Ministry of health Republic of Belarus
Establishment of education "Gomel state medical university"

Department of histology, cytology and embryology

MANUAL
for 1-st year students of faculty of foreign students on gynecology

Topic: 12:
HISTOPHYSIOLOGY OF THE MALE REPRODUCTIVE SYSTEM

Duration 4 hours

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THE MOTIVATIONAL CHARACTERISTIC OF THE THEME

Organs of sexual system take part in maintenance and safety of a biological kind owing to inherent in them reproductive functions. Function of sexual glands is important also endocrine.

THE PURPOSE

Studying of a microscopic and ultramicroscopic structure and histophysiologies of man's sexual system.

PROBLEMS

The student should know:

1. Development, structure and histophysiologies of testis.
2. Features of a microscopic structure of different parts of testis.
3. The Microscopic structure prostate.

The student should able:

1. To define organs of male sexual system and their tissues at a microscopic level.
2. To explain the maintenance and essence of phases spermatogenesis.
3. To explain mechanisms of regulation of endocrine function.
4. To explain features embryonic developments of organs of male Sexual system.

REQUIREMENTS TO THE INITIAL LEVEL OF KNOWLEDGE

For full mastering a theme it is necessary for student to repeat from a rate of medical biology a structure and phases of spermatogenesis

CONTROL QUESTIONS FROM RELATED SUBJECTS

1. The Structure spermatozoid
2. Phases of spermatogenesis
3. The structure of man's genitals

CONTROL QUESTIONS ON THE THEME

1. Developments of sexual cells and organs
2. A structure, functions and fabric structure of organs of male sexual Systems.

THE PRACTICAL PART

1. The Scheme embryogenesis of male's sexual system – to bring designations (Exercise №1 in album)
2. Development sources of urinogenital system – to fill the table (Exercise №2 in album)
3. The Scheme of spermatogenesis -enter designations (Exercise № 3 in album)
4. Microscopy histological preparations and their sketch in an album (Exercise № 5, 8 and 9 in album)
5. The Scheme of structure of blood testicular a barrier, to enter designations (Exercise № 6 in album)

6. Hormonal regulation and functions of cells of sertoli – to study (Exercise № 7 in album)

7. To study diagrams

SLIDES

1. Testis
2. Spermatozoid.
3. Prostate

QUESTIONS FOR SELF-CHECKING KNOWLEDGE.

1. Sources of embryonic development of germ cells and organs of the male reproductive system.
2. Structure, functions and tissues of organs of the male reproductive system.
3. Somniferous tubule.
4. Reproductive function of the testes. Spermatogenesis.
5. Endocrinal function of testes.
6. Epididymis: development, structure, functions.
7. Ducts deferens: development, structure, functions.

HISTOPHYSIOLOGY OF THE MALE REPRODUCTIVE SYSTEM

The testes develop retro peritone all in the dorsal wall of the abdominal cavity and later are suspended within the scrotum at the ends of the spermatic cords, each carrying with it a serous sac derived from the peritoneum called the tunica vaginalis. This tunic consists of an outer parietal and an inner visceral layer, covering the tunica albuginea on the anterior and lateral sides of the testis. The scrotum has an important role in maintaining the testes at a temperature below intra-abdominal temperature.

The male reproductive system is composed of the testes, genital ducts, accessory glands, and penis [1 – 3].

TESTIS

The testis has 2 functions – reproductive and hormonal.

It is surrounded by a thick capsule of collagenous connective tissue, the tunica albuginea. On the posterior surface of the testis the tunica albuginea to form the mediastinum testis, from which fibrous septa penetrate the gland, dividing it into about 250 testicular lobules. Each lobule contains one to four highly convoluted seminiferous tubules, which produce the spermatozoa. Small blood vessels and lymphatic channels, as well as the *interstitial* or *Leydig cells* lie between the tubules. These are endocrine cells that produce steroid hormones, including testosterone.

The seminiferous tubules open into the *tubuli recti,* which form the first segment of the genital duct system. These ducts are continuous with the *rete testis,* a system of epithelial-lined spaces in the mediastinum.

The genital duct system includes the tubuli recti and rete testis, which lie within the testis; and the ductuli efferentes, ductus epididyrnidis, and ductus deferens, which constitute the ducts lying outside of the testis.

The accessory glands include the seminal vesicles, prostate, and bulbourethral glands.

The genital ducts and accessory glands produce secretions which provide a medium

essential for the transport, maintenance, and further maturation of the sperm. Spermatozoa plus these secretions comprise the semen [1 – 4].

Hormones, primarily testosterone, function in the regulation of the development of the spermatozoa. These hormones also influence the development of secondary sex characteristics and, to some extent, sexual behavior.

Seminiferous Tubules

The seminiferous tubules consist of the following components:

a) a tunica of fibrous connective tissue; *This outer layer* of fibrous tissue which also contains muscle-like (myoid) cells. Contractions of these cells probably help to move spermatozoa along the tubule;

b) a well-defined basal lamina;

c) a complex seminiferous epithelium.

It consists of two general types of cells: spermatogenic cells and Sertoli cells. Sertoli *cells* also called supporting or sustentacular cells [4].

The spermatogenic cells are stacked in 4-8 layers that occupy the space between the basal lamina and the lumen of the tubule. They represent various stages in the continuous process of differentiation of the male germ cells.

The Sertoli cells are less numerous and nonproliferating population. The Sertoli cells are columnar cells with complex apical and lateral processes that surround the adjacent spermatogenic cells and fill the spaces between them. The Sertoli cells extend through the full thickness of the seminiferous epithelium *from the basement membrane to the lumen.* **The nucleus of Sertoli cells is ovoid or angular, large and lightly stained and often contains a large nucleolus.** They have one or more deep infoldings and lye in the basal portion of the cell near and parallel to the basement membrane.

The cytoplasm contains abundant smooth and some granular endoplasmic reticulum, numerous mitochondria, a well-developed Golgi complex, and varying numbers of microtubules, lysosomes, lipid droplets and glycogen granules. In humans, the basal cytoplasm also contains *inclusion bodies of Charcot-Bottcher* – slender, crystalloid inclusions. They consist of the dense filaments. The chemical nature and function of these inclusions are unknown [4 – 6].

Adjacent Sertoli cells are bound together at the level of the spermatogonia **by** unique junctional complex including **tight junctions.**

Junctional complexes between the Sertoli cells divide the seminiferous epithelium into two compartments: a basal and an adluminai compartment. . Tight junctions may temporarily open to permit the passage of spermatogenic cells from the basal into the adluminal compartment.

The compartmentalization enables the Sertoli cells to establish microenvironments that allow the spermatogenesis and serve as the **blood-testis barrier** [3]**.**

Large molecules (plasma proteins and circulating antibodies) cannot pass from the blood into the lumen. The spermatogonia are in the basal compartment (deep to the level of the tight junctions) and the more mature forms such as primary and secondary spermatocytes and spermatids are in the adluminal compartment. The function of the blood-testis barrier may be to prevent an auto-immune reaction. Spermatozoa and spermatocytes are recognized as "foreign" (not self) by the immune system because they are first produced at puberty long after the individual has become immunocompetent**.** Mature sperm (and their antigens) arise long after immune tolerance is established; therefore, a male animal is capable of making antibodies against his own sperm. Therefore, the blood-testis barrier

serves an essential role in isolating the spermatogenic cells from the immune system. Injection of sperm antigens causes inflammation of the testis (autoimmune orchitis) and reduced fertility [2].

Functions of the Sertoli cells include:

1. Providing mechanical support for the spermatogenic cells.
2. Mediating the movements across the seminiferous epithelium of steroids, metabolites, and nutrients for the spermatogenic cells.
3. They secret fluid that facilitates passage of the maturing sperm into the intratesticular ducts.
4. Participation in the formation of the blood-testis barrier. Protection from waste substances and immune attack.
5. Phagocytosing degenerating spermatogenic cells and the excess cytoplasm shed from the differentiating spermatids as the residual bodies
6. Secreting androgen-binding protein, which is necessary to concentrate testosterone in the lumen. The Sertoli cells are the primary target for FSH and testosterons. Therefore, the Sertoli cells are the primary regulators of spermatogenesis.
7. Secreting of the polypeptide hormone inhibin. Inhibin acts at the level of the pituitary to reduce the secretion of follicle stimulating hormone [1].

Sertoli cells in humans and other animals do not divide during the reproductive period. They are extremely resistant to adverse conditions such as infection, malnutrition, or x-ray irradiation and survive these insults much better than the spermatogenic cells.

Spermatogenic cells are spermatogonia, primary and secondary spermatocytes, spermatids and spermatozoa (sperm). The spermatogenic cells represent sequence stages in the formation of spermatozoa. They are organized in 4-5 layers of progressive development between adjacent Sertoli cells. Spermatogonia and primary spermatocytes are located in the basal compartment, other cellular stages of spermatogenesis are located in the adluminal compartment. The *spermatogonia* rest on the basal lamina. The *spermatocytes* lie above the spermatogonia. The *spermatids* and *spermatozoa* occupy the site closest to the lumen.

Spermatogenesis is the process by which stem cells develop into mature spermatozoa.

There are three phases of spermatogenesis: *Spermatocytogenesis (Mitosis), Meiosis, and Spermiogenesis* [3].

Spermatogonia (singular = spermatogonium) are the first cells of spermatogenesis. They arise from primary germ cells. The primary germ cells originate in the 4^{th} week of fetal development in the endodermal walls of the yolk sac and migrate to the primordium of the testis, where they differentiate into spermatogonia. Spermatogonia remain dormant until puberty. They are always in contact with the basal lamina of the tubule.

There are two types of spermatogonia in the human seminiferous epithelium. *Type A* spermatogonia have a rounded nucleus with very fine chromatin granules and one or two nucleoli. They are stem cells which divide to form new generations of both type A and type B spermatogonia.

Type B spermatogonia have rounded nuclei with chromatin granules of variable size, which often attach to the nuclear membrane, and one nucleolus. Although type B spermatogonia may divide repeatedly, they do not function as stem cells and their final mitosis always results in the formation of primary spermatocytes [2, 3].

Spermatocytogenesis (also called *Mitosis).* Stem cells (Type A spermatogonia) divide mitotically to replace themselves and to produce cells that begin differentiation (Type B spermatogonia).

Meiosis is the process by which the diploid number of chromosomes present in spermatogonia is reduced to the haploid number present in mature spermatozoa.

Primary spermatocytes are cells in prophase of the first meiotic division. Primary spermatocytes lie in the cell layer luminal to the spermatogonia. They appear larger than spermatogonia. They immediately enter the prophase of the first meiotic division, which is extremely prolonged (about 22 days). A large number of primary spermatocytes is always visible in cross-sections through seminiferous tubules.

Cell divisions, from the formation of primary spermatocytes and onwards, to the production of the spermatocytes, are incomplete. The cells remain connected by bridges of cytoplasm. The bridges remain until sperm are fully differentiated.

The primary spermatocytes increase in size and demonstrate distinctive nuclear morphology as they pass through the leptotene, zygotene, pachytene, and diplotene stages of the meiotic prophase [1 – 3].

The *first meiotic division* results in the formation of *secondary spermatocytes*, which are smaller than primary spermatocytes. They rapidly enter and complete *the second meiotic division* and are therefore seldom seen in histological preparations. Their division results in the formation *of spermatids.*

Spermatids are spherical cells with interphase nuclei, positioned high in the epithelium. Since spermatids go through a metamorphosis into spermatozoa, they occur in early through late stages.

They are small (about 10 fxm in diameter) with an initially very light (often eccentric) nucleus. The chromatin condenses during the maturation of the spermatids into spermatozoa, and the nucleus becomes smaller and stains darker.

The process by which a spermatid becomes a spermatozoon is called spermatogenesis. The nucleus undergoes condensation and changes shape to form the head. The Golgl complex is transformed into the acrosomic cap which comes to lie over one side of the nucleus. The acrosome marks the future anterior pole of the spermatozoon. It contains hydrolytic enzymes, enable the mature spermatozoa to pass between the cells and penetrate the membranes that invest the egg [3].

The centriole divides into two parts which are at first close together. They migrate to the pole of the cell that is away from the acrosome. The axial filament grows out of the distal centriole. The region occupied by the two centrioles later becomes the neck of the spermatozoon. The proximal centriole probably forms the basal body. The part of the axial filament between the head and the annulus becomes surrounded by mitochondria, and together with them forms the middle piece. Most of the cytoplasm of the spermatld is shed, and is phagocytosed by Sertoli cells. The cell membrane persists as a covering for the spermatozoon.

Complete spermatogenesis takes about 64 – 74 days. The lower temperature is essential for sperm production. Within the scrotum the temperature of the testes is 2-3 °C degrees below body temperature.

The space between the seminiferous tubule is filled with *interstitial tissue. It contains* blood vessels and *interstitial* or *Leydig cells. Leydig cells* constitute the endocrine component of the testis [2].

Leydig cells occupies about 12 percent of the total testicular volume, the number of

Leydig cells is constant and does not decline in the elderly.

They are large – about 15-20 um, polygonal cells. The nucleus is large, round and often located eccentric in the cell.

The cytoplasm is strongly acidophilic, and contain smooth endo-plasmic reticulum, mitochondria with tubular cristae and lipid droplets.. These ultrastructural features are seen in steroid-secreting cells [4 – 6].

Rod shaped crystalloids (Retnke's crystalloids) are also present Contains yellow granules which are seen by EM to be vacuoles containing various enzyme.

Leydig cells occur in clusters, which are variable in size and richly supplied by capillaries. They synthesize and secrete the principal circulating androgen, *testosterone.*

High local levels of testosterone within the testis are necessary for normal maturation of the sperm. The lower peripheral level of testosterone is necessary for the normal differentiation of the central nervous system and the reproductive system; development and maintenance of secondary sexual characteristics; anabolic and general metabolic processes, including skeletal growth skeletal muscle growth; distribution of subcutaneous fat, and kidney function; behaviour, including libido.

Spermatogenesis depends on the follicle stimulating (FSH) and luteinizing (LH) hormones of the pituitary gland. LH acts on the interstitial cells, stimulating the production of testosterone. FSH to act on the Sertoli cells, stimulating the synthesis of androgen-binding protein (ABP). This protein combines with testosterone and is secreted into the lumen of the seminiferous tubules. Spermatogcnesis is inhibited by estrogens and progestogens [3].

INTRATESTICULAR GENITAL DUCTS

The intratesticular genital ducts are the tubuli recti (straight tubules), the rete testis, and the ductuli efferentes.

The main segment of the straight tubules consisting of cuboidal epithelium supported by a dense connective tissue sheath.

The straight tubules continue into the rete testis, a labyrinthine system of cavities in the mediastinum. A simple cuboidal epithelium lines the channels of the rete testis. These cells have a single apical cilium and few microvilli.

Approximately 20 efferent ductules arise from the rete testis. Efferent ductules are lined by ciliated columnar epithelium, which consists of both absorptive (cells reabsorb much of the fluid secreted by the seminiferous tubules) and ciliated cells, and have a thin layer of circular smooth muscle. Movement of spermatozoa is facilitated by ciliary action, and by peristaltic contraction of smooth muscle. The height of the two cells types, which form the epithelium of the ductuli efferentes, is variable which gives the lumen a characteristic wavy outline.

The ductuli efferentes leave the testis and open into a common highly coiled duct, *the ductus epididymidis* (about 6 m long) [1, 2].

The epididymis plays an essential role in the development of the functional spermatozoa, providing both the essential environment and some of the molecular products required for their maturation. As the spermatozoa are released from the testis, they demonstrate limited motility (no directed movement) and are incapable of fertilizing ova. As they pass through the epididymis, they develop the capacity for forward motility and the ability to fertilize ova. These changes are accompanied by changes in the plasma membrane structure including the binding of surface glyco-proteiris of epididymal origin to the sper-

matozoa. These maturational events are androgen-dependent and require protein synthesis by the epididymis [1 – 3].

It is lined by a very tall pseudostratified columnar epithelium. Most cells of the epithelium, also called principal cells, have long stereocilia. Stereocilia are non-motile structures, which resemble large microvilli. The principal cells demonstrate features typical of both secretory and absorptive cells.

The epithelium is surrounded by a thin lamina propria and an outer investment of smooth muscle. Through the head and body regions the muscle layer consists of smooth muscle cells oriented circumferentially around the duct. In the body region, a few bundles of longitudinally or obliquely oriented fibers form an incomplete outer layer. In the tail region, typical large smooth muscle cells increase in number distally along the duct. In the distal portion of the tail region, the muscle bundles are organized into three layers (inner longitudinal, middle circular, and outer longitudinal). Differences in the morphological organization of the muscle layers are correlated with differences in the muscular activity of the different regions.

Peristaltic contractions of smooth muscle cells surrounding the ductus epididymidis move the spermatozoa towards the middle segment of the duct, which is the site of final functional maturation of the spermatozoa – now they are motile. The terminal segment of the ductus epididymidis is the site of storage of the mature spermatozoa. Smooth muscle fibres of the terminal part of the ductus epididymidis do not contract spontaneously. They contract during sexual stimulation concurrently with the contraction of the musculature of the duct into which it opens, the vas (ductus) deferens [5].

Functions of the epididymis: phagocytosis of defective spermatozoa; absorption of excess fluid; secretion of substances (sialic acid, glycerylphosphoryl-choline) that play a role in maturation of spermatozoa.

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Ductus deferens (vas deferens)

The wall of the *ductus deferens* consists of thin *mucosa,* thick *muscularis* surrounded by *adventitia.* The mucous membrane shows a number of longitudinal folds so that the lumen appears to be stellate In section. The lining epithelium is simple columnar, but becomes pseudostrati-fled columnar in the distal part of the duct. Similar to the epididymis, cells have long stereocilia

The muscularis is well developed and consists of a thick circular layer of smooth muscle between thinner inner and outer longitudinal layers.

The terminal dilated part of the ductus deferens Is called the ampulla. It has the same structure as that of the seminal vesicle.

Ductus deferens enters the abdomen as a component of the spermatic cord (the spermatic cord includes the testicular artery, the pampiniform (venous) plexus, and nerves) and behind the urinary bladder joins with the seminal vesicles to form the *ejaculatory duct.* The muscular layer is absent in the wall of the ejaculatory duct. The ejaculatory duct then pierces the prostate gland and opens into the urethra [3 – 6].

The wail of each seminiferous tubules is made up of an outer layer of connective tissue and inner layer of the epithelium.

ACCESSORY GENITAL GLANDS

The accessory genital glands are the seminal vesicles, the prostate gland, and the

bulbourethral glands.

The seminal vesicles consist of 2 highly tortuous tubes 15 cm in length. They arc not reservoirs for spermatozoa. When the organ is sectioned, the same tube is observed sectioned in different orientations. It has a folded mucosa lined with pseudostratified columnar epithelium that exhibits great individual variations' depending on age and other conditions. The epithelium consists of a discontinuous layer of rounded basal cells and a layer of taller superficial cuboidal or low columnar cells, rich in secretory granules. They have ultrastructural characteristics of protein-synthesizing cells. The lamina propria of the seminal vesicles is rich in elastic fibers and surrounded by a thin layer of smooth muscle. The viscid, yellowish secretion of the seminal vesicles contains unusually high concentrations of fructose, as well as citrate, inositol, prostaglandins, and several proteins. Seventy percent of human ejaculate originates from the seminal vesicles. The height of the epithelial cells of the seminal vesicles and the degree of activity of the secretory processes are testosterone-dependent. In the absence of testosterone, the epithelium of the seminal vesicles atrophies. This atrophy can be reversed by the administration of testosterone [1].

THE PROSTATE is a collection of 30- 50 branched tubulo-alveolar glands whose ducts empty into the prostatic urethra. The prostate produces prostatic fluid and stores it in its interior for expulsion during ejacsmooth muscle cells, which probably help to move the sperm along the duct, and by loose connective tissue rich in blood capillaries.

The surface of the columnar cells is covered with long and irregular microvilli, called stereocilia. Ste-reoeilia have neither basal bodies nor internal micro-tubules, whereas true cilia have both. When observed with the electron microscope, the principal cells are seen to contain numerous cisternae of rough endo-plasmic rcticulum in their basal cytoplasm and a large Golgi complex that encircles the nucleus. No secretory granules are present, but there is evidence of endocytosis utilizing coated vesicles. The prostate is surrounded by a fibroelastic capsule rich in smooth muscle. This capsule emits septa that penetrate the gland and divide it into lobes that are indistinct in the adult male. An exceptionally rich fibromuscular stroma surrounds the glands

The glands of the prostate- – mucosal, submu-cosal, and main glands – are arranged in ***3*** **concentric areas** around the urethra. The epithelium is usually simple columnar or pseudostratified, the former being found in the main glands while the latter is characteristic of mucosal and submucosal glands. These cells contain an abundance of rough endoplasmic reticulum, a large Golgi complex, large numbers of secretory granules, and numerous lysosomes [1].

Secretory products of the prostate include amylase; proteolytic enzymes, including fibrmolysin; citric acid; acid phosphatase; and lipids. Acid phosphatase activity is elevated in the blood of patients with carcinoma of the prostate. Measuring this enzyme activity is important in the diagnosis of this tumor as well as in following the results of therapy.

The main glands contribute most to the volume of the prostatic secretion. For unknown reasons – often after age 40 – the mucosal and submucosal glands begin to hypertrophy. This can lead to partial or total obstruction of the urethra. Carcinoma of the prostate, a frequent tumor in older men, usually starts in the main glands. The secretory process of the prostate depends upon dihydrotestosterone [1, 2].

Small spherical bodies of glycoprotein composition, 0.2-2 mrn in diameter, are frequently observed in the lumen of prostatic glands. They are called prostatic concretions, or corpora amylacea. These bodies are often calcified. Their significance is not understood, but their number increases with age.

The bulbourethral glands (Cowper's glands), 3-5 mm in diameter, are located proximal to the membranous portion of the urethra and empty into it. They are tubulo-alveolar glands lined with mucus-secreting simple cuboidal epithelium. Skeletal and smooth muscle cells arc present in the septa that divide each gland into lobes. The secretion is a clear mucus that acts as a lubricant [1].

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