Faculty of Medicine
Department of Medicine
First year of medical school
2024-2025

Human Embryology Course
Head of Teaching
Prof. N. BOURENANE

GAMETOGENESIS

Introduction

The life of an organism is cyclical, alternating between a haploid phase and a diploid phase, the duration of which varies depending on the species. The life cycle of a given species is the set of processes that ensure the perpetuation of that species from generation to generation. In an adult individual, there are two categories of cells: one group consists of **diploid** cells that do not undergo meiosis and make up all somatic cells, and the other group forms the germ line, which undergoes chromosomal reduction during maturation. The **haploid** cells thus formed constitute the functional cells (**gametes)**, and the process leading to their formation is called **gametogenesis.**
We refer to male gametes (**sperm**) or female gametes (**eggs)** depending on the sex chromosome complement.

Gonocytes appear during the first weeks of embryonic development.

Oogenesis and **spermatogenesis** differ greatly in their timing and physiology. However, one fundamental commonality is **meiosis**, which allows for chromosomal maturation, gene recombination, and the production of a reproductive cell whose genetic material has been reduced by half compared to the mother cell.

1- **Spermatogenesis**

As its name suggests, spermatogenesis is a biological process whose purpose is to produce male gametes, or spermatozoa. Spermatozoa contain only **23** chromosomes because they are the product of a sexual stem cell (spermatogonium) that has undergone **meiosis.**

It begins at puberty and continues **uninterrupted (continuously)** until old age. It takes place in the **seminiferous tubules** in the testicles, and the spermatozoa formed are then transported to the outside via a system of ducts.

The testes, male sex glands, are the site of spermatogenesis as well as the synthesis of the male hormone, **testosterone.**

1-1 Review of the male reproductive system

The male reproductive system consists of the following on each side:

– a testicle, topped by the epididymis and housed in the scrotum.

– a vas deferens, which extends from the epididymis,

– an ejaculatory duct, which follows the vas deferens.

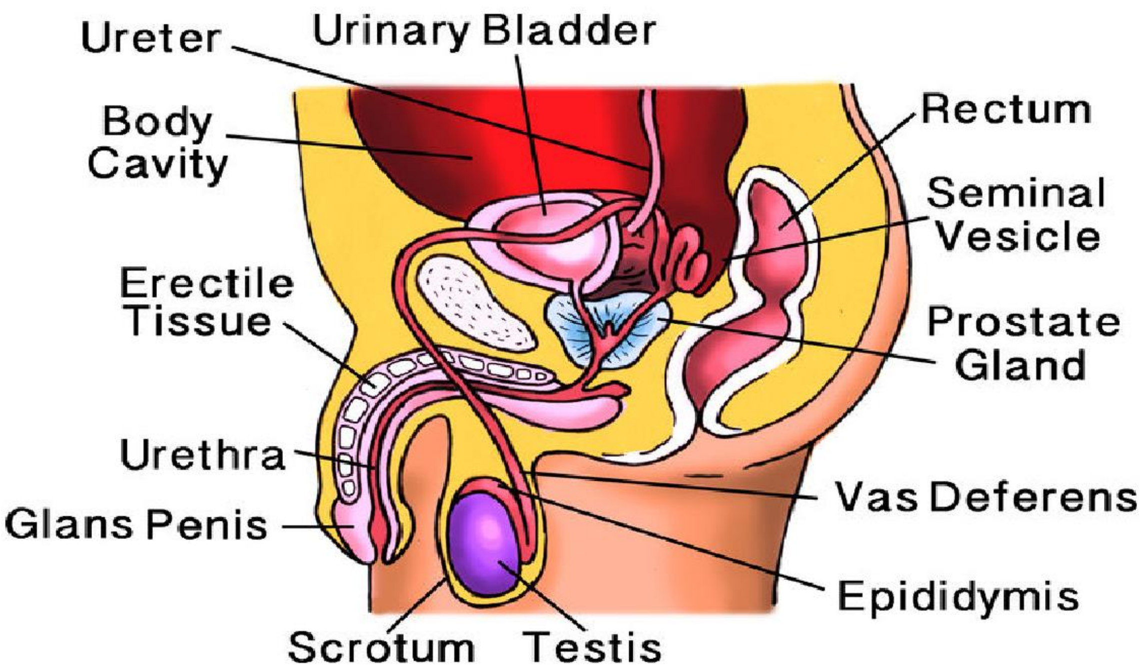


Figure 1: Male reproductive system

- The testicle is an ovoid organ surrounded by the tunica albuginea, a fibrous connective capsule with little elasticity, whose thickening at the upper pole forms Highmore's body (containing the **rete testis**). Starting from Highmore's body, thin connective partitions delimit the testicular lobules, of which there are 200 to 300 per testicle. Each lobule contains a cluster of seminiferous tubules (1 to 4 per lobule). The seminiferous tubules of each lobule converge into a **straight tube** 1 mm in length. The straight tubes communicate with a network of channels, the rete testis.

-The epididymis covers the testicle and has three parts of decreasing thickness from the upper pole: the head, the body, and the tail. It contains two types of ducts: the

efferent cones, located in the head of the epididymis, and the epididymal duct.

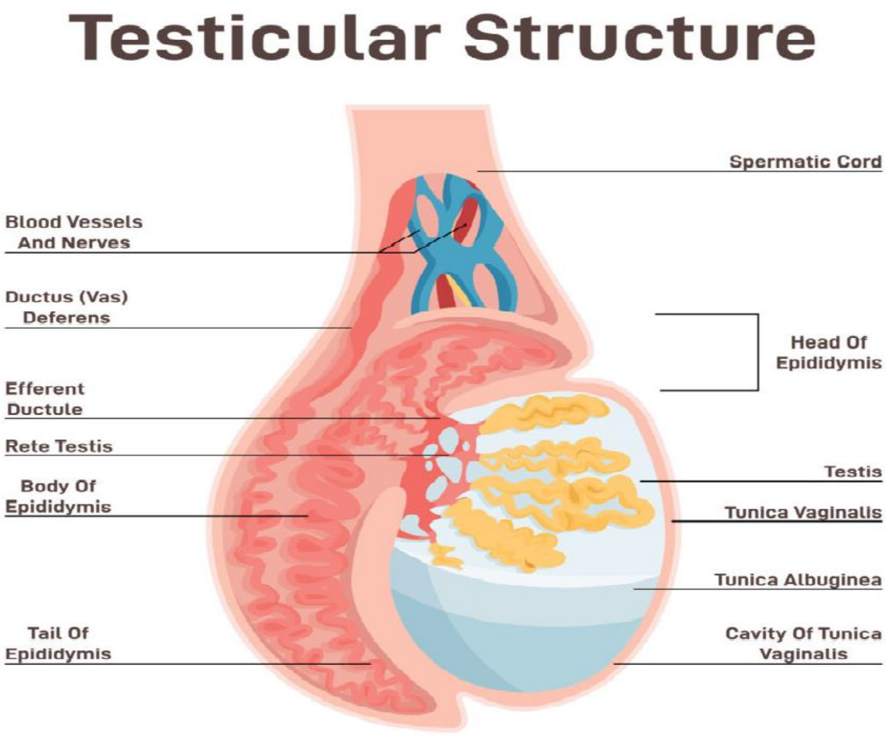


Figure 2: Structure of the testicle

The testicles contain **seminiferous tubules**, which are the exclusive site of spermatogenesis. Between the seminiferous tubules (interstitial medium) is connective tissue containing endocrine cells, called **Leydig** cells, which secrete testosterone.

Two types of cells occupy the wall of the seminiferous tubules: large conical cells, called **Sertoli** cells, and **germ** cells.

Sertoli cells are large, roughly pyramid-shaped cells that occupy the entire thickness of the epithelium. They have multiple extensions and are connected to each other by tight junctions.

The germ line cells are found in the basal compartment, against the basement membrane, between the Sertoli cells, with which they are connected ly by various junction systems. Arranged in more or less regular layers, they represent, from the periphery to the center of the tube, the successive stages of spermatogenesis: spermatogonia, primary spermatocytes, secondary spermatocytes, spermatids, and spermatozoa.

In the loose connective tissue surrounding the seminiferous tubules, there are clusters of interstitial cells, or **Leydig** cells**,** arranged in cords or isolated around capillaries. They are responsible for the secretion of androgens (testosterone).

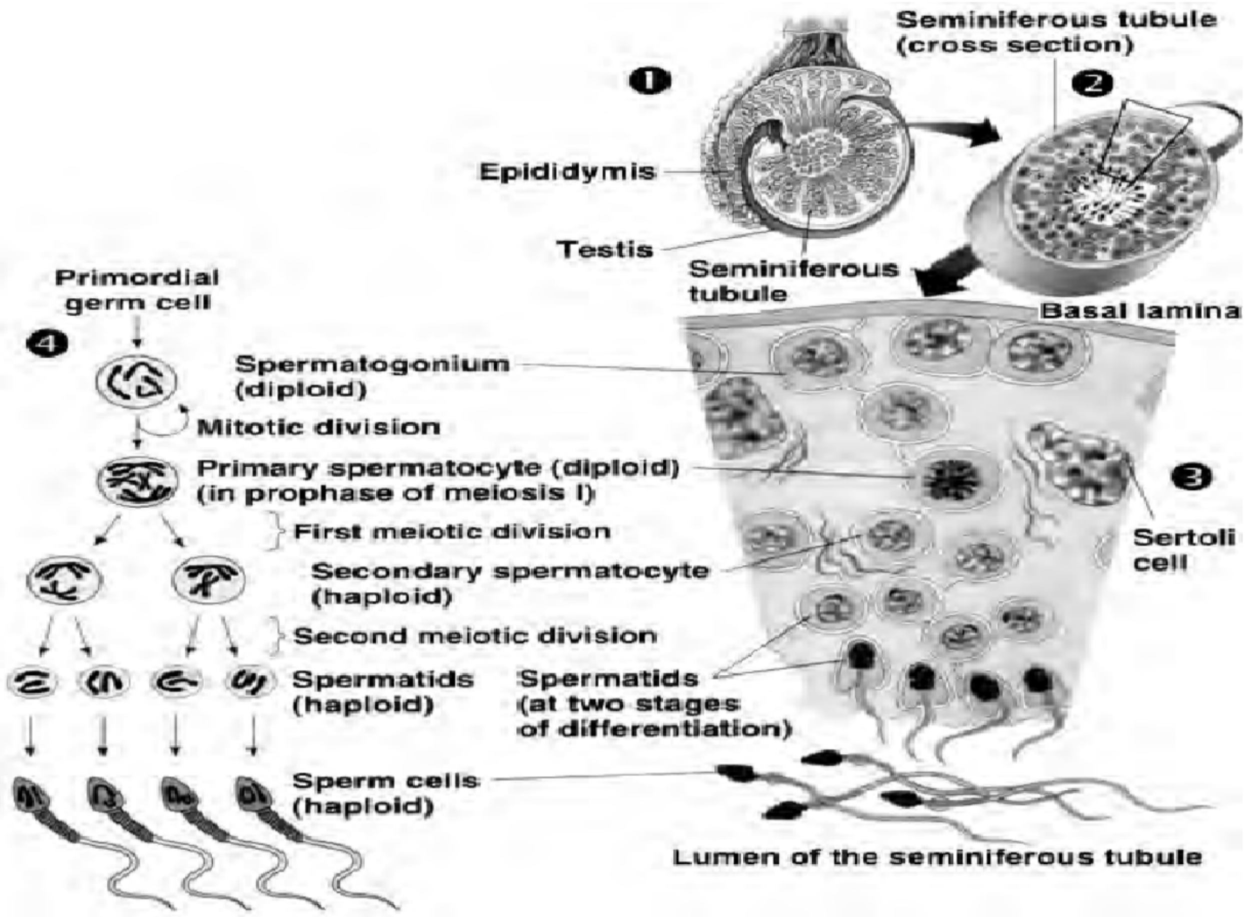


Figure 3: Schematic structure of the seminiferous tubule:

1-2 Phases of spermatogenesis

- **Multiplication phase** This involves spermatogonia, diploid stem cells located at the periphery of the tube, against the membrane itself. These cells undergo a series of mitoses (maintaining the spermatogonia pool), the last of which results in the formation of primary spermatocytes, which are also diploid (one spermatogonia produces four primary spermatocytes).

- **Maturation phase** Preceded by a growth phase, this corresponds to meiosis and involves both generations of spermatocytes (primary I or secondary **II**). A spermatocyte **I** with 2n chromosomes undergoes the first **meiotic** division **(reduction mitosis)**, producing two spermatocytes **II** with n chromosomes. Each spermatocyte II undergoes the second meiotic division (**equational mitosis)** and produces 2 **spermatids** with n chromosomes.

A spermatocyte I therefore produces 4 spermatids at the end of meiosis.

- **Differentiation phase**, also known as **spermiogenesis**, this phase does not involve division but rather the differentiation of spermatids into spermatozoa (the process of forming the structures that will give them mobility and the ability to penetrate the egg). This transition is characterized by:

- A reduction in the cytoplasm of the spermatid.

- The appearance of an acrosome formed from the condensation of Golgi vesicles.

- The formation of a flagellum from microtubules originating in the distal centriole.

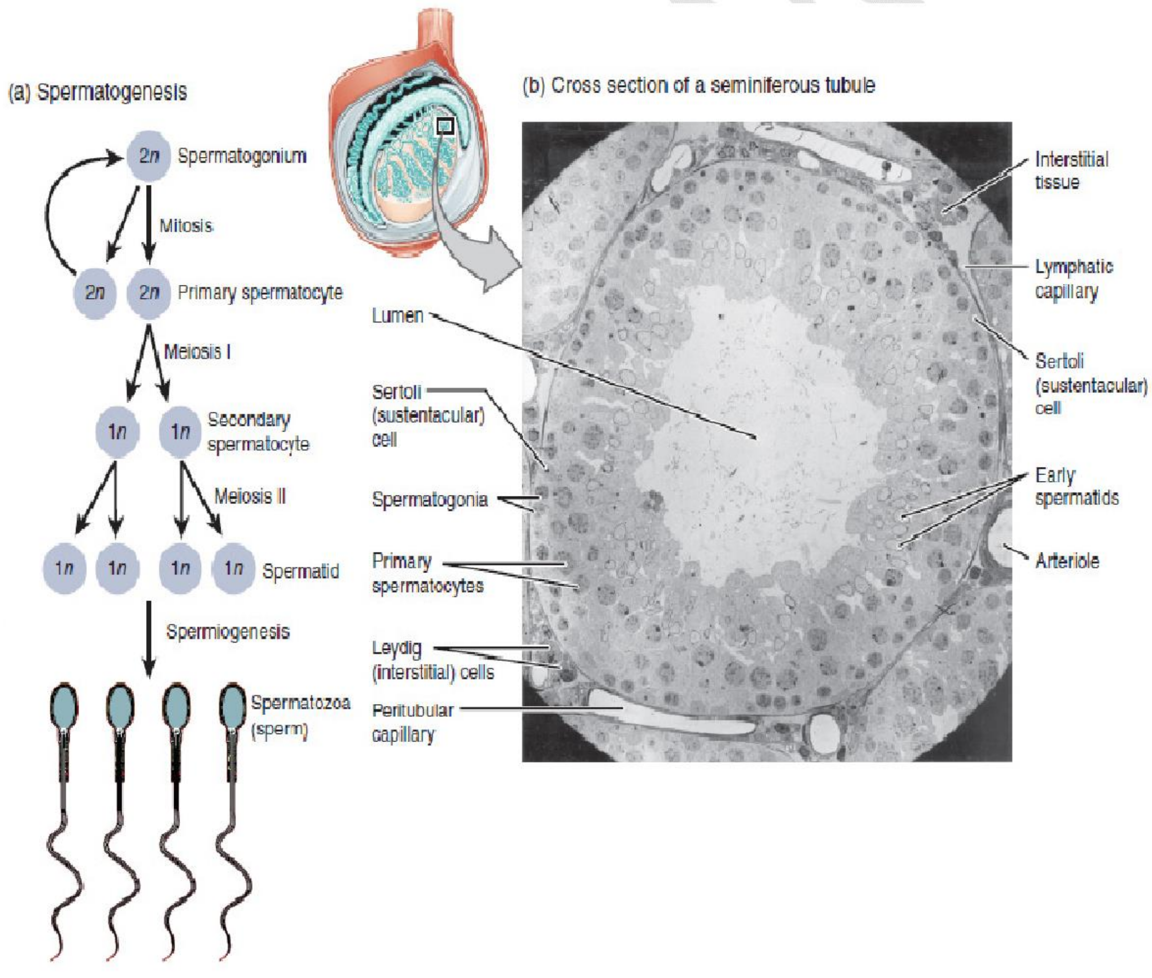


Figure 4: Diagram of spermatogenesis

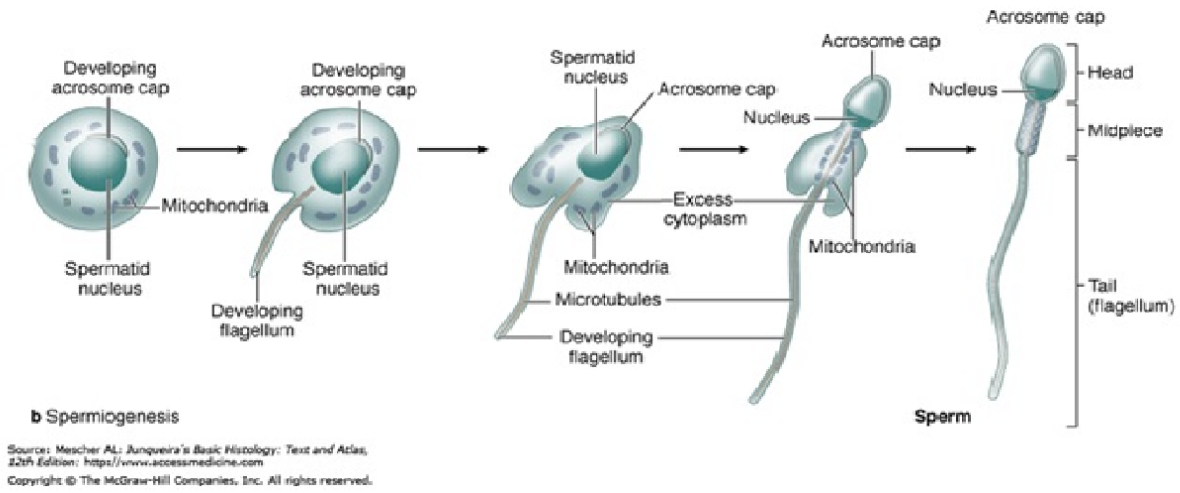


Figure 5: Stages of spermiogenesis or differentiation

1-3 Sperm emission Sperm are produced and formed in the testicles, then released into the epididymis. They first pass from the rete testis to the head of the epididymis, in the efferent cones that continue through the epididymal duct. The gametes are modified throughout their journey through the genital tract.

- In **the epididymis**, under the action of androgens (particularly testosterone) secreted by Leydig cells, sperm acquire their motility (sperm produced in the testicles have very little motility). In the epididymis, the proteins responsible for binding to the egg become functional: sperm acquire their ability to bind to the zona pellucida of the egg, a necessary step in fertilization.

It is also in the epididymis that sperm are **decapacitated** by seminal fluid: sperm then **temporarily** lose their ability to fuse with other membranes.

In summary, functional maturation of sperm is ensured during their passage through the epididymis. This stage is characterized by:

- the acquisition of mobility
- suppression of fertilizing power
- establishment of molecules that recognize the zona pellucida

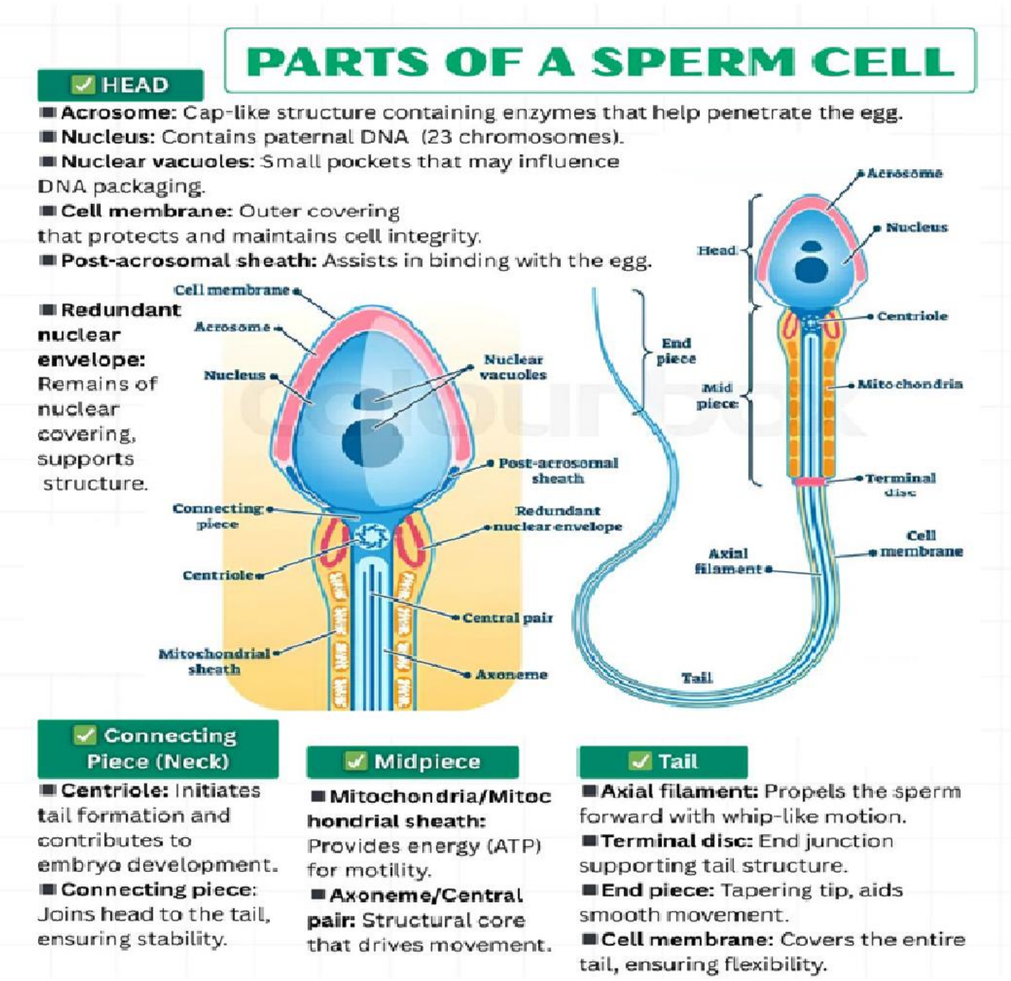


Fig. 6: Sperm: explanatory diagram

Sperm morphology: Sperm are very elongated cells composed of three parts visible under an optical microscope: the head, the flagellum, and the neck, a narrow portion connecting the flagellum to the head.

1) **The head**: it is roughly ovoid, but slightly flattened. It consists of a nucleus and an acrosome, enveloped by a thin hyaloplasmic layer and the plasma membrane. The nucleus occupies most of the head.
2) **The acrosome** is a flattened vesicle covering the upper two-thirds of the nucleus. The texture of the acrosome is finely granular and uniform. It contains numerous hydrolytic enzymes: hyaluronidases, acid phosphatase, neutral proteinases (acrosin) and acids, CPE or Corona Penetrating Enzyme, etc. These enzymes are involved in penetrating the oocyte's membranes. The plasma membrane is classic and has no morphological features.
3) **The** narrower **intermediate piece** with the centriole gives rise to the flagellum and mitochondria arranged in a helix around the flagellum, forming a sheath and providing the energy necessary for the flagellum's movements.
4) **The flagellum:** starting from the neck, there are three parts of decreasing diameter along its length: the intermediate piece, the main piece, and the terminal piece.

2- Testicular abnormalities

Cryptorchid or ectopic testicles

Cryptorchidism is one of the most common abnormalities at birth in young boys (affecting almost 5% at birth in Europe), and 30% of premature male infants have at least one *undescended* testicle. It is often associated with physical problems of sexual differentiation, renal and urethral malformations, dysplasia

The testicles or male gonads normally produce two types of products:

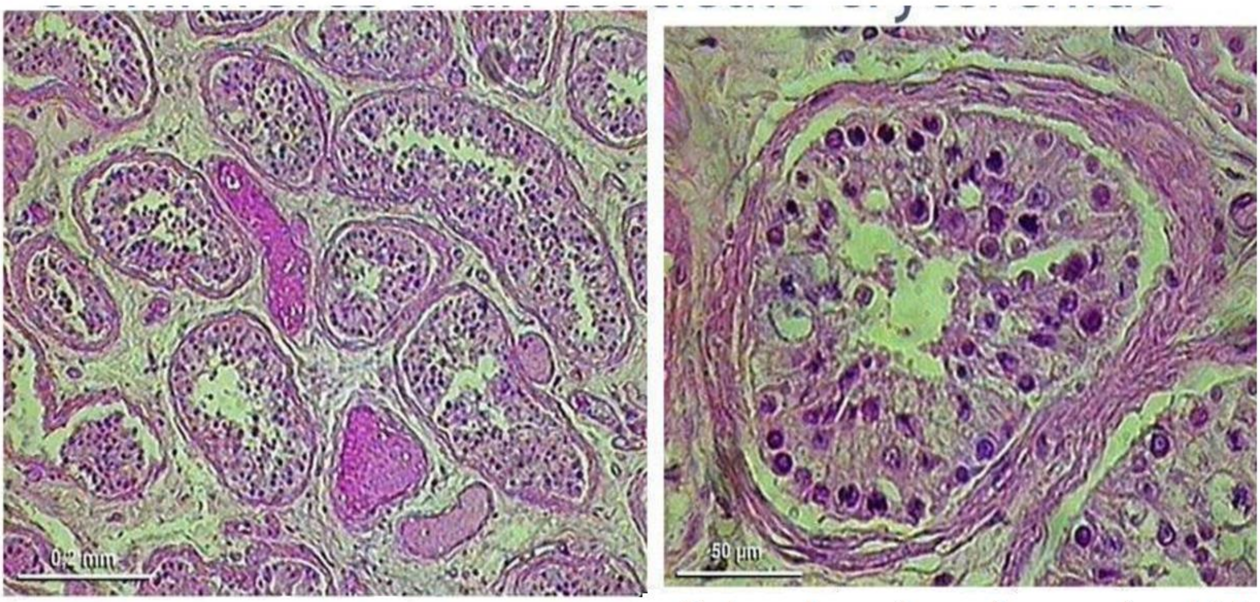
***sperm** or male gametes in the seminiferous tubules.

*the male sex hormone "**testosterone**" by cells located between the tubes, called interstitial cells for this reason.

However, proper spermatogenesis within the tubes requires slight **cooling**, which occurs when the testicles migrate to the scrotum.

In the event of non-migration, the testicles that remain hidden in the abdomen (hence their name **cryptorchids**) do not produce spermatozoa, while testosterone production by the **interstitial (Leydig)** cells is maintained.

Histological sections (figure below) of these ectopic testicles are almost empty of gametes, which leads to sterility but with the maintenance of male secondary sexual characteristics.



Colored section of a cryptorchid testicle observed under an optical microscope at 100x Gr

Colored section of a cryptorchid seminiferous tubule observed under an optical microscope at 400x Gr

Figure 7: Testicular abnormality (cryptorchid testicle)

3. Neuroendocrine control

The "conductor" of testicular function is **GnRH** (gonadotropin-releasing hormone). It is thanks to the pulsatile production of this hormone by neurons in the hypothalamus (production increases significantly during puberty) that testicular function is established.

GnRH triggers the pituitary gland to secrete two hormones, **FSH** and **LH**.

In the testicles, these hormones have the following effects:

□ **FSH** enables the development of **Sertoli** cells and spermatogenesis. FSH binds to membrane receptors on Sertoli cells and plays a triple role:

- it activates spermatogenesis
- it stimulates the formation of **ABP** (Androgen Binding Protein);
- Finally, it triggers the secretion **of inhibin**, a hormone that exerts negative feedback control on FSH secretion, either on hypothalamic neurons by decreasing GnRH secretion, or directly on pituitary gonadotropic cells.

 LH ensures the multiplication of Leydig cells and the secretion of **testosterone** (endocrine function of the testicle):

- Most of the testosterone enters the cytoplasm, where it binds to ABP to regulate the development of the seminal epithelium and the proper functioning of the genital tract (seminal fluid).

- Free testosterone passes into the bloodstream and has two effects: a positive effect on the genital tract and accessory glands, and a negative feedback effect on LH secretion, either indirectly on hypothalamic neurons or directly on pituitary gonadotropic cells.

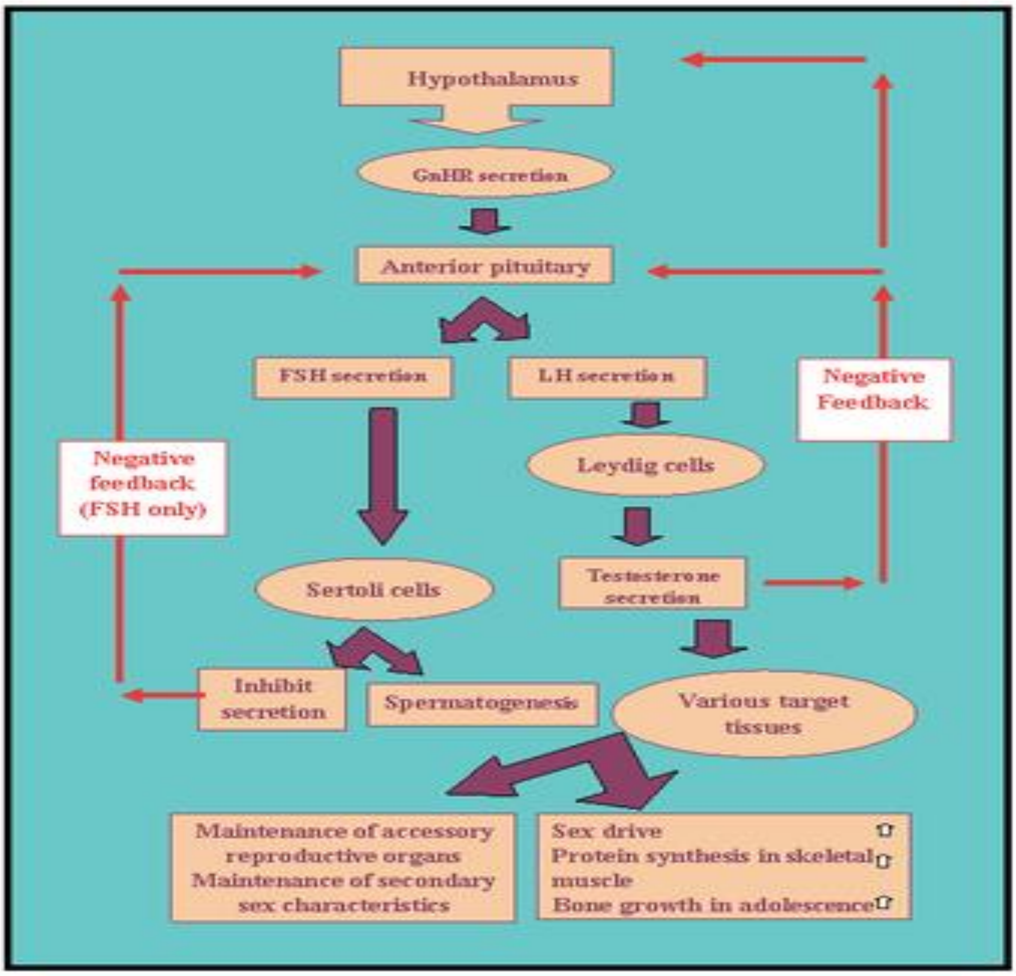


Figure 8: Regulation of spermatogenesis

4- Sperm abnormalities

Sperm abnormalities are the most common cause of male infertility. Although produced in sufficient numbers, sperm may be immature, abnormally shaped, or unable to move properly, characteristics that will deprive them of their ability to fertilize an egg. Normal sperm may also be produced in abnormally low numbers, resulting in a decreased chance of fertilization.

Oligoasthenozoospermia (**OATS**) refers to a set of abnormalities detected in a man's sperm. The sperm are too few in number to fertilize an egg (**oligospermia),** too immobile to reach the egg **(asthenospermia**), and have abnormalities in shape (**teratospermia)**. OATS is very often the cause of male infertility. There are many causes of OATS:

- **Past or recent genital infections** - the presence of a **varicocele** , smoking and drug abuse , obesity, excessive exposure to heat (particularly in certain professions), radiation, certain medications, stress, etc.

5- Factors influencing spermatogenesis

Many factors are **harmful** to spermatogenesis

• **Infectious,** inflammatory, and viral **diseases** such as **mumps** can lead to infection of the genital organs or cause testicular **atrophy**.

• Approximately 25% of men who contract mumps after puberty become **infertile**.

• **Endocrine** or hormonal **disorders** account for only a small percentage (approximately 2-5%) of cases of male infertility. Insufficient production of the hormones that control testosterone secretion and sperm production (FSH-LH).

• **Immune problems -** some men produce **antibodies** that attack their own sperm, leading to insufficient motility or **agglutination**.

• **Environmental** and lifestyle factors such as exposure to radiation and certain cancer treatments (either temporarily or permanently).

Anatomical abnormalities obstructing the genital tract can lead to infertility when they partially or completely block the flow of seminal fluid. Some of these abnormalities are congenital or genetic in origin, while others may develop as a result of infection or inflammation of the urogenital tract.

Conclusion

From the point of view of chromosomal equipment, there are two types of spermatozoa. Meiosis separates the two elements of the XY pair, producing an equal number of spermatozoa with 22 autosomes + X and others with 22 autosomes + Y. They are not morphologically distinguishable from each other, but there are ways to separate them in vitro. The sperm cell is a very simplified and specialized cell, perfectly adapted to its function, as it contains only the essential components: - a nucleus, with a highly compacted haploid genome, which facilitates its transport and protects it from genotoxins; - an acrosome, equipped with enzymes that enable it to penetrate the egg cell's envelope; - a flagellar apparatus ensuring its movement towards the female gamete, which is immobile; - mitochondrial equipment providing the energy necessary for flagellar movements; - membrane and cytoplasmic proteins enabling fertilization. However, ejaculated sperm are temporarily incapable of fertilization because they are **decapacitated.** To become fertile, they must subsequently be **capacitated** in the female genital tract.