; N-DRC: nexin-dynein regulatory complex; MIA: modifier of inner arms complex; CSC: calmodulin- and spoke associated complex; DP: distal protrusion; MS: mitochondrial sheath; FS: fibrous sheath; IADs: inner arm dyneins; OADs: outer arm dyneins (Adapted from Coutton, Escoffier, Martinez, Arnoult, & Ray, 2015; Wang et al., 2019).

heading

10) Sperm Anatomy and Motility (see Figures 16, 17)

Content

a) **Head** – The genetic material transported by the spermatozoa is located in the nucleus of the head region. The nuclear chromatin is densely packed and homogeneous. Sperm nuclei contain either the X or Y chromosome. It is therefore the male gamete that determines the sex of the offspring. The head region also contains the acrosome, which covers a large portion of the nucleus like a cap. The acrosome contains hydrolytic enzymes that, upon release (the acrosome reaction), function in the penetration of the cumulus and zona pellucida surrounding the egg and facilitate fertilization. The absence of the acrosome (a genetic defect) is termed “round-headed sperm” or globozoospermia (See Chapter 14 for details).

b) **Neck** – also called the connecting piece. At the base of the nucleus is the proximal centriole (*CEP135* is a gene encoding a key protein in this structure), followed by an atypical distal centriole and the axoneme, which are all located in the connecting piece.

c) **Midpiece** – contains the mitochondria (mitochondrial sheath), which is the main machinery for trapping, conserving, and supplying the energy needed for motility. Also, the beginning of the axoneme, which makes up the flagellum.

d) **Principal Piece and End Piece** – The flagellum of the tail of the spermatozoon. It is surrounded by a dense fibrous sheath.

heading

11) Sperm Motility Characteristics

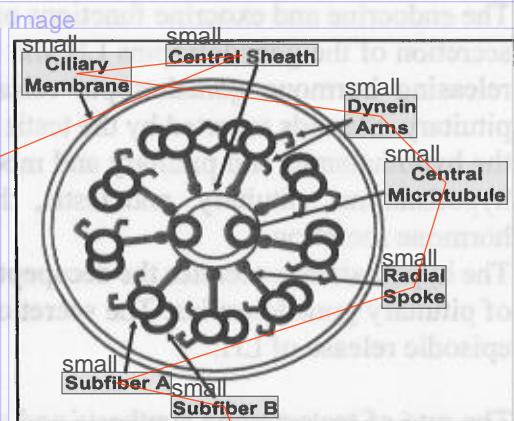
Content

a) The sperm tail beats approximately 10 times/sec. In seminal plasma, the sperm velocity ranges from 10-60 micrometers per second (top speed of 13,400 m.p.h!). The average motility for a normal male is approximately 50%-60% within 0.5-1 hour of ejaculation.

Tobacco, sexual lubricants, saliva, alcohol, and drugs may decrease sperm motility. Genetic defects can also impact sperm motility.

Content

b) **Axonemal Structure of Sperm Tails and the Sliding Microtubule Theory (Figure 9):** The microtubule structure of the human sperm tail is the same as that of most plants and animals. The axoneme, or central core of the sperm tail, originates within the mitochondrial sheath and extends the length of the sperm tail (Amelar et al., 1980). The axoneme consists of two central microtubules surrounded by nine microtubule doublets, which has been referred to as the “9+2 configuration” (Figure 17). Each axonemal doublet is composed of two subfibers, A and B. Subfiber A is a complete microtubule while subfiber B is a “C-shaped” microtubule which is



figure

Figure 17. Simplified illustration of the basic 9+2 axoneme of the sperm tail.
Keel 2006, after Amelar et al., 1980.

Content

attached to a subfiber A (Figures 16, 17). Radial spokes, or arms, composed of dynein extend from each subfiber A to the adjacent subfiber B.

When powered by ATP hydrolysis, the microtubule doublets “walk along” each other by means of their dynein arms. Given the shear resistance within the axoneme, as the microtubule doublets walk along each other bends form in the tail and propagate in such a way as to produce the characteristic movements of the sperm tail (Amelar et al., 1980). This propagation of movement due to the sliding of microtubules along each other is called the “Sliding Microtubule Theory” (Amelar et al., 1980).

The presence of the dynein arms is crucial for proper flagellar movement, as are the other structures shown in Figure 16 and 17 and described in more detail in Chapter 14. If these dynein arms are absent, sperm will display complete asthenozoospermia (no motility). For example, Kartagener syndrome (also called immotile sperm or immotile cilia syndrome) is a hereditary condition characterized by ciliary immotility due to the absence of dynein arms (Aitken, 1983). Men with this syndrome will suffer infertility due to immotile sperm. The condition is also associated with other abnormalities due to immotile cilia, such as bronchiectasis and chronic sinusitis. However, in this case, the sperm are not dead, just immotile. Eosin vital staining (a dye exclusion test) can differentiate between dead sperm (or necrozoospermia) and severe asthenozoospermia.

Content

12) **HORMONAL CONTROL OF SPERMATOGENESIS:** The proper hormonal environment is essential for spermatogenesis. The hormones testosterone, FSH, and possibly growth hormone are involved directly with the developing germ cells. In addition, FSH, LH, and prolactin may be involved indirectly.

Heading

a) The Hypothalamic-Pituitary-Testicular Axis:

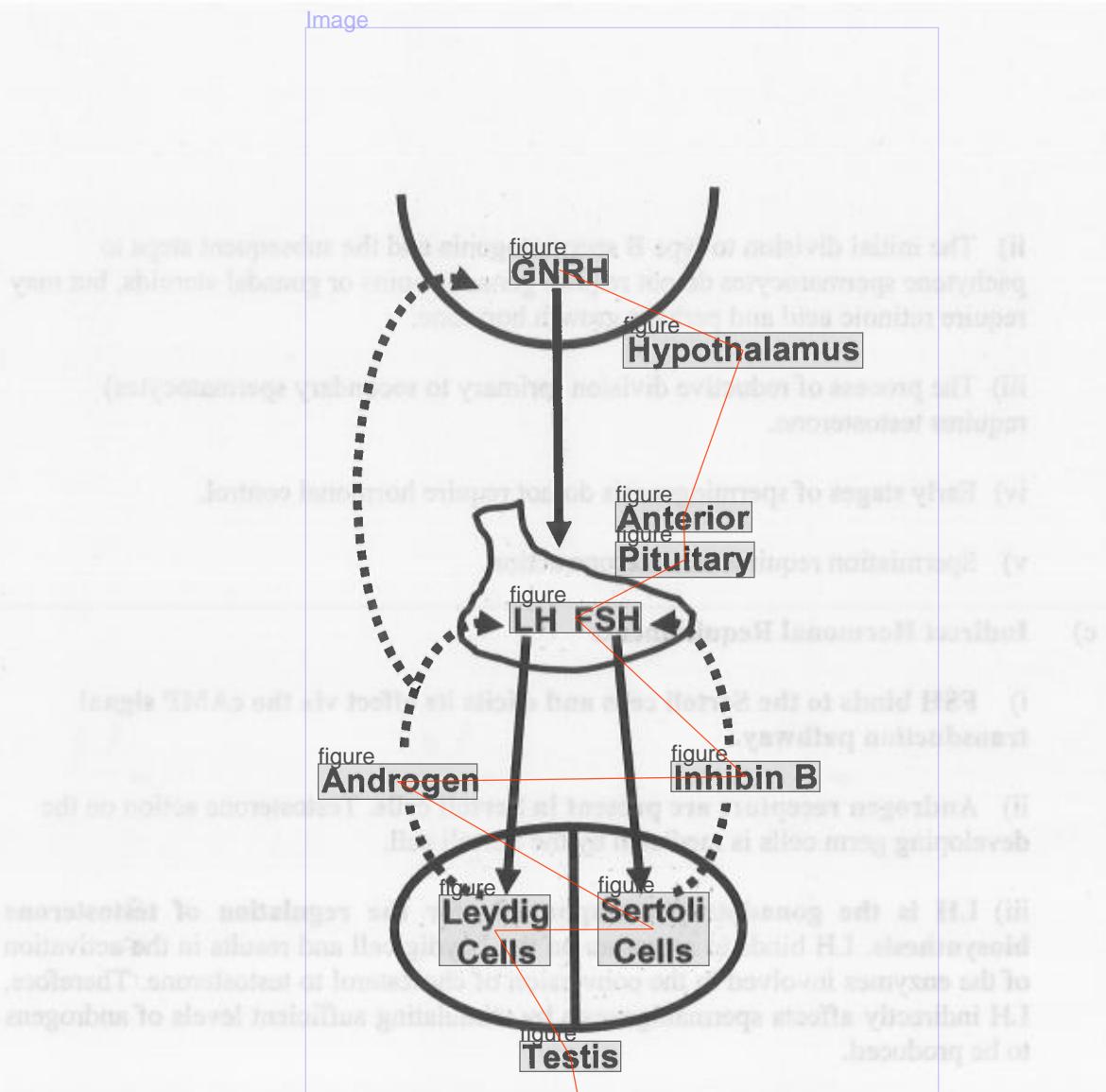
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As discussed earlier, the hypothalamic-pituitary-testicular axis is a closely integrated series of closed loop feedback systems involving the higher centers in the central nervous system, the hypothalamus, the pituitary, and the testicular endocrine and germinal compartments.

The endocrine and exocrine functions of the testis are under the control of the pituitary through its secretion of the gonadotropins LH and FSH (Figure 18). The hypothalamic secretion of the LH-releasing hormone gonadotropin releasing hormone (GnRH), in turn, regulates the anterior pituitary. Steroids secreted by the testis under the influence of the gonadotropins can feedback on the hypothalamus and pituitary and modulate their secretions. The interrelationships between the hypothalamus, pituitary, and testis, therefore, represent a fine-tuned control mechanism for hormone secretion.

The hypothalamus secretes the decapeptide GnRH, which is responsible for stimulating the release of pituitary gonadotropins. The secretion of GnRH is episodic rather than constant and results in episodic release of LH.

The rate of testosterone synthesis and secretion by the Leydig cells is primarily dependent upon the amount of LH secreted. The secretion of LH is reciprocally controlled by the action of testicular steroids on the hypothalamus and pituitary. When either androgen or estrogen concentrations



[imageDescription](#)

Figure 18. Illustration of the hypothalamic-pituitary-testicular axis and feedback control. Solid lines refer to positive feedback, and dotted lines refer to negative feedback (Keel 2006).

[Content](#)

increase in the blood circulation, LH levels decline (negative feedback). This action of testicular steroids can occur at the hypothalamic level, reducing the amount of GnRH secreted, or at the pituitary level, modulating the sensitivity of the pituitary to GnRH. When gonadal steroid levels decline, LH levels increase. These interactions result in a delicate balance between pituitary and testicular function.

Secretions from the Sertoli cells modulate the pituitary in much the same way that testicular steroids do. The Sertoli cell produces and secretes inhibin, which can selectively modulate the release of FSH from the pituitary.

There are two forms of inhibin: inhibin A and inhibin B, which are formed from three subunits. Inhibin A is made up of one α subunit and one βA subunit. Inhibin B is made up of one α subunit and one βB subunit. Human males only produce inhibin B.

[Heading](#)

b) Direct Hormonal Control

[Content](#)

- The transformation of the primordial germ cells to the primitive type A spermatogonia may require testosterone during the ontogeny of the fetal testis.

Content
Content

- ii) The initial division to type B spermatogonia and the subsequent steps to pachytene spermatocytes do not require gonadotropins or gonadal steroids, but may require retinoic acid and perhaps growth hormone.
- iii) The process of reductive division (primary to secondary spermatocytes) requires testosterone.
- iv) Early stages of spermiogenesis do not require hormonal control.
- v) Spermiation requires testosterone action.

heading

c) Indirect Hormonal Requirements

Content

- i) FSH binds to the Sertoli cells and elicits its effect via the cAMP signal transduction pathway.
- ii) Androgen receptors are present in Sertoli cells. Testosterone action on the developing germ cells is mediated by the Sertoli cell.
- iii) LH is the gonadotropin responsible for the regulation of testosterone biosynthesis. LH binds to receptors on the Leydig cell and results in the activation of the enzymes involved in the conversion of cholesterol to testosterone. Therefore, LH indirectly affects spermatogenesis by stimulating sufficient levels of androgens to be produced.
- iv) Prolactin synergizes with LH to stimulate testosterone production. Leydig cells have receptors for prolactin. Prolactin causes an increase in the numbers of LH receptors on Leydig cells and may function in this way to potentiate LH action.
- v) Retinoic acid acts directly on the germ cells to stimulate their entry into the meiotic pathway and also to affect Sertoli cell cyclicity
- vi) Thyroxine regulates Sertoli cell numbers during development

Headline

14) TEMPERATURE REGULATION OF THE TESTIS

Content

- a) The testes in humans are located outside the body and are contained in a sac-like structure called the scrotum. The scrotum is a highly specialized structure which is designed to keep the intratesticular temperature at a constant 34°C, which is several degrees cooler than normal body temperature. This cooler temperature is absolutely crucial for maintaining normal spermatogenesis.
- b) In order to ensure proper intra-testicular temperature, the cremasteric muscle in the scrotum raises the testes closer to the body when the ambient temperature is low and relaxes to lower the testes away from the body when the ambient temperature is hot. The

Content

scrotum also has sparse hair and is rugose (“wrinkled”), which serves to increase surface area allowing further cooling of the testes.

c) The pampiniform plexus (see **Figure 1**) is a network of interconnected veins, which drain the blood from the testes. The pampiniform plexus plays an important functional role in maintaining testicular temperature in the appropriate range for sperm production by cooling blood in the testicular artery before it enters the testes. Abnormalities of the pampiniform plexus, such as seen with a varicocele (varicose veins in the spermatic cord of the scrotum), can have adverse effects on spermatogenesis by interfering with the cooling mechanics of the plexus. It can also negatively affect spermatogenesis through a variety of other poorly understood factors.

heading

15)

MALE GENITAL TRACT

Content

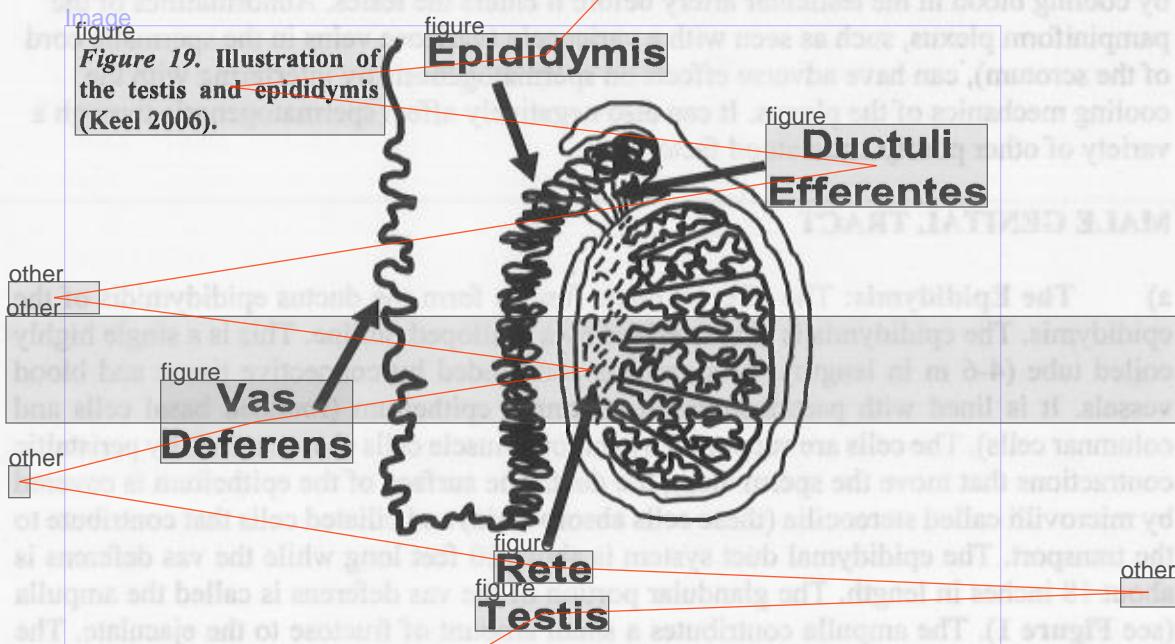
a) **The Epididymis:** The efferent ducts fuse to form the ductus epididymidis of the epididymis. The epididymis is characterized by a scalloped outline. This is a single highly coiled tube (4-6 m in length). This canal is surrounded by connective tissue and blood vessels. It is lined with pseudostratified columnar epithelium (rounded basal cells and columnar cells). The cells are supported by smooth muscle cells characterized by peristaltic contractions that move the sperm along the duct. The surface of the epithelium is covered by microvilli called stereocilia (these cells absorb fluid) and ciliated cells that contribute to the transport. The epididymal duct system is about 20 feet long while the vas deferens is about 18 inches in length. The glandular portion of the vas deferens is called the ampulla (see **Figure 1**). The ampulla contributes a small amount of fructose to the ejaculate. The secretions from these glands are the third in sequence to be expelled during ejaculation and contain the spermatozoa.

b) **Functions:** The epithelium uptakes and digests the residual bodies remaining after spermatogenesis. During transit through the epididymis, the sperm acquire the ability to be motile (progressive motility required for fertilizing capacity). There are three regions: the head or caput, the body or corpus, and the tail or cauda. The height of the epithelium varies in thickness depending upon which portion of the epididymis is examined (increasing thickness from head to tail). Sperm epididymal maturation requires approximately 10 days. Thus, the period of time from the initiation of spermatogenesis to the release of mature sperm into the lumen of the tubules (64 days) plus the time required for sperm to migrate to the head of the epididymis (10 days) is approximately 74 days.

The epididymis (**Figure 19**) is comprised of several ductuli efferentes that empty into a single, highly coiled ductus epididymidis, which ends as the straight ductus (vas) deferens. The epididymis is divided anatomically into the caput (head), the corpus (body), and the cauda (tail). Sperm transport through the epididymis takes approximately 16 days in humans. This amount of time added to the 74 days defined above suggests that a total of approximately 90 days is required from the time of initiation of spermatogenesis to the time when mature sperm are ready for ejaculation. Therefore, the adverse effects of any insult to the testis (fever, etc.) that results in damage to spermatogenesis may not be seen in the ejaculate for as long as 3 months.

Content

During the time of epididymal migration, spermatozoa undergo maturation, gain the capability of motility, and gain the capacity to fertilize. The sperm are then stored in the cauda epididymis and the vas deferens. Depending on the frequency of ejaculation, there is equilibrium between the breakdown of aged spermatozoa and the fullness of the epididymis.



heading

c) The epididymis serves several functions in the male:

i) **Maturational Changes of Spermatozoa:** As spermatozoa emerge from the testis and appear in the caput epididymis, they possess no progressive motility and have no in vivo fertilizing capacity. Sperm acquire these two properties gradually during transit through the epididymis. Maturation may involve deposition of specific glycoproteins on the sperm surface. Additional changes include a change in net sperm surface charge; alterations in sperm-lectin binding properties; changes in immunoreactivity and iodination characteristics; acquisition of an increased capacity for glycolysis; modification of adenylate cyclase activity; alterations in cellular phospholipid and phospholipid-like fatty acid content; formation of disulfide bonds within the nucleus and tail and oxidation of sperm membrane sulfhydryl groups; and an increased ability to adhere to the zona pellucida. Full fertilization capacity and motility of spermatozoa is probably not achieved until they reach the cauda epididymis. The motility and fertilization capacity of epididymal sperm is regulated by androgens.

d) **Release of Spermatozoa:** The release of spermatozoa during ejaculation is mediated by short, adrenergic contractions of the cauda epididymis and vas deferens. Spermatozoa are then mixed with the secretions of the accessory glands (see below).

e) **Elimination of Aged Spermatozoa:** Although the epididymal environment is favorable for survival of sperm, they are not preserved indefinitely and gradually age and lose their viability:

i) After prolonged sexual rest, the spermatozoa first lose their fertilizing ability, then motility, and finally disintegrate.

ii) Unejaculated spermatozoa may be eliminated by phagocytosis or spontaneous emissions or may be flushed from the urethra by urine.

iii) Unless older spermatozoa are eliminated at regular intervals, their incidence in the ejaculate increases with less frequent intercourse. After long periods of anejaculation, the first few ejaculates contain more aged spermatozoa, and fertility may be reduced.

heading

f) Summary of Epididymal Function

- i) Sperm maturation
- ii) Stabilization of condensed chromatin
- iii) Changes in surface charge of the plasma membrane
- iv) New sperm surface proteins
- v) Sperm storage
- vi) Sperm transport by peristalsis

16) **Vas Deferens:** is located within the spermatic cord. The vas deferens is severed at the time of vasectomy, a simple surgical sterilization procedure.

a) Lining epithelium: Pseudostratified columnar cells

b) Muscular wall: Inner and outer layers of longitudinally oriented muscle separated by a middle circular layer.

17) **Spermatic cord:** contains not only the vas deferens, but also the cremaster muscle, spermatic artery and veins of the pampiniform plexus.

18) **Ampulla:** the dilated portion of the ductus deferens leading to the ejaculatory duct, which passes through the prostate to empty into the prostatic urethra at the seminal colliculus.

19) **Prostate:** The largest accessory gland of the male urogenital tract consisting of 30-50 branched tubuloalveolar glands that empty into the prostatic urethra. Prostatic fluid contributes 15%-30% or about 0.5 mL to the volume of the semen. The clear, slightly acidic fluid is characterized by a high citric acid content, as well as acid phosphatase and zinc. Citric acid may be important in maintaining the osmotic equilibrium in semen. Prostatic fluid contains the enzymes required for liquefaction of the ejaculate coagulum.

heading

a) Regions of the Prostate:

- i) Periurethral mucosal glands
- ii) Periurethral submucosal glands
- iii) Peripheral compound glands (main glands)

Content

b) **Cell types:** The glands are lined by simple or pseudostratified columnar epithelium. The lumen contains prostatic concretions (corpora amylacea) rich in glycoproteins and sometimes calcium deposits.

c) **Prostate Functions:** Prostatic fluid contributes 15%-30% or about 0.5 mL to the volume of the semen. The clear, slightly acidic fluid is characterized by a high citric acid content, as well as acid phosphatase and zinc. Citric acid may be important in maintaining the osmotic equilibrium in semen. Prostatic fluid contains the enzymes required for liquefaction of the ejaculate coagulum. Secretions are acidic (pH 6.5). The prostate secretes prostate-specific acid phosphatase, prostate-specific antigen-amilase, and fibrinolysin

20) **Seminal Vesicles:** The epithelial cells have a large Golgi with secretory granules. The fluid from the seminal vesicles contributes 45%-80% (2.0-2.5 mL) of the ejaculate volume. The fluid is rich in fructose and prostaglandins. Fructose is the major source of glycolytic energy available to the spermatozoa. Fructose is often used as a marker for seminal vesicle presence function and ejaculatory duct obstruction in the azoospermic human. The seminal vesicles and the vas deferens are derived from the same embryonic origin. If the vas deferens is congenitally absent, the seminal vesicles will also be absent, and fructose will be absent in the ejaculate. Therefore, the absence of fructose in the ejaculate is indicative of congenital bilateral absence of the vas deferens and/or seminal vesicles. The absence of fructose may also be indicative of obstruction of the ejaculatory ducts. Seminal prostaglandins may play a role in the urethral muscle contractions that occur during ejaculation or may aid sperm transport in the female reproductive tract. Fluids from the seminal vesicles also contain the enzymes required for the formation of the ejaculate coagulum. The seminal vesicle is an androgen-dependent organ that is characterized by the presence of:

- i) Outer connective tissue layer
- ii) Middle circular and longitudinal smooth muscle layer
- iii) Inner folded mucosa: Lined by simple cuboidal-to-pseudostratified columnar epithelium

heading
b) **Function of the Seminal Vesicles:**

- i) Fructose
- ii) Fluid: Contributing about 50%-70% of the seminal fluid

heading
21) **Male Accessory Structures:**

a) The urethra in a human male is 20 cm long

- i) Prostatic urethra: Receives the ejaculatory duct and ducts of the prostate
- ii) Membranous urethra: The shortest segment
- iii) Penile urethra: Receives the ducts of the bulbourethral glands
- iv) Cell Types:

(1) **Transitional urothelium:** changes from a pseudostratified-to-stratified columnar epithelium in membranous and penile urethra.

(2) **Muscle layer:** in membranous urethra with smooth muscle sphincter (involuntary) and a striated muscle sphincter (voluntary) that controls the passage of urine or semen.

b) **Cowper and Littré Glands:** The Cowper (bulbourethral) glands and glands of Littré (urethral glands) secrete the fluid forming the first part of the ejaculate. The combined secretions of these glands, equal to approximately 0.1-0.2 mL (about 5% of the total ejaculate), is a clear fluid rich in mucoproteins, which are thought to lubricate the distal urethra.

i) **Bulbourethral glands:**

(1) **Histology:** Lined with mucus-secreting epithelium

(2) **Function:** Secretions including galactose and sialic acid have a lubrication function and precede emission of semen along the penile urethra.

heading

c) **Penis**

i) **Tissue Organization:**

(1) **Three cylindrical masses of erectile tissue**

(2) **Corpora cavernosa:** Irregular and communicating blood spaces or sinusoids supplied by an artery and drained by venous channels.

(3) **Ventral corpus spongiosum**

(4) **Penile urethra:** Transverses the penis

(5) **Glans penis:** The tip of the corpus spongiosum

ii) **Erection:** Arterial blood fills the sinusoids. They enlarge and compress the venous channels to engorge the penis. The process of erection is controlled by nitric oxide and the cGMP signaling pathway.

heading

SEMINAL PLASMA AND SEMEN

Heading

22) **Seminal Plasma**

Content

a) During ejaculation, the sperm become mixed with the combined secretions of the accessory sex glands. The mixture of these secretory fluids constitutes the **seminal plasma**, which serves as a vehicle for the ejaculated spermatozoa. The combination of seminal plasma and sperm is termed the **semen**. The chemistry and volume of the seminal plasma varies greatly among animal species. In the cat, the ejaculate can be less than 1.0 mL; in the boar, the volume reaches 500 mL; in the human, the ejaculate averages 3-4 mL.

b) All of the accessory sex glands (see Figure 1) do not secrete their constituents simultaneously. The glands of Cowper and Littré emit first, followed by the prostate, the ampulla, epididymis (containing the spermatozoa), and finally the seminal vesicles. It is important to note that the sperm are contained in the first portions of the ejaculate. Therefore, loss of this first portion during collection could result in artificially reduced sperm counts.

Table 3. Anatomic sources of ejaculated fluid

Source	Volume	Characteristics
Urethral and Bulbourethral glands	0.1-0.2cc	Viscous, clear
Testes, epididymis and vas deferens	0.1-0.2cc	Sperm present, carnitine
Prostate gland	0.5-1.0cc	Acidic, rich in citrate, watery
Seminal vesicles	1.0-3.0cc	Gelatinous appearance, fructose
Complete ejaculate	2.0-5.0cc	Liquefies in 20-25 minutes

Content

23) **Coagulation and Liquefaction of the Semen:** Human semen is ejaculated as a thick, viscous fluid that coagulates immediately after ejaculation. The coagulum usually liquefies, i.e., becomes very fluid-like and watery, within 5-20 minutes. The formation of the clot is catalyzed by the action of a clotting enzyme upon a coagulating substrate produced and secreted by the seminal vesicles. Lysis of the clot is caused by proteolytic enzymes secreted by the prostate. An ejaculate that fails to clot may be indicative of seminal vesicle malfunction (or absence of the vas deferens), while a coagulated ejaculate that does not completely liquefy may suggest prostatic dysfunction.

24) **Ejaculation:** Ejaculation is a complex 2-part spinal reflex that involves emission, the movement of semen into the urethra, and ejaculation proper, the propulsion of semen out of the urethra at the time of orgasm. Just prior to ejaculation, the testes are brought up close to the abdomen, and fluid is rapidly transported through the vas deferens toward the region of the ejaculatory ducts and subsequently into the prostatic urethra. After ejaculation, intravasal fluid is transported back toward the epididymis and occasionally into the seminal vesicles as well. The retrograde transport of sperm to the seminal vesicles has been documented by video radiography during ejaculation after vasography. The return of sperm to the seminal vesicles after ejaculation may help explain the prolonged presence of sperm in the ejaculate for some men after vasectomy.

a) **Emission:** Transport of semen to the bulbous urethra is termed emission. It is controlled primarily via the sympathetic nervous system acting through adrenergic receptors. Stimulation of the presacral nerves results in bladder neck closure and seminal emission. Failure of the bladder neck to close may result in retrograde ejaculation in which case the sperm are expelled into the bladder.

b) **Ejaculation:** Expulsion of semen from the urethral meatus is ejaculation. Propulsion and expulsion is caused by rhythmic contractions of the bulbocavernosus and ischiocavernosus muscles. The ejaculatory contractions involve the entire length of the penile urethra. Ejaculation proper is a parasympathetic response.

25) MALE INFERTILITY

Content

a) **Varicocele** (Strauss & Barbieri, 2004): Varicocele is a condition resulting from a varicosity of the pampiniform plexus, possibly interfering with the temperature regulation of the testis. Varicocele is usually, but not always, found on the left side. Varicocele can be palpated in about 40% of men with oligozoospermia. However, varicocele can also be detected in about 20%-25% of normal men, thus raising questions regarding the true association of varicocele with infertility. Varicoceles can be surgically treated, and this will be beneficial for a subset of infertile couples resulting in a 30%-35% pregnancy rate. Varicoceles can be present in children and, in the setting of associated testicular atrophy, will be surgically repaired.

b) **Kartagener Syndrome** (Aitken et al., 1983; Strauss & Barbieri, 2004) Patients presenting with Kartagener syndrome will have severe asthenozoospermia. These patients are characterized by an absence of dynein arms of the axoneme, thus rendering the sperm incapable of movement. Kartagener syndrome patients will also have a history of other cilia abnormalities (due to absence of dynein arms) including multiple sinus and pulmonary infections, history of chronic sinusitis and bronchiectasis, etc. These patients should have an eosin vital stain performed during the semen analysis to confirm asthenozoospermia and not necrozoospermia.

c) **Cryptorchidism** (Abney & Keel, 1989) Cryptorchidism is a condition characterized by failure of the testes to descend properly into the scrotum during fetal development. This condition may be unilateral or bilateral (i.e., one or both testes). Cryptorchidism occurs in as many as 6% of full-term births. If the testes have not descended by 6 months of age, medical intervention is required, either surgically or hormonally, to induce descent. Cryptorchidism will result in abnormal elevation of testicular temperature that can have profound effects on spermatogenesis. Furthermore, prolonged increased testicular temperature may lead to tumorigenesis, which further necessitates medical treatment.

d) **Retrograde Ejaculation** (Strauss & Barbieri, 2004) Retrograde ejaculation results from incomplete bladder neck closure (often from a dysfunctional internal sphincter) during ejaculation. This often causes the semen to be ejaculated into the bladder instead of out of the penis. Patients who have a history of retroperitoneal lymph node dissection will often have retrograde ejaculation. This condition is asymptomatic, although patients may complain of a “dry ejaculation” due to severe hypospermia. Semen analysis in these patients will often display severe hypospermia. A postejaculation urine analysis will show marked increase in the presence of sperm. These patients can be treated by collecting a postejaculation urine sample into buffer, isolating, and washing the sperm by centrifugation, with subsequent artificial insemination of the prepared sperm.

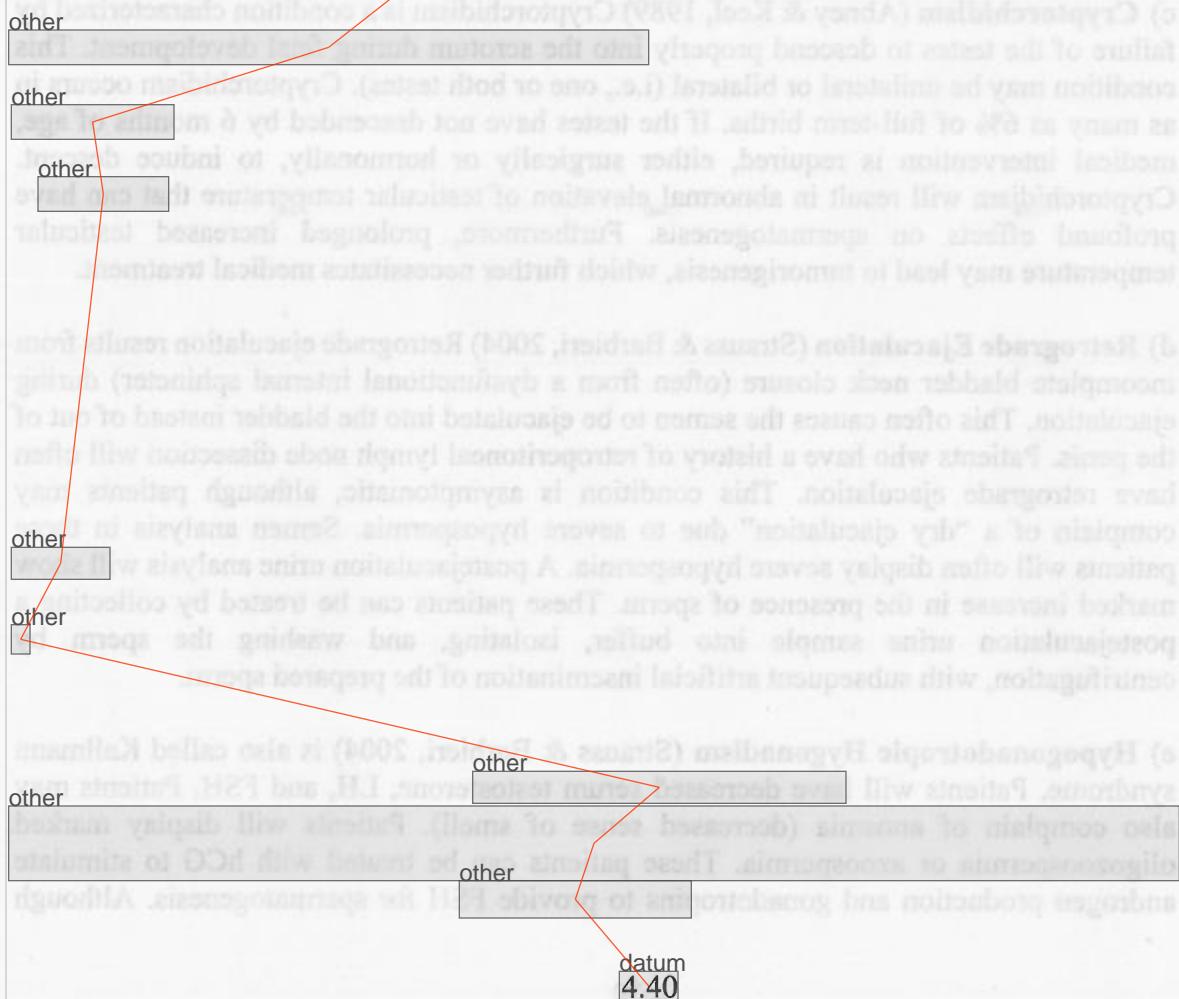
e) **Hypogonadotropic Hyponadism** (Strauss & Barbieri, 2004) is also called Kallmann syndrome. Patients will have decreased serum testosterone, LH, and FSH. Patients may also complain of anosmia (decreased sense of smell). Patients will display marked oligozoospermia or azoospermia. These patients can be treated with hCG to stimulate androgen production and gonadotropins to provide FSH for spermatogenesis. Although

Content

low sperm counts result from treatment, these patients often are capable of causing a pregnancy without the need for an assisted reproductive technology.

f) Spermatogenic Failure (Cryptozoospermia, Hypospermatogenesis, Early or Late Maturation or Meiotic Arrest), Sertoli Cell-Only Syndrome: In this condition, Sertoli cells are present, but the germinal epithelium is absent, and sperm are rarely present. Microdissection testicular sperm extraction, where the urologist dissects open the entire testis and searches tubule by tubule for rare foci of spermatogenesis results in improved sperm retrieval for ICSI-IVF. Damage to the seminiferous epithelium in this condition will result in a loss of inhibin, which results in a removal of the negative feedback on FSH, causing elevated serum FSH. However, since the Leydig cells are unaffected, serum LH will be normal.

g) Congenital Bilateral Absence of the Vas Deferens (CBAVD) results in obstructive azoospermia. This is associated with a congenital absence of the seminal vesicles as well. Therefore, fructose will be absent in the semen of these men. CBAVD is observed in men with cystic fibrosis.



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