Sheets Physiology

Number 11

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Physiology of the reproductive system

In physiology, we are concerned with the mechanisms in which the system functions, and how the system responds to different changes to maintain homeostasis. The purpose of maintaining homeostasis in most of the organ systems is to stay alive **(survival of the individual)**, while here in the reproductive system, distortion of system homeostasis doesn't threaten lives of individuals, but it's essential for maintaining human existence**(Survival of human species)**.

Homeostasis cannot be accomplished by one sex, males alone cannot maintain human species, females alone can't too, so **the two must function together** in order to reach homeostasis and maintain the species.

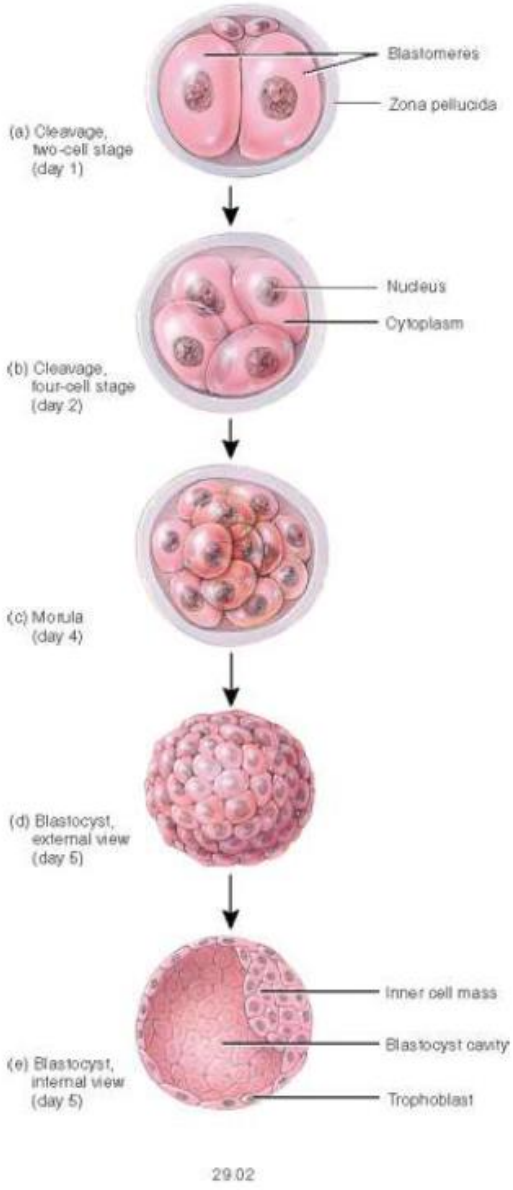
The main function of male reproductive system is to produce **germ cells**, each one of these cells has many special criteria, the most important one is having **half the number of human chromosomes**. Female reproductive system also produces germ cells that have half the number of chromosomes.
When a male germ cell **unites** with a female germ cell for the purpose of maintaining the species, the **full number** of chromosomes is reformed; the male germ cell, the **sperm**, penetrates the female germ cell, the **oocyte**, and transfers its genetic material to the oocyte, the end structure is the **zygote**.
The zygote is the starting point of the new individual, and by developing this individual we reach homeostasis of the reproductive system.

The female reproductive system has another important function; it **nurses** the new individual during the development stages. The zygote will undergo series of **division and differentiation** to produce the new human being and other structures which are important for its survival, during these stages it needs a specific environment that allows the proper development to take place.

Stem cells

You know that cells differ in their capability to divide and proliferate, stem cells have huge division capacity.
Stem cells differ in the types of cells produced after division:
- Unipotent stem cells divide and produce one type of cells
- Multipotent stem cells divide and produce few types of cells
- **Pluripotent** stem cells can produce any type of cells in the human body
- **Totipotent** cells can produce any type of cells in the human body or **placenta**.

The zygote and the cells produces after few rounds of its division are of totipotent type of cells, which means that if we split the cells in the two-cell stage and provided them with proper conditions we can have two individuals. If we split the cells at the four-cell stage we can have four individuals, but if we split the cells in the hundred-cell stage we CAN'T have hundred individuals!

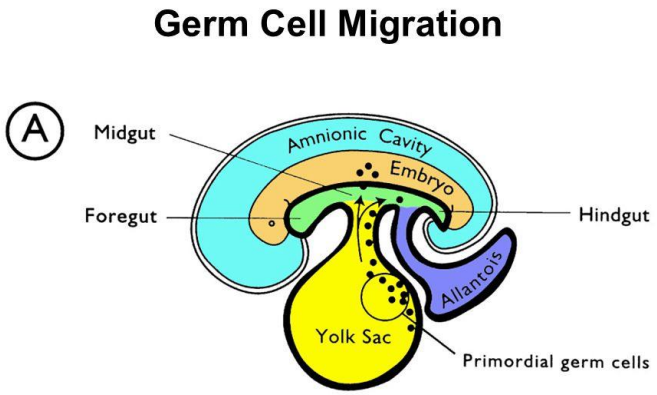


We conclude that at one point between four and hundred, certain cells lost some of their differentiation potential; they went few steps into specialization and became unable to produce all types of cells in the human being. Some cells differentiate into **inner cell mass** which will form the human being, other cells will differentiate into **trophoblast** which will form membranes that link the embryo to the uterus and supply it with nutrients and remove waste products.

During embryogenesis many cells migrate between different areas, and we have factors that regulate this movement to terminate in certain areas.
Here we are concerned with cells that migrate to form the reproductive organs.

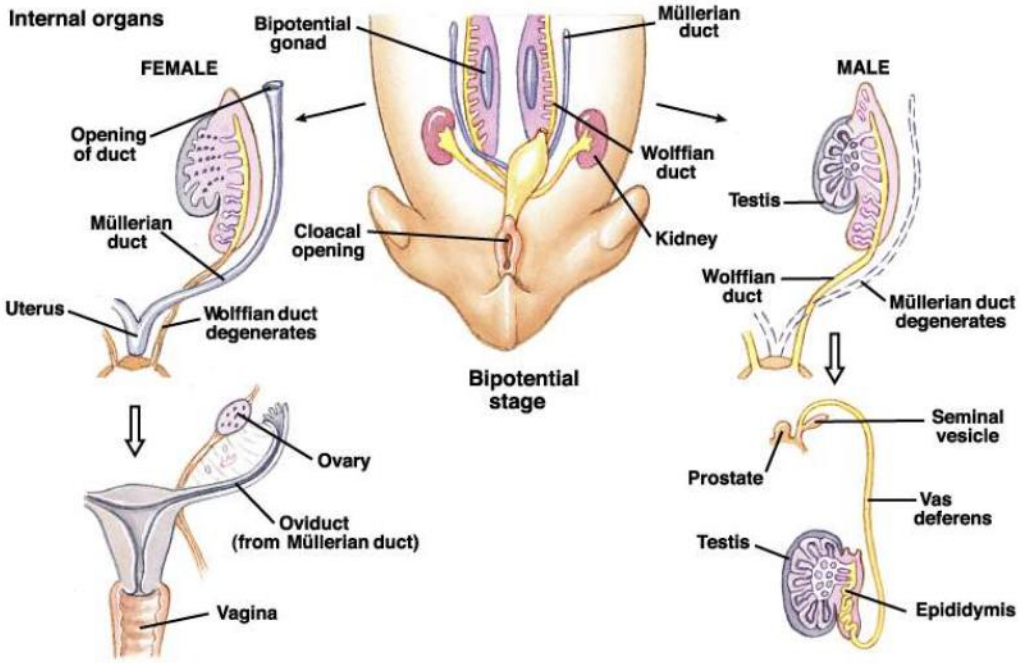
At this stage of development, **primordial germ cells** migrate from the **yolk sac** and stop in a certain site in the embryo called **genital ridge**(where we find the bipotential gonads).

In each embryo, two tubes are formed on each side and from these tubes the gonads will be produced.
One is called **Müllerian** duct (one left and one right) and the other is **Wolffian** duct (also one left and one right).



Migration begins by the 4 week of gestation in cow and human.

Note: *In the bipotential gonads stage we cannot differentiate between a male embryo and a female embryo anatomically and histologically; both of them have the same primitive structure which is the bipotential gonads.*



When the germ cells migrate to the bipotential gonads certain interactions occur between them, and according to the genetic material of the germ cells the bipotential gonads will develop into testes or ovaries.
The migrating germ cells either have Y chromosome (being XY) or not (being XX).
If it's XY, some proteins encoded in segments of Y chromosome will be translated to proteins, these proteins won't be produced in the case of XX.

Male reproductive system development:

One of the proteins that are coded on the **Y** chromosome is the **Müllerian inhibitory factor**, the Y chromosome also codes for some **enzymes** that convert cholesterol to **testosterone**.

The Müllerian inhibitory factor and testosterone produced by the germ cells in the site of bipotential gonads **work locally**:
- Müllerian inhibitory factor inhibits the growth of the Müllerian ducts and the end result is **degeneration** of these ducts in the male embryo
- Testosterone stimulates the growth of Wolffian ducts which will produce the epididymis, vas deferens, seminal vesicles, the prostate, and part of the ejaculatory ducts (male sex organs).

Note: each Wolffian duct produces half of the prostate and then the two unite.

Female reproductive system development:

Here things are different, neither Müllerian inhibitory factor nor testosterone are present, so the opposite will occur:
- The Wolffian ducts won't be stimulated so they won't grow and at the end they will be degraded.
- The Müllerian ducts won't be inhibited so they will grow and produce fimbriated Fallopian tubes, the uterus, and the upper third of the vagina

*Each Müllerian duct produces one Fallopian tube, half of the uterus and half of the upper third of the vagina on the same side.

After these changes (which occur in **6^{th}-7^{th} week**), we can differentiate between male embryo and female embryo anatomically and histologically.

Note: the rest of the sex organs are formed from the urogenital sinus.

Experiments:

What would happen if we injected an antagonist or blocker to the Müllerian inhibitory factor on the right side of a male embryo?
- The products of Wolffian duct will be formed normally on both sides, but a fallopian tube, half of the uterus, and upper third of the vagina will also be formed on the right side (**only** at the side of injection because the effect is **local** not through circulation)

What would happen if we removed the migrating germ cells from the right side of a male embryo?
- The left side will be normal and products of Wolffian duct will be formed, while on the right side there won't be Y chromosome so neither Müllerian inhibitory factor nor testosterone are formed so Wolffian duct will be degraded and products of the Müllerian will be formed (on the right side only)

What would happen if we injected a blocker for Müllerian inhibitory factor and a blocker for testosterone receptor on the right side of a male embryo?
- Products of Wolffian duct would be formed normally on the left side male sex organs, while on the right side Wolffian duct would be degraded and Müllerian duct will grow to form female sex organs on that side.

Müllerian duct will be degraded in the presence of Müllerian inhibitory factor, and will grow in the absence of the factor.
Wolffian duct will grow in the presence of testosterone, and will be degraded in the absence of testosterone.

*Note: make sure you differentiate between **gonads,** primary sex organs, (testes and ovaries) and **sex organs**, secondary sex organs, (from penis to epididymis and from vagina to uterine tubes).*

Sex hormones synthesis

We know from endocrine system that **steroidogenesis** happens in the adrenal glands, it's the process of converting **cholesterol** enzymatically to pregnenolone, then from pregnenolone it proceeds in certain regulated pathway to end up with formation of mineralocorticoids (aldosterone) or glucocorticoids (all are C21).

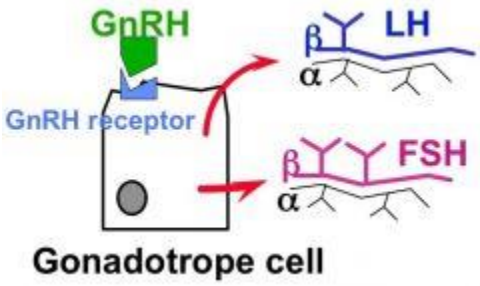
In gonads, similar pathway is taken but under different regulators. Cholesterol is converted to pregnenolone under the effect of LH. Then, pregnenolone is converted to **androgens** (C19), and some androgens are converted to **estrogen** (C18).

What regulates androgens synthesis?

It's the hypothalamic-pituitary axis (it regulates steroidogenesis ingeneral).
The hypothalamus has connections with many areas in the brain, one of them is a loose connection with the **median eminence**. Neuroendocrine cells in the **arcuate nucleus** of the hypothalamus release hormones into the median eminence, these hormones are called "releasing hormones" and here we are concerned with one of them which is the **gonadotropin releasing hormone (GnRH)**.

GnRH works on the anterior pituitary, its effect is on certain cells that have GnRH receptors. These receptors are linked to three different pathways producing three different mRNAs, each one produces different structure at the end:
- One leads to synthesis of a β subunit.
- Another leads to synthesis of a different β subunit.
- And another one leads to synthesis of α subunit.

When α subunit combines with β subunit they form LH, and when α subunit combines with the other β subunit they form FSH, which means that **LH and FSH share the common α subunit but they differ in the β subunit**.Then LH and FSH control and regulate the production of sex hormones and germ cells.



Neuroendocrine cells of the hypothalamus didn't originate there, they also **migrated** from somewhere else and resided in the hypothalamus during embryonic development. If these cells **lost the way** during migration they would end up in any other site of the body, and their axonal terminals won't be in the median eminence, so the hormones won't reach the median eminence and the axis is blocked.

Development of the testes

The migrated cells that have XY chromosomes start to divide and increase in number to form the **spermatogonia**, they divide by **mitosis** which means that daughter cells are similar to the parent cell in all aspects especially the **nucleus**; they have the same chromosomes. Then these cells start making relationships with the surrounding structures ending up with formation of the testes.

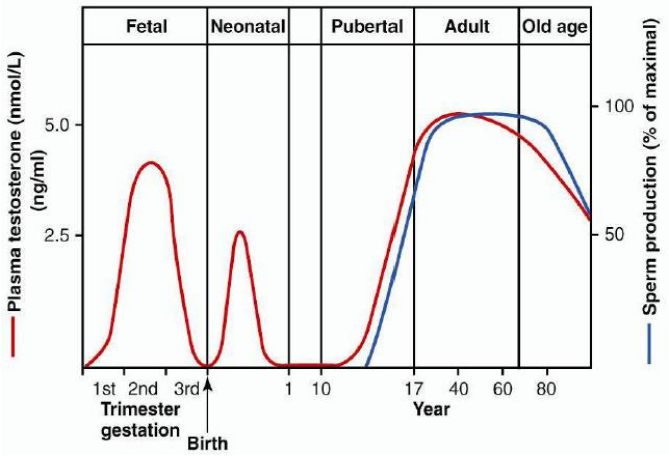
We mentioned two migrations so far:
1- Migration of germ cells from yolk sac to the genital ridge.
2- Migration of neuroendocrine cells to the arcuate nucleus of the hypothalamus.

A third migration that is important in formation of the male reproductive system is the **migration of the testes:**
The testes originate in the posterior part of the abdominal cavity, but they get outside the body (to the scrotum), this occurs in third trimester of pregnancy.

After a period of time the testes enlarges and become well developed, now it can perform its functions which are:
1- Production of germ cells (that have half the number of chromosomes).
2- Production of hormones.

Production of testosterone:

Look at this figure which shows changes in the amount of testosterone in the plasma with time: (*Note that time in the X axis is not uniform)*



Production of testosterone begins in the 6^{th}-7^{th} week of intrauterine development as we mentioned before, it's secreted from the migrated germ cells to the bipotential gonads, and its secretion there is crucial for the development of the Wolffian duct and formation of male sex organs.

Germ cells will divide and increase in number so the amount of **testosterone increases**, then they will make a relationship with the surrounding structures to form the testes which contain seminiferous tubules and **surrounding cells**, the surrounding cells start to do one of their functions which is also the production of testosterone, so the amount of **testosterone increases more and more**.

Then the amount of testosterone **starts to decrease although** the cells that produce it are still there and are still able to produce testosterone but they're inhibited, so at the time of delivery there is very low amount of testosterone in the plasma.

For a short time after delivery, the amount of testosterone **increases again**, which means that inhibition surrounding cells is removed. During delivery, a placental hormone enters the body of the newborn and stimulates the surrounding cells to produce testosterone.
Soon after that, the placental hormone disappears from the body of the newborn, so the surrounding cells are inhibited again and the amount of testosterone **decreases almost to zero**, this situation continues until puberty.

Example from the endocrine system:
If a patient administered dexamethasone (a corticosteroid drug) for a long time what will happen? It will suppress the production of ACTH form the hypothalamus; ACTH is the stimulant for the adrenal gland to produce corticosteroids(mainly glucocorticoids).

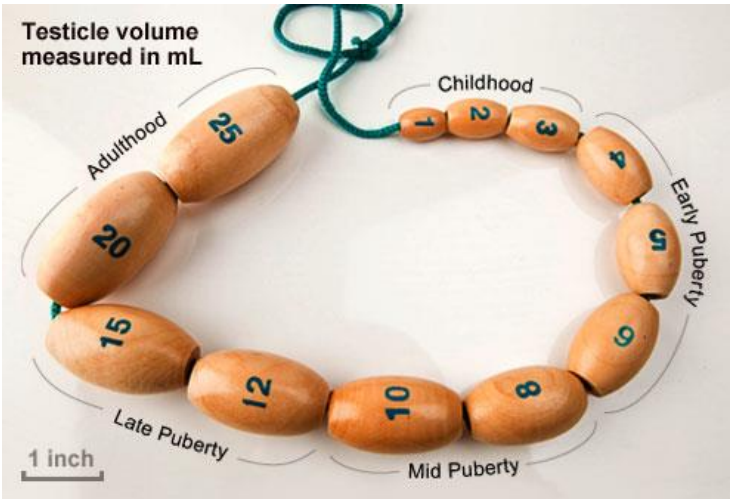
In the absence of ACTH stimulation, adrenal glands will start to decrease in size and function until they become very small in size and almost stop producing corticosteroids.

If dexamethasone is withdrawn, ACTH won't be suppressed anymore, so it will stimulate the structure and function of adrenal glands, then adrenal glands will start to increase back to the normal size and produce corticosteroids.

The same thing happens to testosterone production. In the absence of a stimulant, the gonads (testes) go in deep sleep and produce nothing until a stimulant comes and wakes them up.

At this stage if a child (3 years old for example) is injected with something that stimulates testosterone production (LH and FSH) the amount of testosterone would increase! This means that the machinery is present but it's turned off.

At puberty, the hypothalamic-pituitary axis is **reactivated** and LH and FSH are produced, which means that testes are now stimulated so they start to increase in size **gradually** and produce testosterone (you can see it **increasing** on the chart).



Note the gradual increase in the size of the testis.

Increasing the size of the testis means that its contents are increasing too, the seminiferous tubules and the surrounding cells increase and become more developed, this is accompanied by increase in function so the level of testosterone production **increases**.

With age (after reaching 60), the function of the testes starts to decrease, so the level of testosterone**decreases** but it will never go back to zero.

*Note: in females, the production of sex hormones **does go back to zero**.*

Spermatogenesis

It's the process of producing male germ cells (sperms), it starts at puberty. There's no spermatogenesis during intrauterine life, but the original germ cells are dividing! They divide mitotically and produce similar cells, so the number of cells increases but none of them develops into a mature germ cell (sperm).

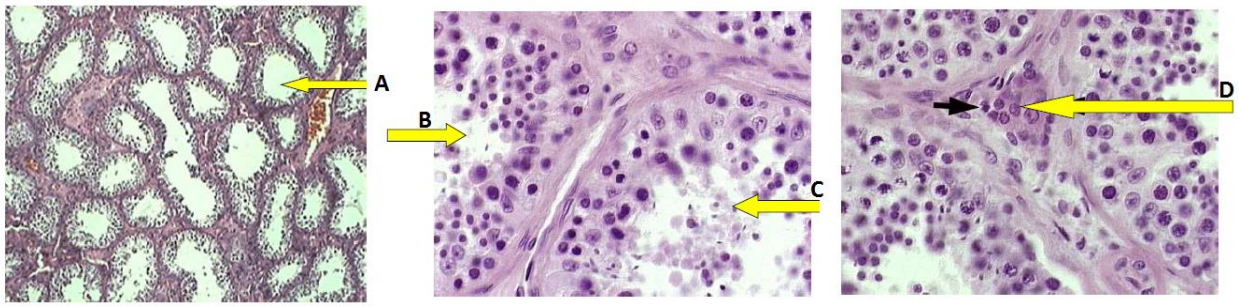
At puberty, some original germ cells start **meiosis** and produce cells with half the number of chromosomes of the original cells, these cells undergo further development to become sperms.

Note: you can see the changes in rate of sperms production with time; it's the blue curve in figure in page 7.

As we said before, the function of testes starts to decline with age (old age), so the rate of sperms production will decrease but it will never get back to zero.

*Note: in females, the production of oocytes **does go back to zero**.*

Cross sections in the testes



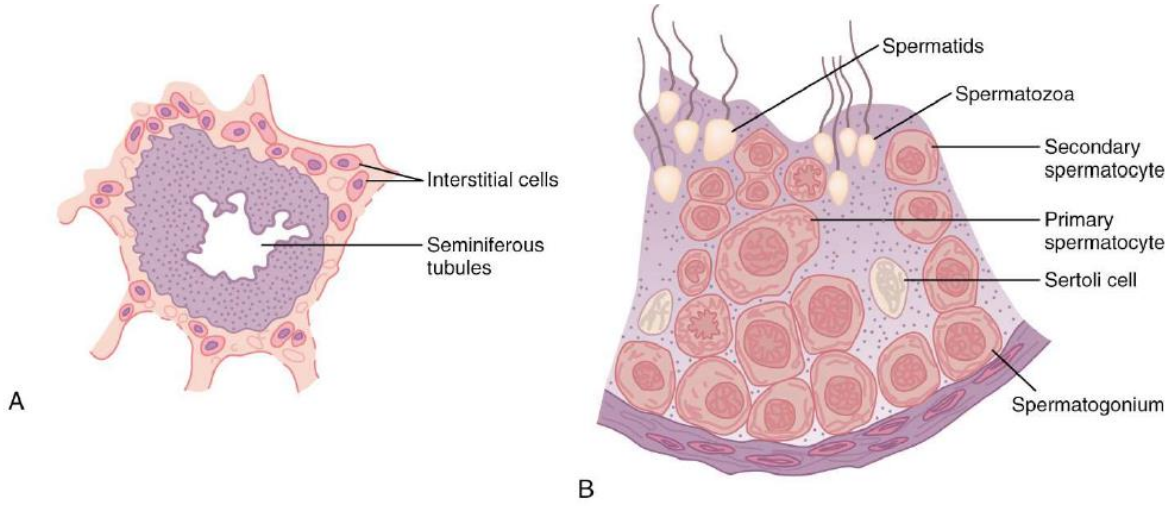
A, B, and C: seminiferous tubules. D: interstitial cells (produce testosterone)

The picture on the right shows a gland-like structure, it looks like the thyroid gland, with follicular and parafollicular cells, yet it's different.
One important difference is that the tubules here are **blind-ended** ducts; they're closed from one side and on the other side they're opened to the rete testes, then to epididymis, so it's a ductal pathway. (Thyroid gland has non-ductal pathway, it secretes its products in the blood).

Another difference is that the cells that line the tubules and the interstitial cells are different from follicular and parafollicular cells respectively.

Types of cells in the seminiferous tubule(shown in the figure below)**:**

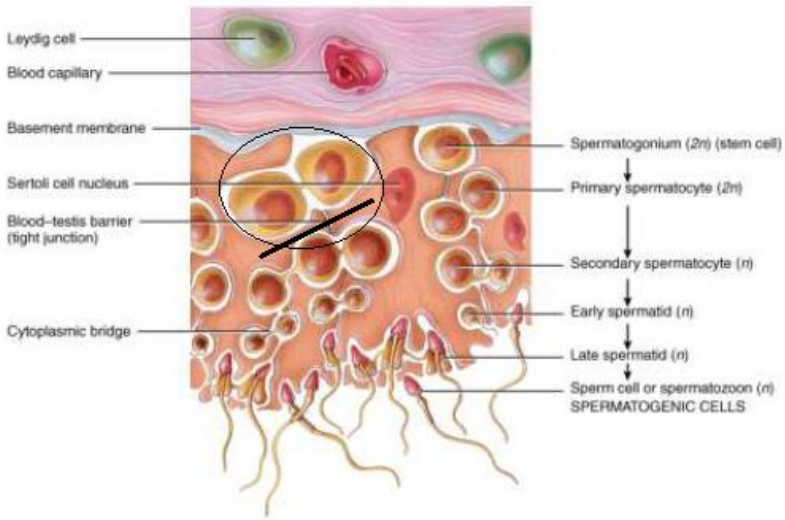
1- Interstitial cells, they produce testosterone
2- Two types of cells lining the seminiferous tubules:
   A- Cells that produce mature germ cells
   B- Nursing cells (Sertoli)



In figure A you can see that a seminiferous tubule has multiple layers of cells lining it, unlike thyroid follicles which are lined by one layer of cells.

*Germ cells in the basal layer divide mitotically and they are larger than the original germ cells.

At puberty, some cells leave the basal layer and travel centrally (toward the center of the lumen), during travelling these cells undergo further developmental changes.

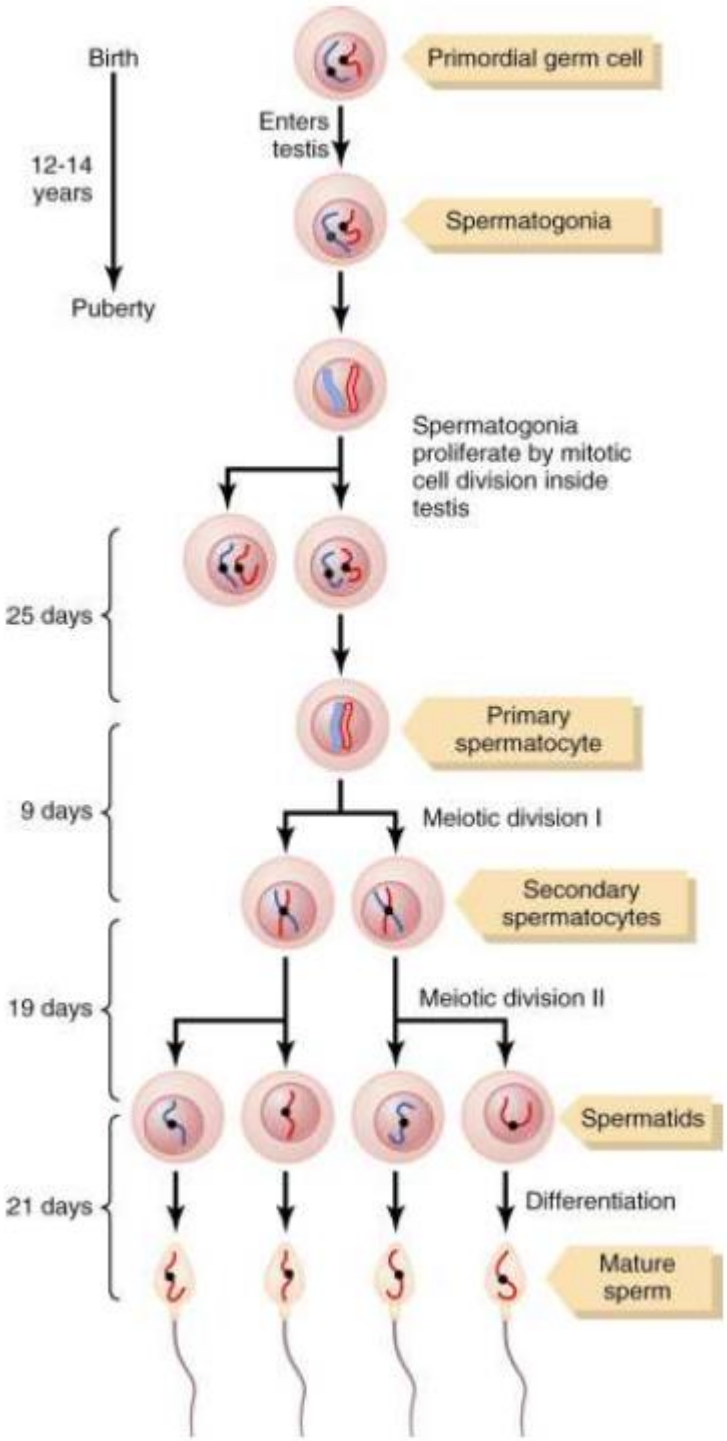


Note that cells in the basal layer (spermatogonia) are dividing mitotically.

Some cells bulge outside the blood testes barrier leaving the basal layer and moving centrally.

Blood testes barrier is a connection between two Sertoli cells.

At puberty and under the influence of LH and FSH, cells in the basal layer of the seminiferous tubules start moving centrally. During this movement, the cells undergo **meiosis**.



Note that some cells that result from mitosis proceed towards meiosis while others just keep doing mitosis.

Primary spermatocytes enter meiosis 1 producing secondary spermatocytes which have half the number of chromosomes. (haploid)

After meiosis II, cells produced are called **spermatids** and these have half the number of chromosomes.

Spermatids have a shape similar to that of the cells that produced them (secondary spermatocytes).

Remember: the more developed

cells are located more toward the center of the seminiferous tubule.

Note that it takes **10 weeks** from the initiation of spermatogenesis (bulging of one spermatgonium outside the blood-testes barrier) until the formation of spermatozoa. This process occurs totally in the seminifrous tubules.

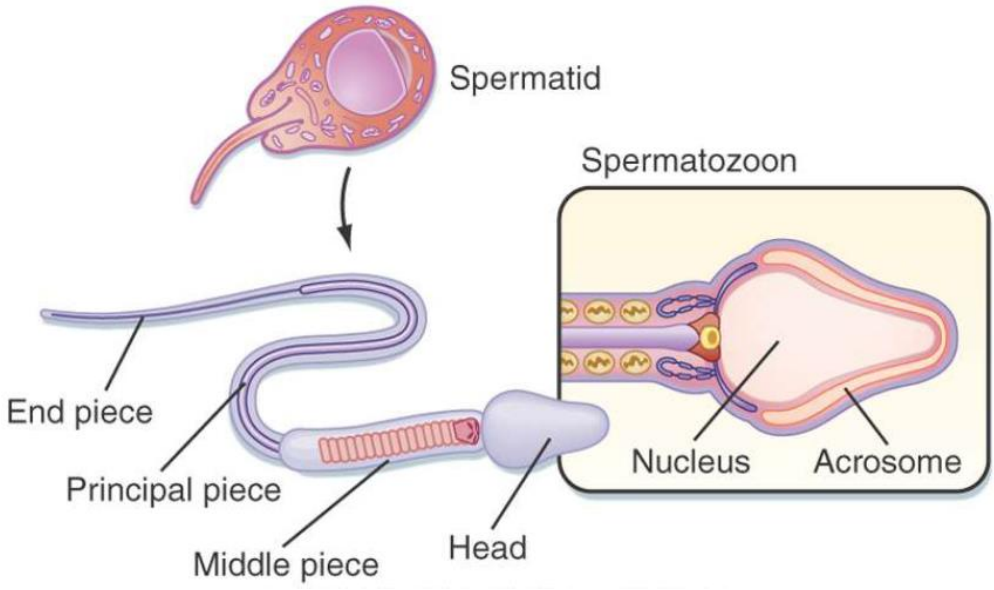
A human male can produce at least 100 million spermatozoa each day, how is that possible knowing that the process of spermatogenesis needs 10 weeks to produce mature spermatozoa?
It's possible because there are a huge number of spermatogonia in the seminiferous tubules, and each one initiates spermatogenesis at a different time. In other words, **at each moment of an adult male life, many spermatogonia initiate spermatogenesis,** that's why you can always find cells of different stages of development in the same seminiferous tubule.
*(It's **not** an ON-OFF mechanism at which all spermatogonia start together and finish together)*

Structural changes on spermatids

The aim of spermatogenesis is to produce cells that have **half the number** of chromosomes and the **ability to move and penetrate the oocyte**.
Spermatids look like spermatogonia, they are rounded cells that are unable to move and penetrate and have half the number of chromosomes, these cells will undergo certain structural changes in which some structures are removed and others are added to become able to move and penetrate. The new cells are called spermatozoa.

One added structure is the **flagellum**; it is a microtubular (contractile) system in the **tail** of the sperm that allows it to move, but it needs energy.
Energy is provided by clusters of **mitochondria** gathered in the **midpeice** of the sperm. In order to move efficiently, any extra load should be removed, meaning that any unnecessary organelles are removed and only the necessary ones are kept.
For penetration, **lysosomes** are needed, and they're gathered in a structure that covers the head of the sperm which is called the **acrosome**, lysosomes contain the enzymes needed for penetration.

Of course the **head** contains the nuclear material which we attempt to deliver to the oocyte using movement and penetration.



All in all, changes in **shape** of the cell, **contents** of the cell, and **distribution** of these contents are needed to transform spermatids into functional spermatozoa.

If the tail structure is not present, the cells won't be able to move, and if the enzymatic system is not present, the cell won't be able to penetrate the oocyte, and both situations the cells are unable to carry the nuclear material to the oocyte so they are nonfunctional.

So if you put a spermatid around the oocyte will it be able to fertilize it?
No because it's not mature yet so it doesn't have the enzymatic system that allows penetration into the oocyte.

If you put a spermatid inside the oocyte will it be able to fertilize it?

Yes, because all what is needed now is the nuclear material and it is present in the spermatid.