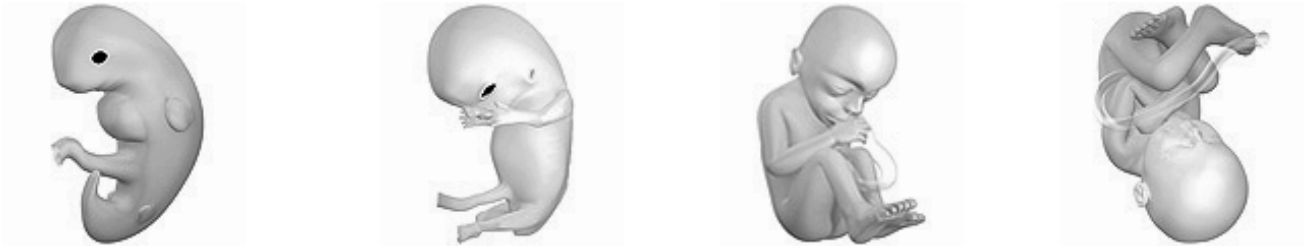
Human Embryology and Congenital Abnormalities

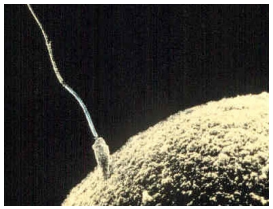


jamie.davies@ed.ac.uk

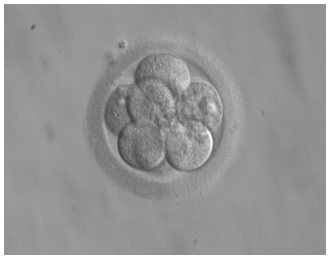
Image credit: Melchior Meijer (Wikimedia Commons)

The structure of the week:

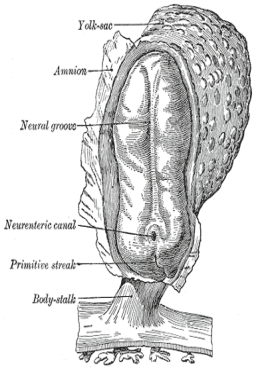
Lect 1



Lect 2



Lect 3



Lect 4-5

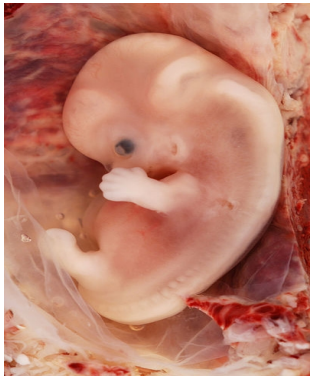


Image credits: PDImages, Gray's Anatomy, Ed Uthman, Lisa J Patton, (all Wikimedia Commons)

Resources on LEARN:

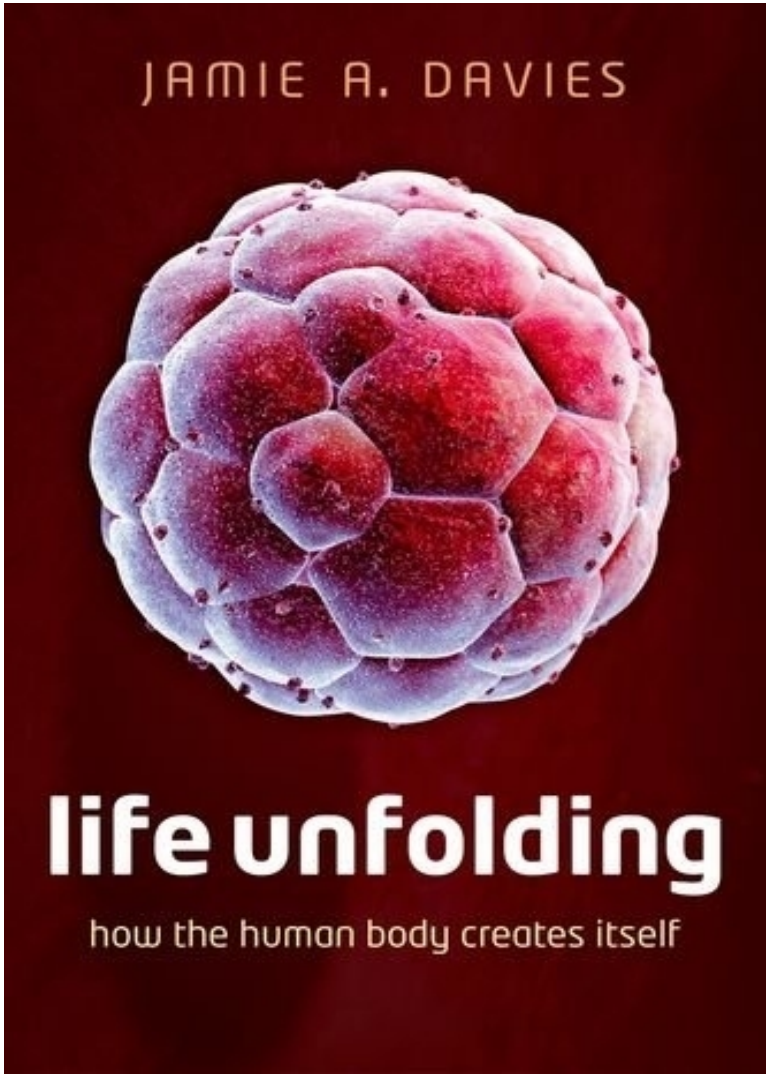
Handout with ‘bare minimum’ summary of what you need to know.

Lecture slides (these ones, as pdfs)

Audio podcasts (same material as these lectures, presented from a slightly different angle – you do not need to listen to these, but they may help if the lectures leave you lost):
http://golgi.ana.ed.ac.uk/coursenotes/mbchbyr1/daviespodcastindex.html

Formative exam-style questions

You may also find this useful (it grew partly out of this course).



Oxf Univ Press, 2014 (also available in Japanese and Russian, and as an audio book)

Outline for Lecture 1

1a • Introduce basic concepts of sex
Introduce the Germ Line

1b • Explain how sperm are produced.

1c • Explain how oocytes are produced

Image: NIH (public domain)

A working definition of "sex";

- *Blending genetic characteristics of two individuals of the n^{th} generation to create the $(n+1)^{th}$ generation*

Disadvantages of sex

- You need to find a partner
- Dilution of a ‘perfect’ set of genes.

Advantages of Sex

- Each individual has a new mix of genes that give it immunity to pathogens (*the Red Queen syndrome)*

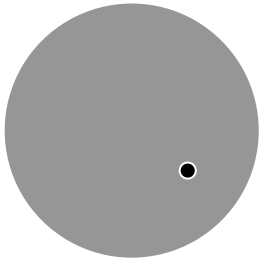
- Each individual has a new mix of genes that determine its environmental interactions.

"A chicken is merely an egg's way of making another egg"
(Samuel Butler)

Sexual reproduction has an innate instability

The Two Sexes*

Female: few, large gametes (*ova*); nurture (yolk, placenta, milk).



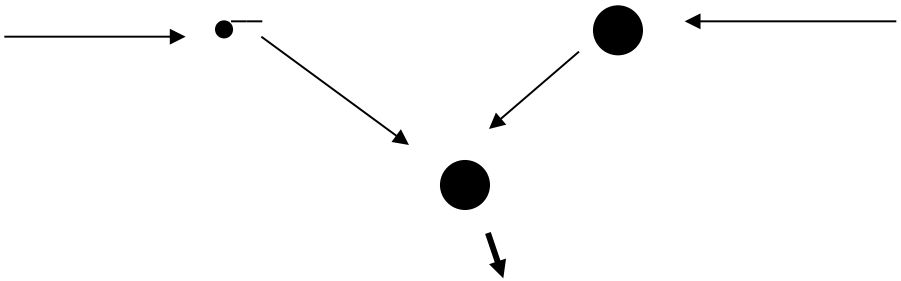
Male: many small gametes (*spermatozoa*); provides nurture behaviourally or not at all.

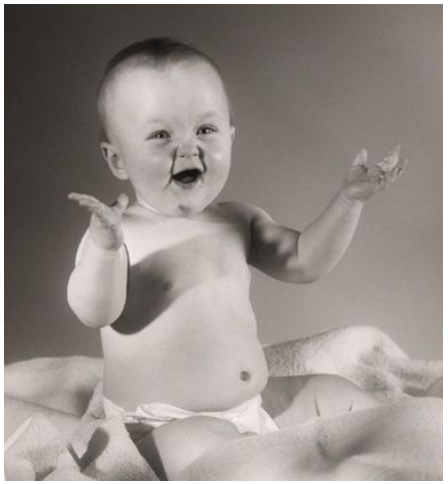
* no disrespect intended to people of non-binary gender: our context here is gamete production for reproduction, and gametes only work properly if they are fully of the male or the female type (whatever the nuanced gender of the person who makes them). We will touch on intersex and other non-binary people in the last lecture of this week.

The general strategy of sexual reproduction

Adult-
5,000,000,000
cells

Single reproductive cells (gametes)





Adult-
5,000,000,000
cells

Images: Richard Sadler, Florence Henry: Kettle's Yard Gallery, Cambridge + Lichfield Photographics

Very early in embryonic development, a set of cells is set aside to become the 'germ line'.

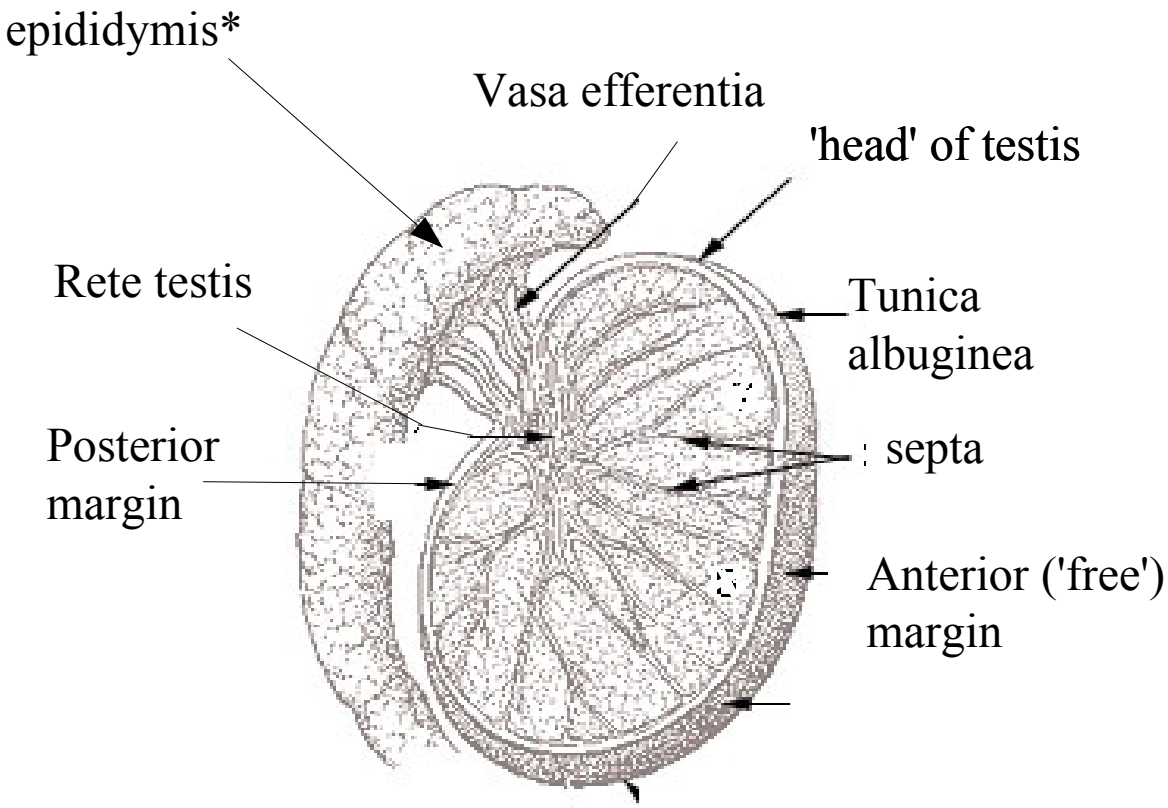
germ line → gametes

rest of the body → 'somatic cells'

Spermatogenesis

Adult testicular anatomy

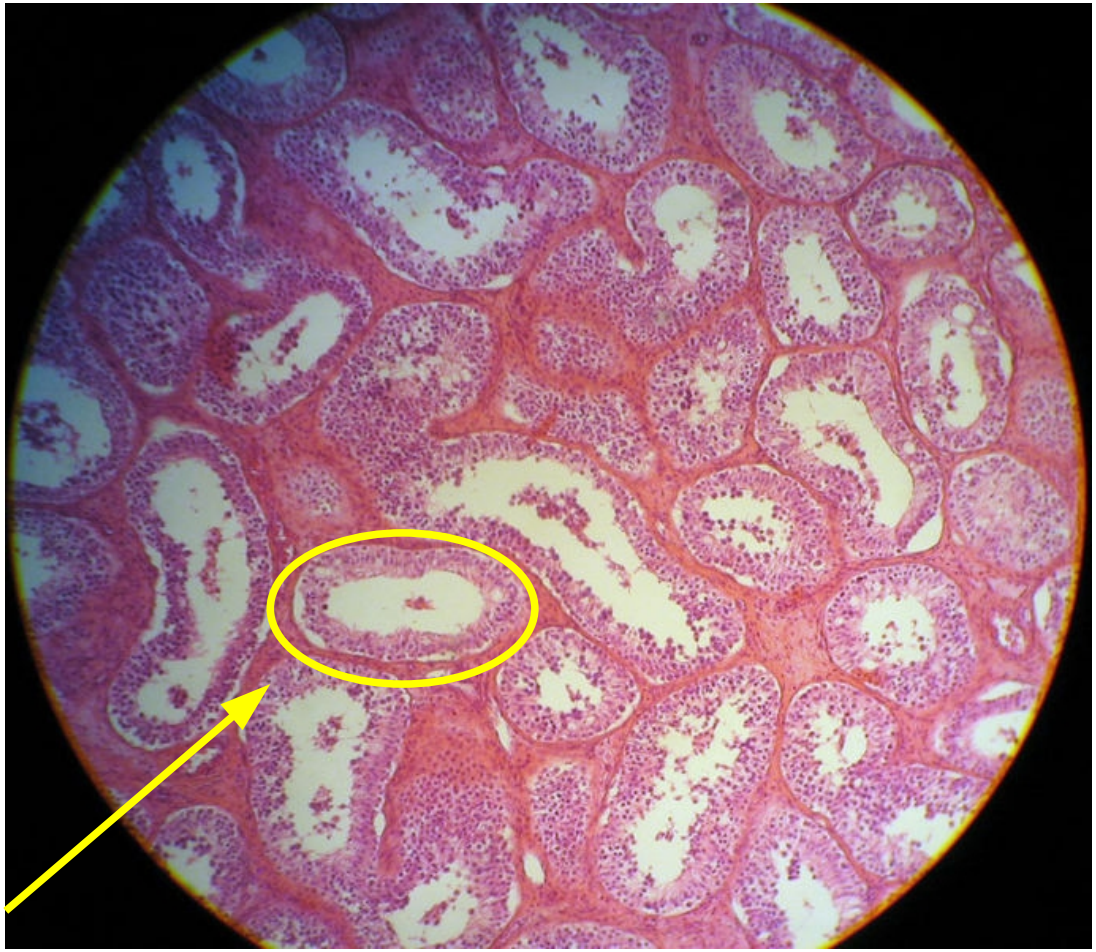
Orientation of diagram
(photo is of a shaved adult)



* The epididymis is not strictly part of the testis

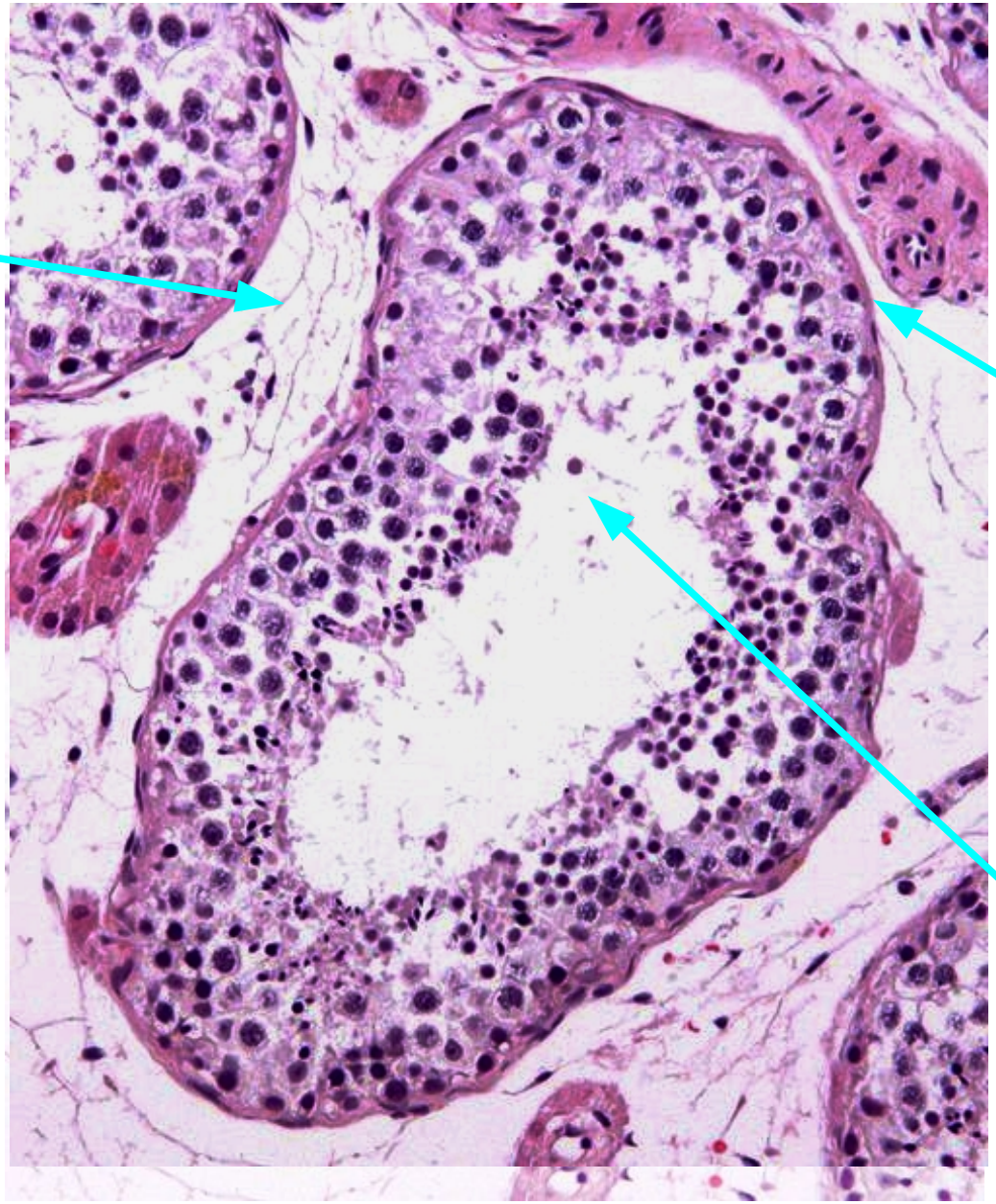
Image credits: 'Juicybnana' and US Govt, both Wikimedia commons

Histological section of adult human testis



Seminiferous tubule

One seminiferous tubule in more detail



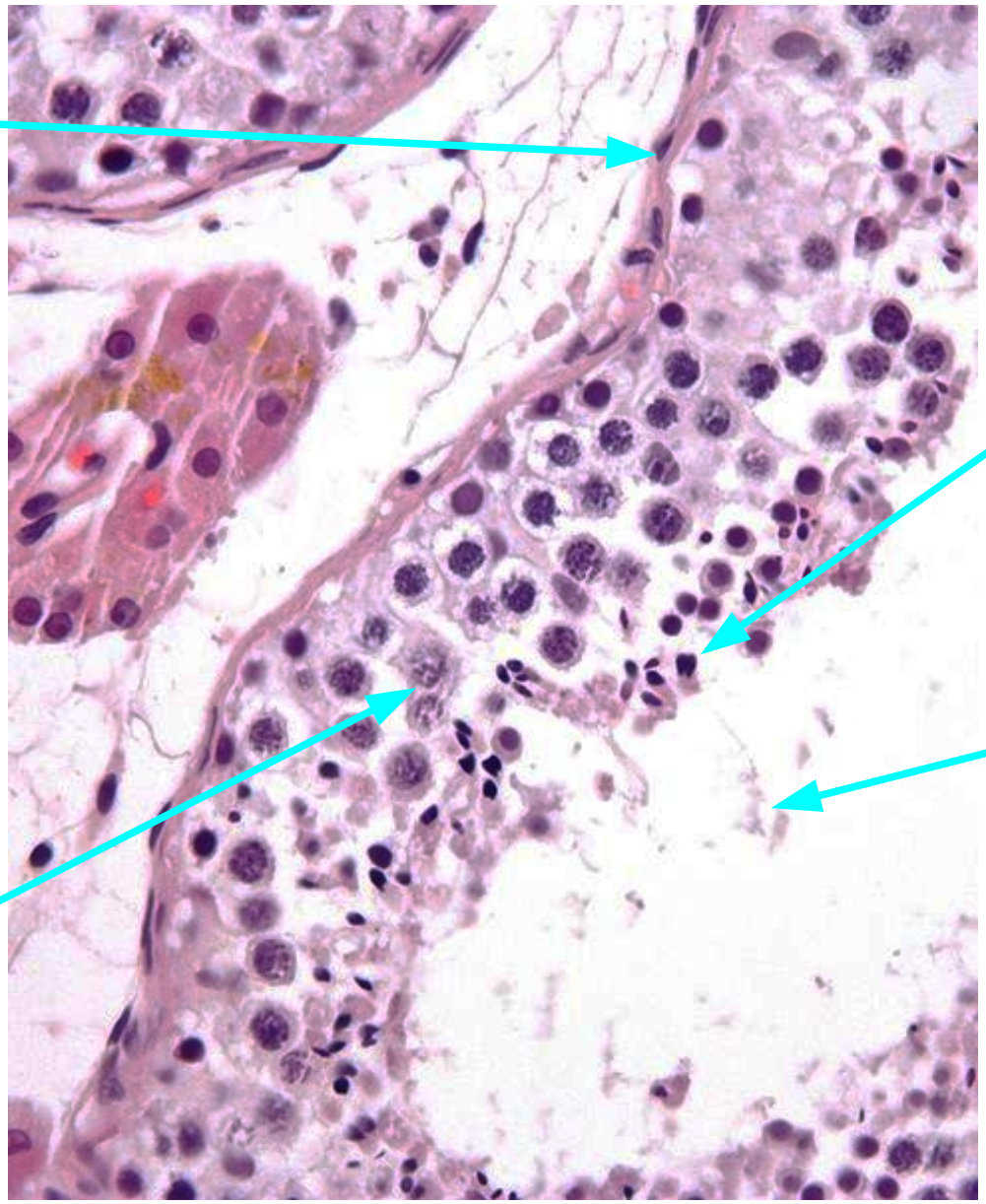
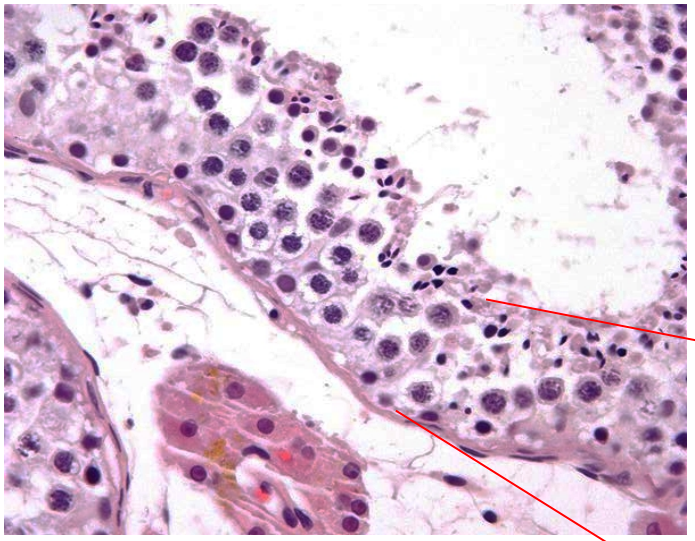
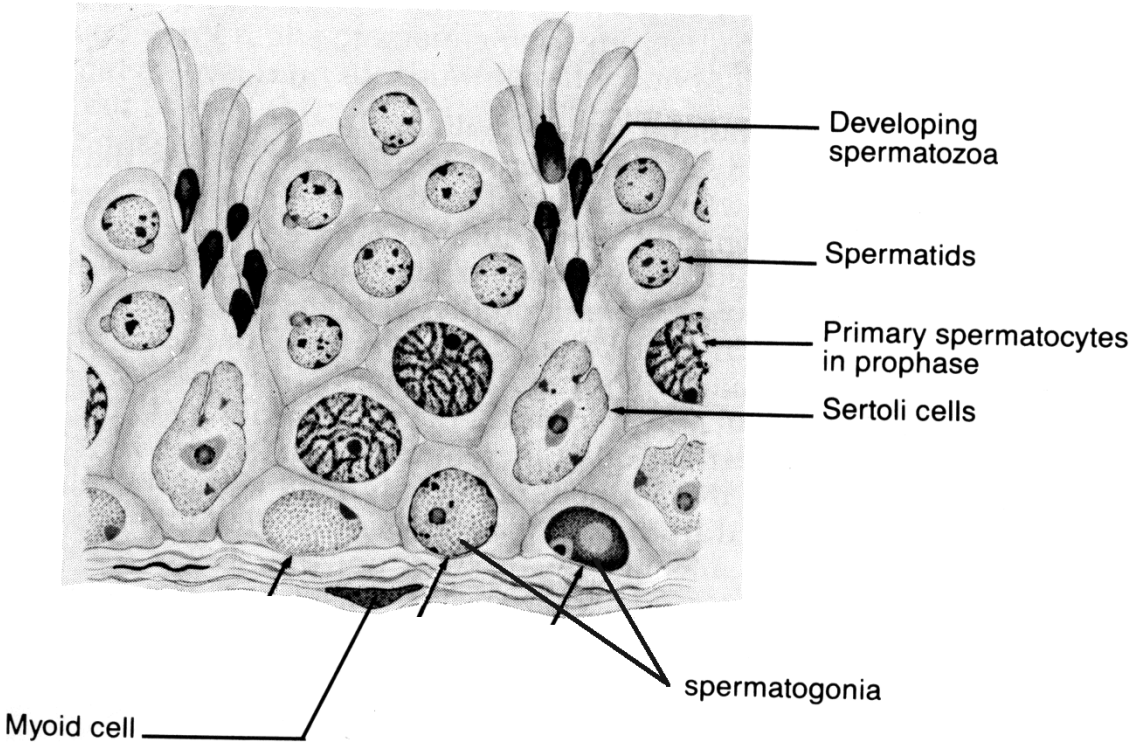


Image credit: 'Nephron': Wikimedia commons

Cross section of seminiferous tubules





NB- don't worry about cell names now – I'll explain them soon & show the slide again

Spermatogenesis

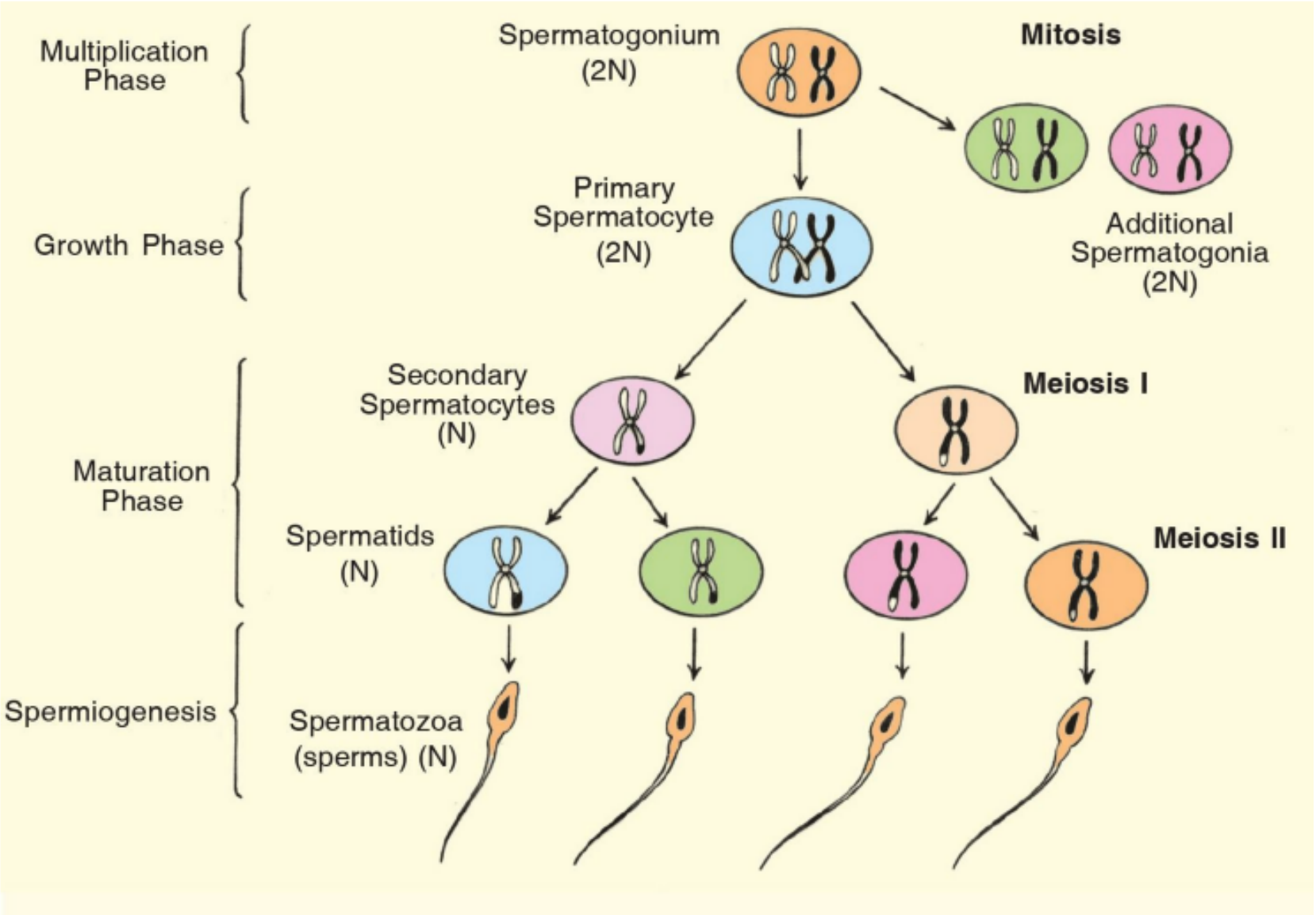
- Proliferation of germ line stem cells by mitosis
- Reduction to haploid state by meiosis
- Differentiation into mature spermatozoa.

Mitotic Proliferation.

- Begins at puberty
- Produces (at your age) about 10,000 sperm *per second*!

- Typically about 10^8 sperm / ml of semen.

  (<$2x10^7$ classified as subfertility)



Daughters of spermatogonium division are cross-linked with cytoplasmic bridges to share metabolism.

Image credit: Dharmendra Gaur, Public Domain, drgpbiology.com

Mitotic proliferation takes place in the *basal* side of the tubule (the side furthest from the lumen).

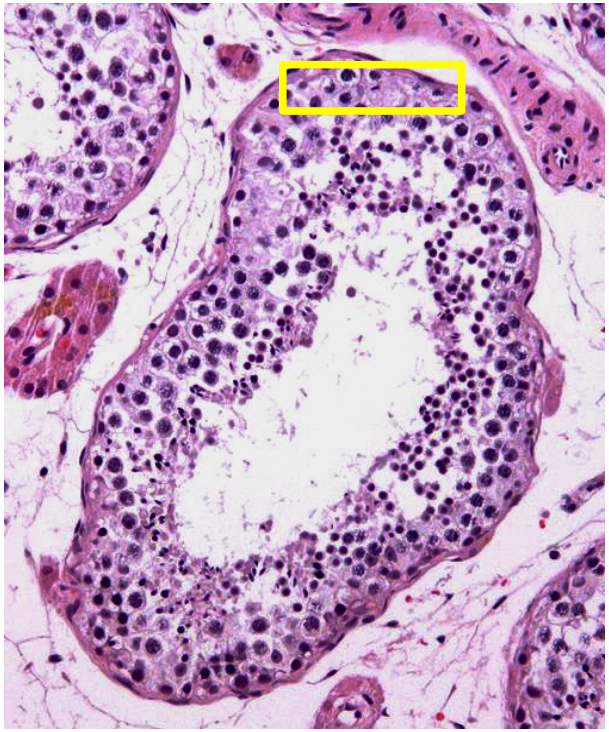
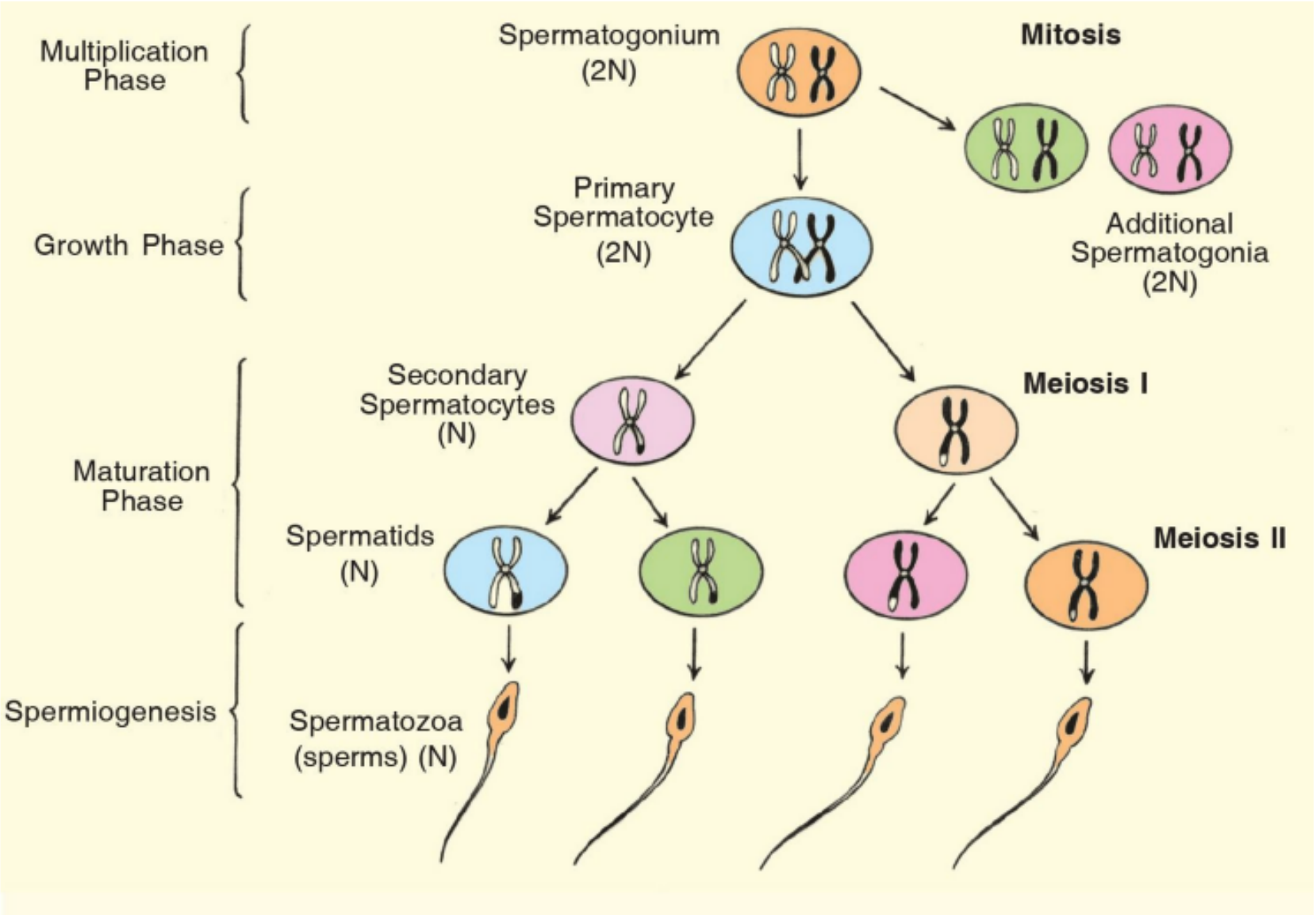


Image credit: 'Nephron': Wikimedia commons



Daughters of spermatogonium division are cross-linked with cytoplasmic bridges to share metabolism.

Image credit: Dharmendra Gaur, Public Domain, drgpbiology.com

Hormonal inputs

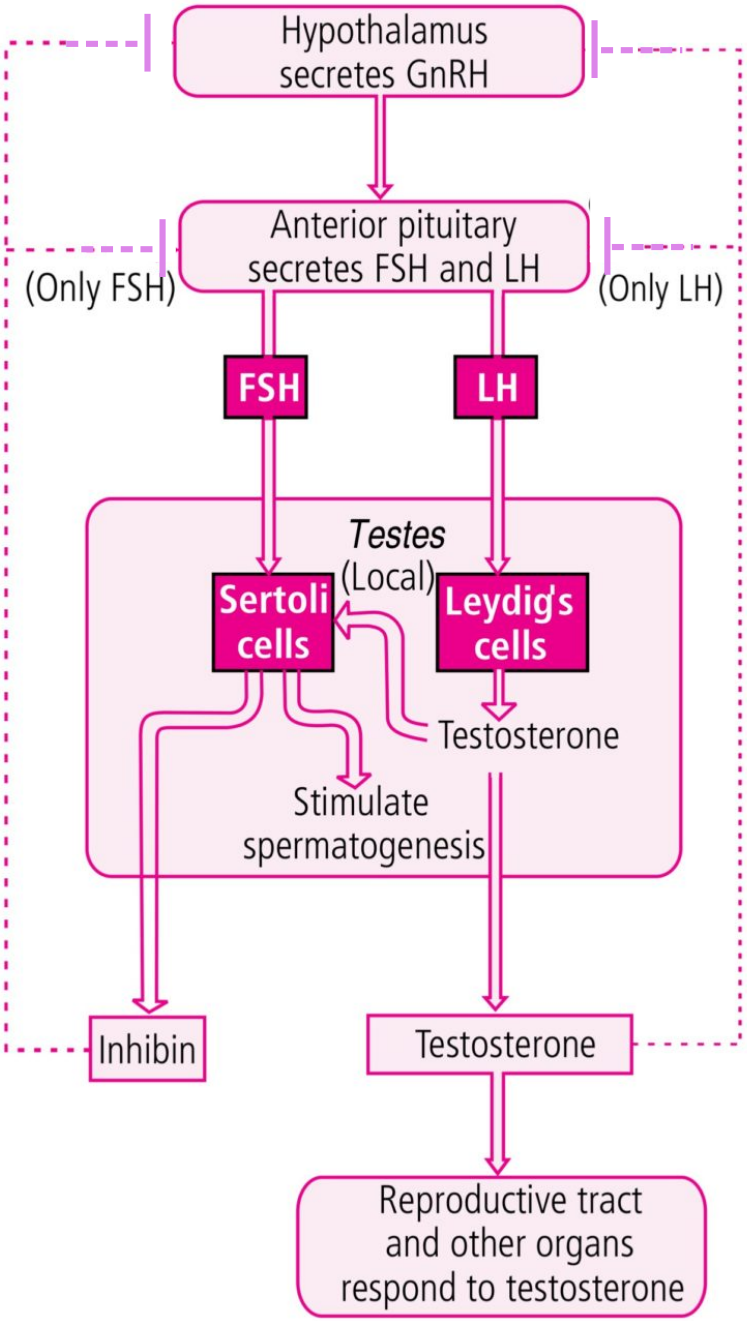
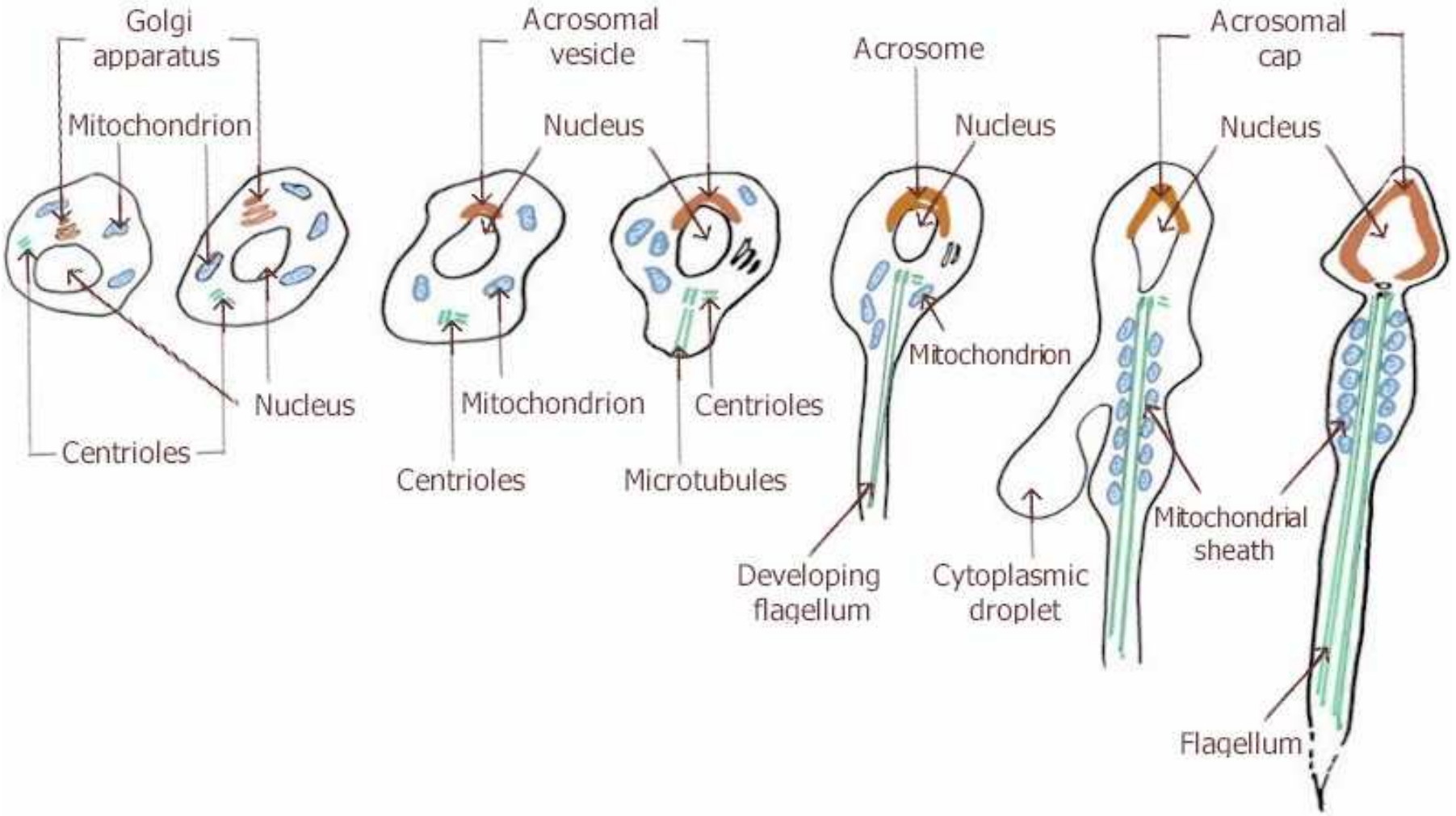


Image credit: Dharmendra Gaur, Public Domain, drgpbiology.com



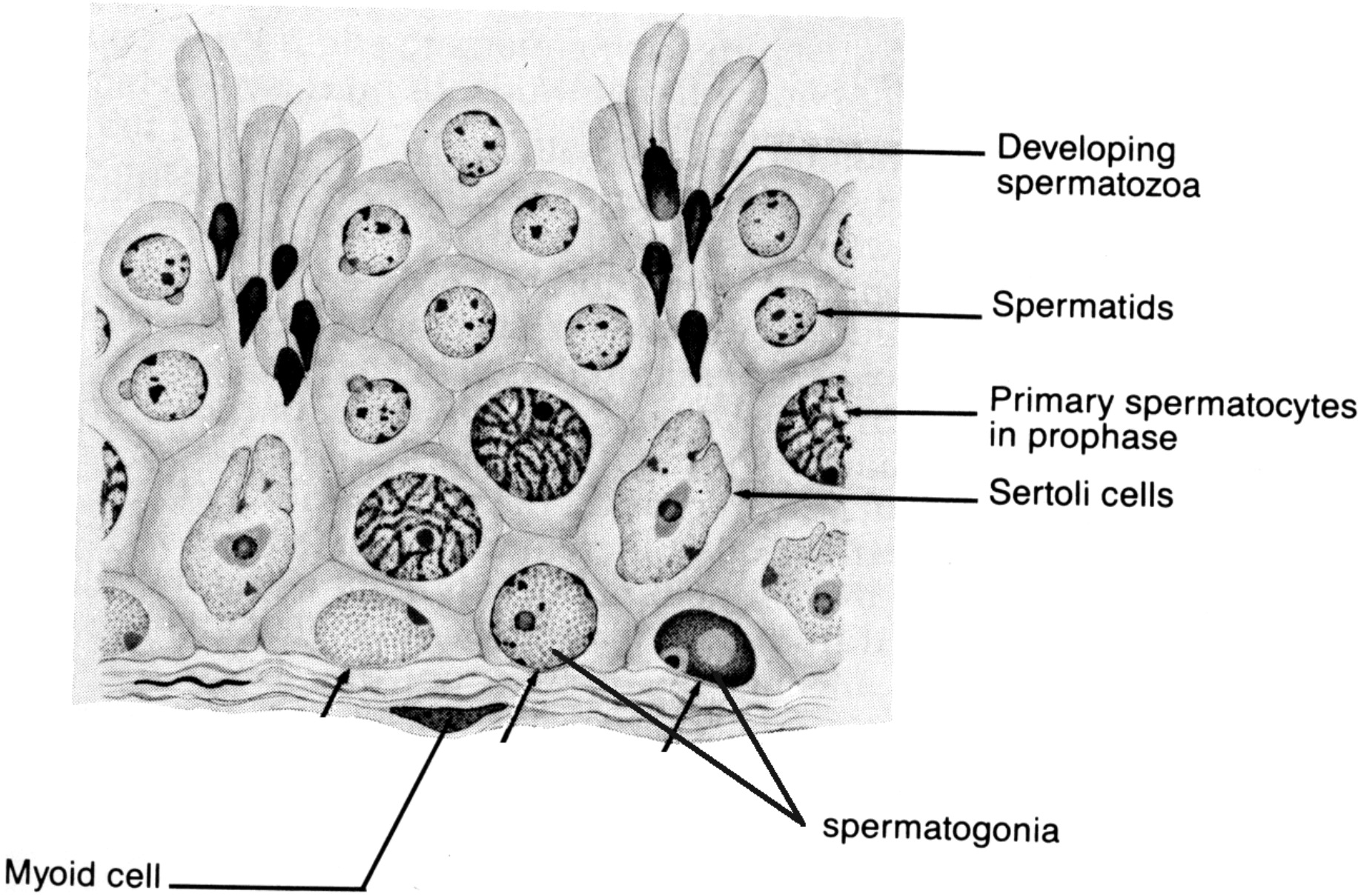


Image credit: US Govt, public domain (via Wikimedia Commons)

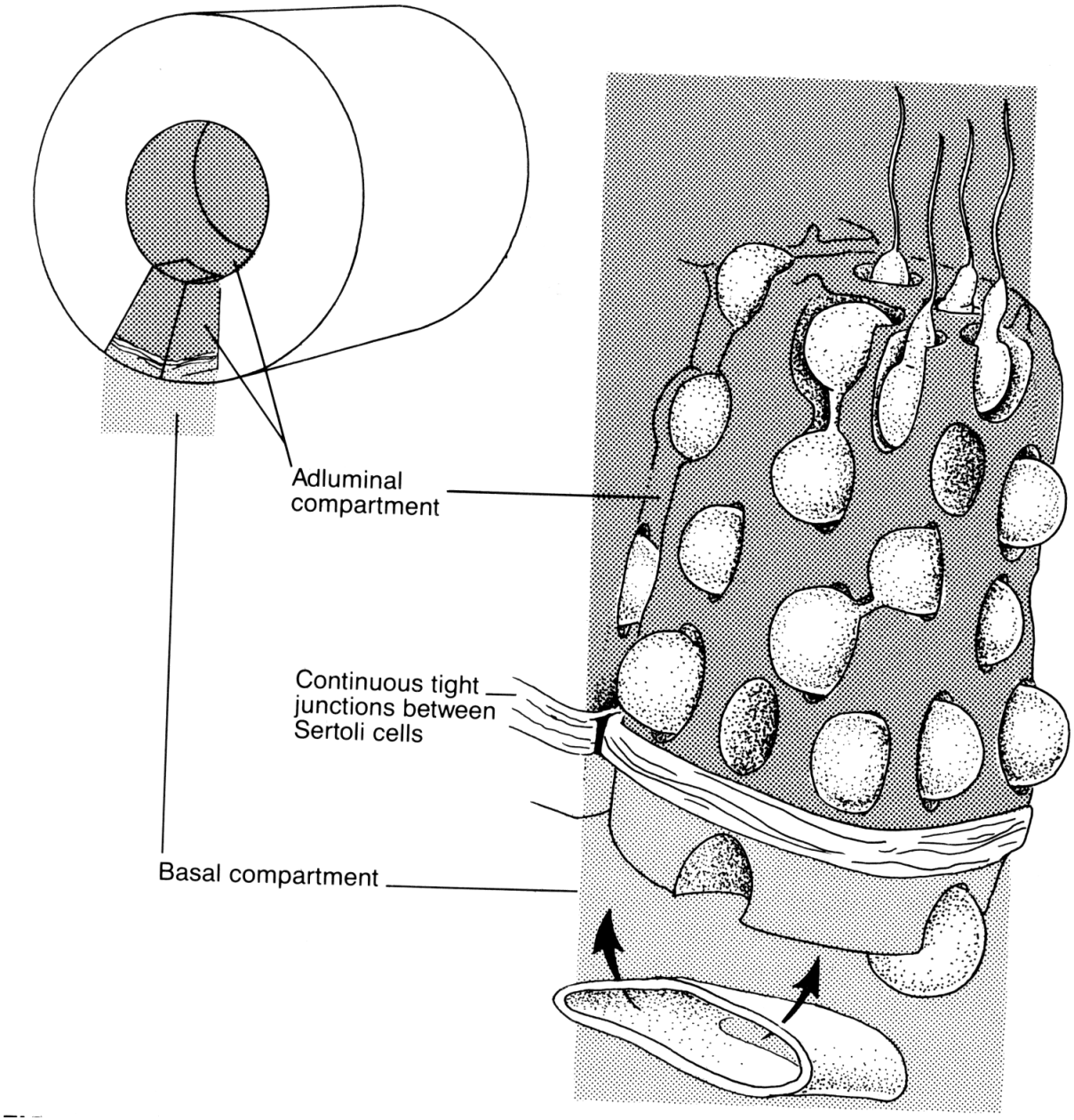


Image credit: US Govt, public domain (via Wikimedia Commons)

Orch- = prefix for testis (*Gk.*)

- eg **orch**itis, **orchid**ectomy, cryp**orchid**ism etc.

(associated with increased risk of testicular cancer – see last slide for info on examination)

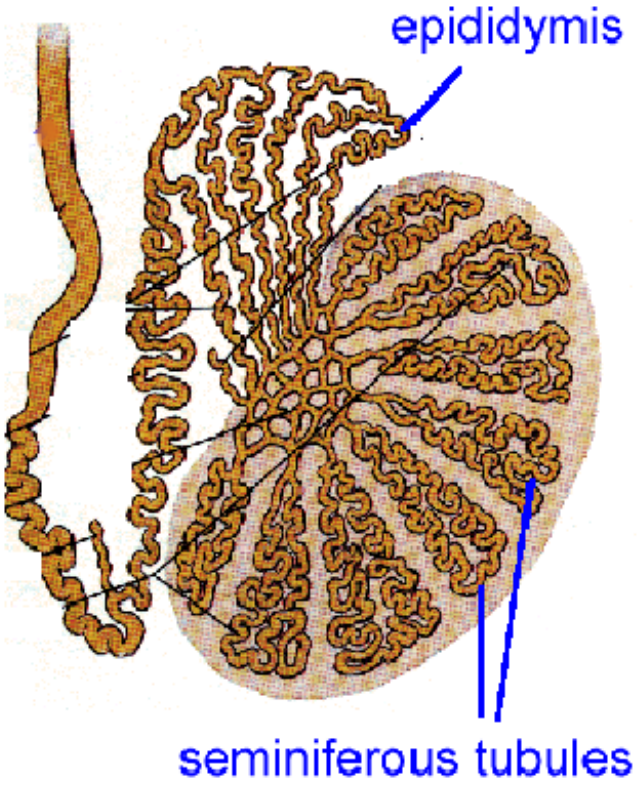
This is an orchid (flower)

Maturation of sperm

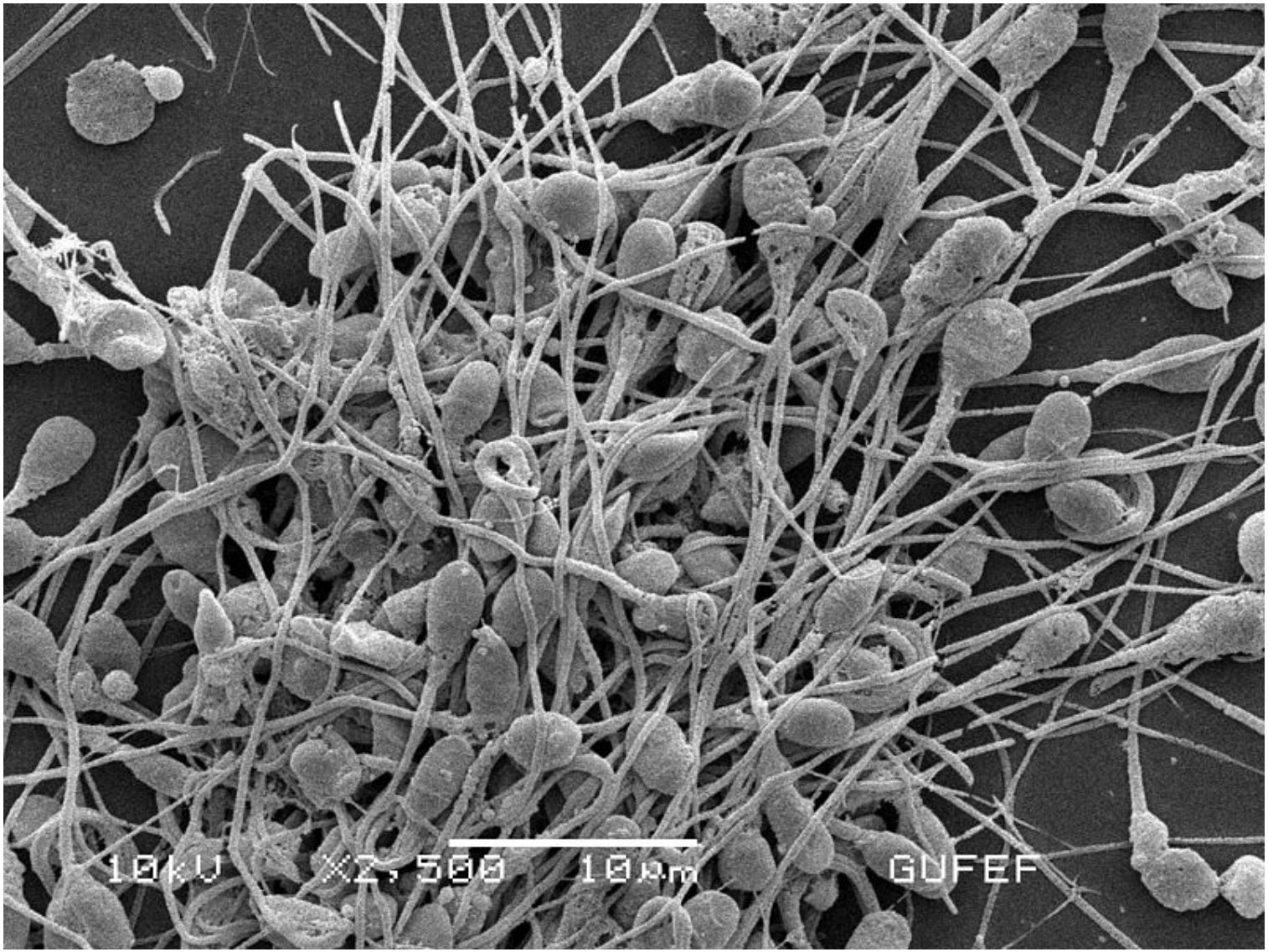
Sperm are shed and flow to the epididymis

The epididymis alters the seminal fluid

Epididymal secretions (glycoproteins etc) activate sperm and make them capable of swimming

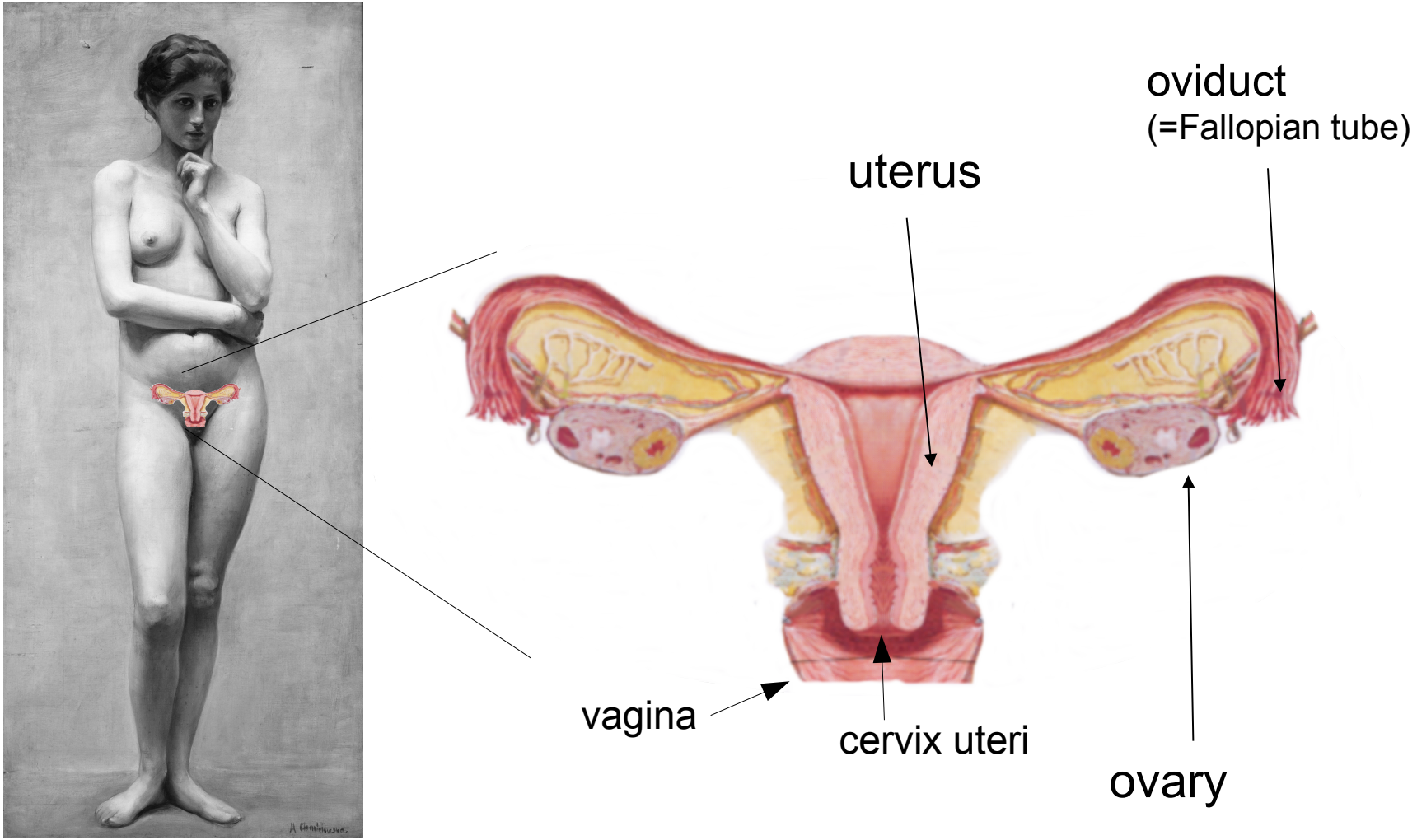


A scanning electron micrograph of sperm



Oogenesis

The ovaries, oviducts & uterus



Images: Maria Chmielowska (oil on canvas, 1895, public domain), overlain with Netter anatomical diagram.

UNLIKE men, adult women have no germ line stem cells

Recent data: they may have oogonial stem cells, but for some reason they do not do anything, so functionally there are no relevant germ-line stem cells.

- Mitosis to bulk up numbers
- Entrance into meiosis
- Pause (for 12-50 years)
- Completion of meiosis

foetal life

childhood

from menarche to menopause

Rate of female gamete production – 13/yr

(compare male – 150,000,000,000 /yr)

The primordial follicle (c. 500,000 in a girl's or young woman's ovaries: source - Macklon NS, Fauser BC. Follicle development during the normal menstrual cycle. Maturitas. 1998 Oct 12;30(2):181-8. doi: 10.1016/s0378-5122(98)00072-3. PMID: 9871911.)

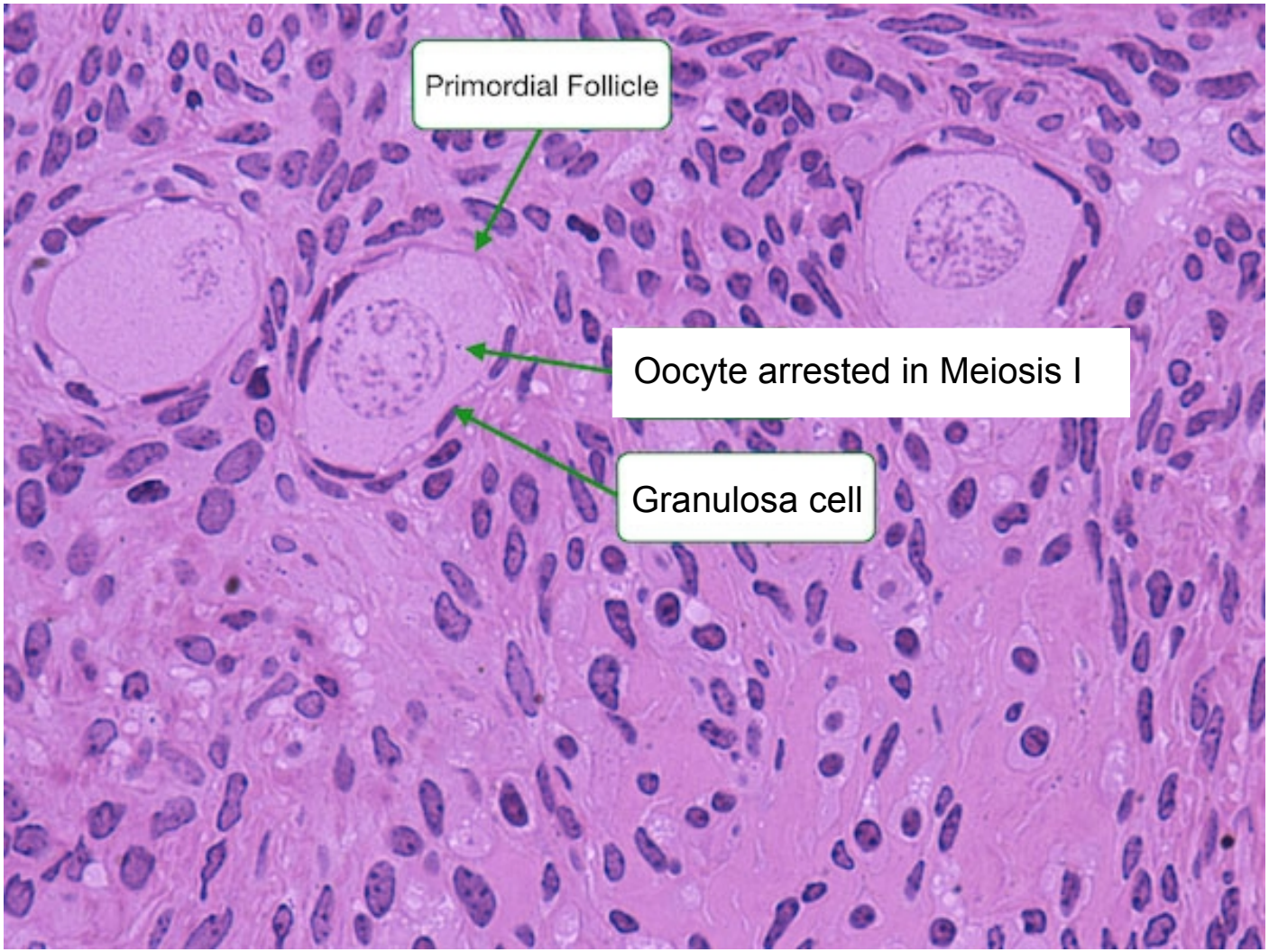
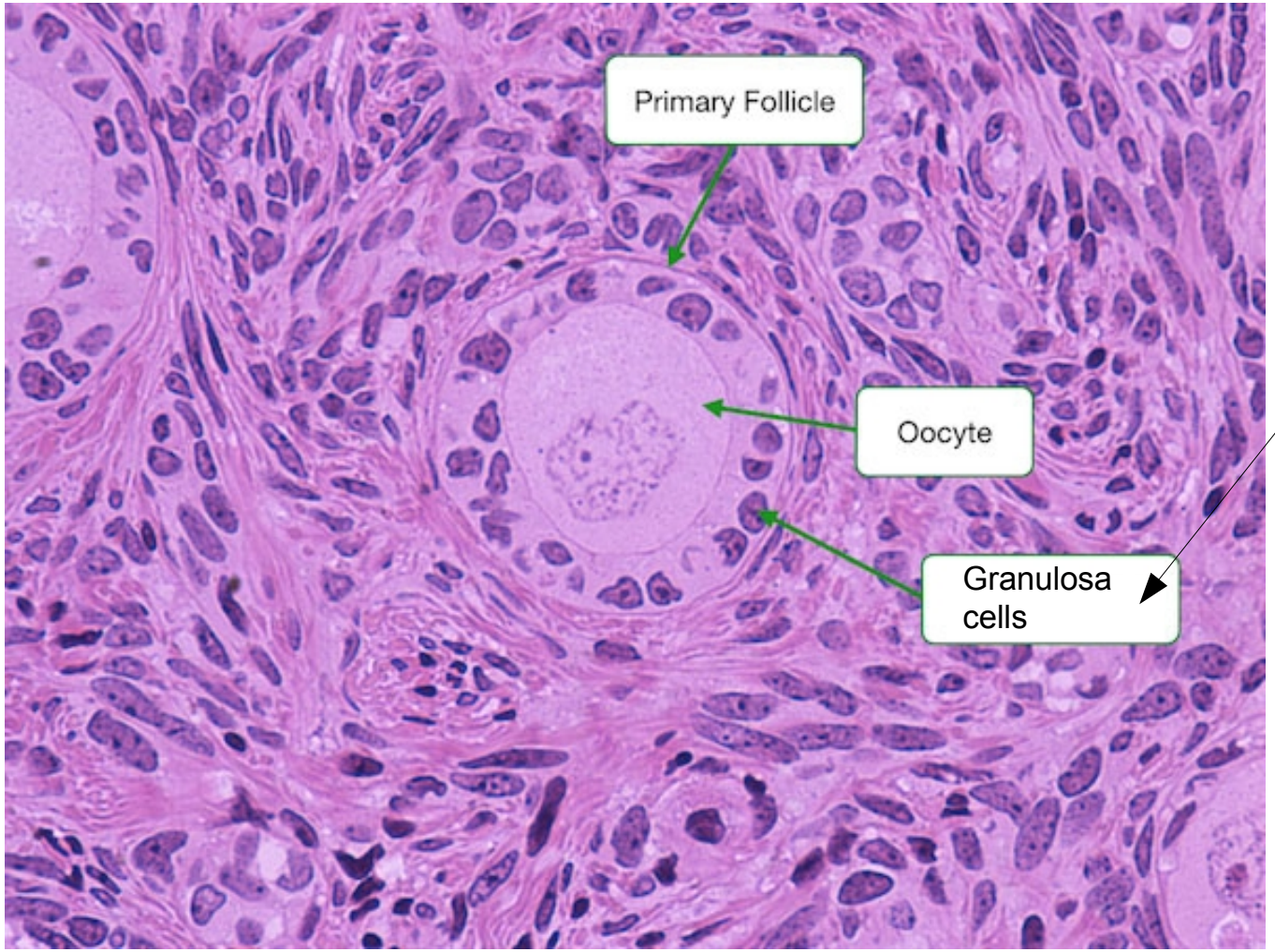


Image credit: Yale University, Pub Dom, via http://medcell.med.yale.edu/histology

A few primordial follicles a day commence further development throughout the woman's reproductive life.

Primary follicle

During this phase (about 85 days), oocyte grows and synthesises rRNA and mRNA. It does *not* progress further through meiosis.

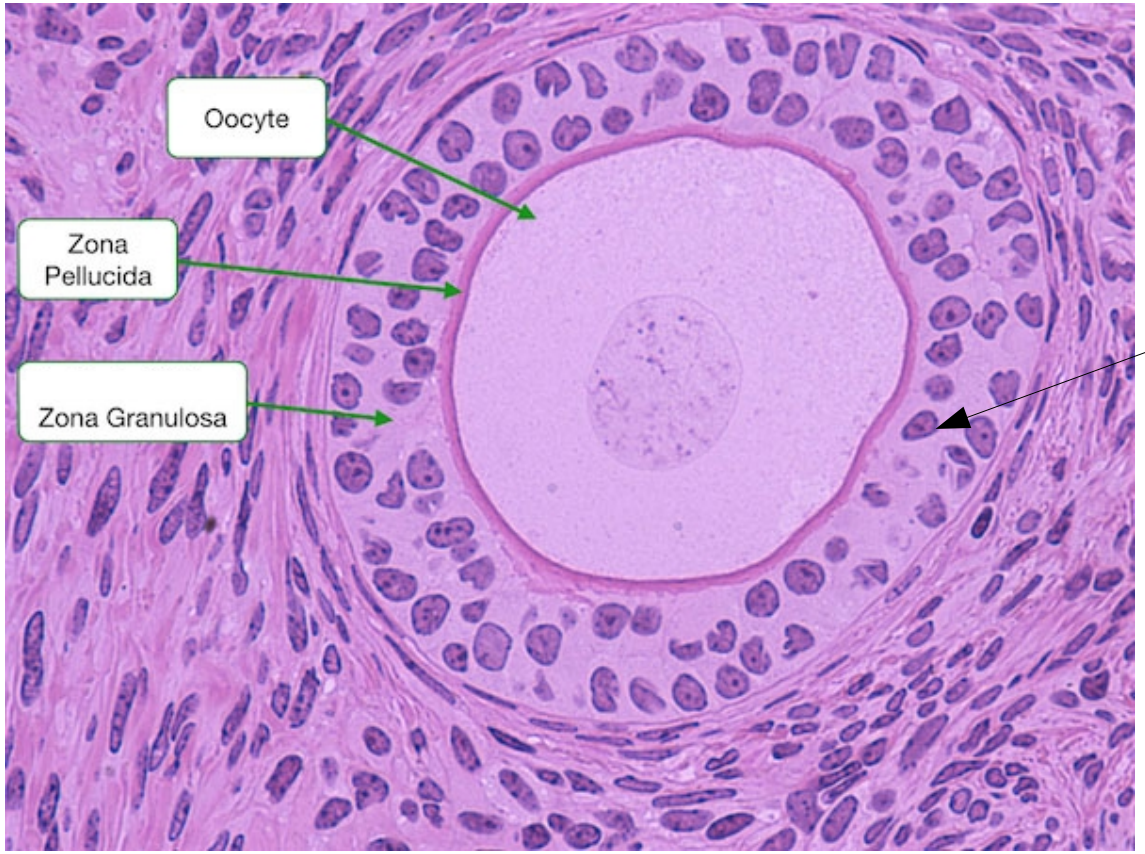


linked by cytoplasmic bridges.

Image credit: Yale University, Pub Dom, via http://medcell.med.yale.edu/histology

Ripening follicle

During this phase (10 days), the oocyte synthesises a glycoprotein zona pellucida, and granulosa cells multiply.



linked by cytoplasmic bridges.

Image credit: Yale University, Pub Dom, via http://medcell.med.yale.edu/histology

Next, granlulosa cells secrete follicular fluid that form the fluid-filled "antrum"

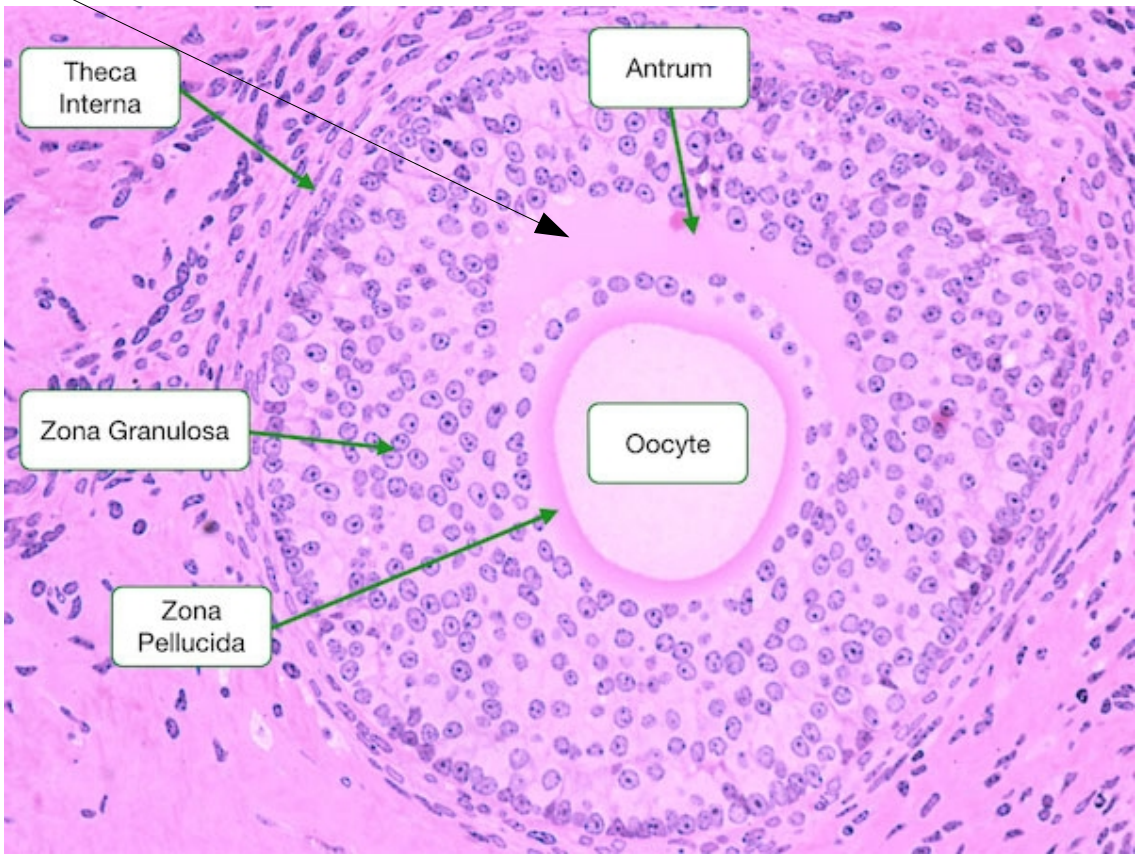
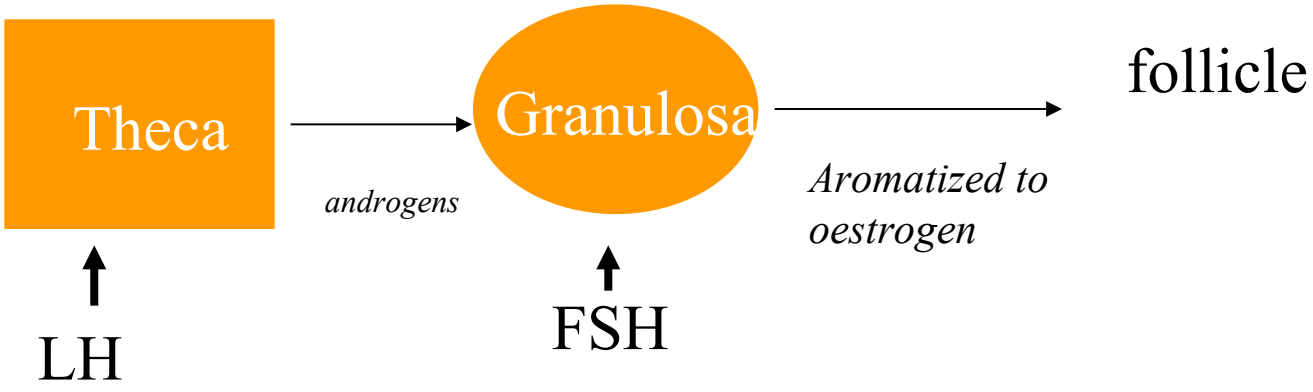


Image credit: Yale University, Pub Dom, via http://medcell.med.yale.edu/histology

At this stage (formation of antrum), the Theca gains LH receptors and the Granulosa cells gain receptors for FSH



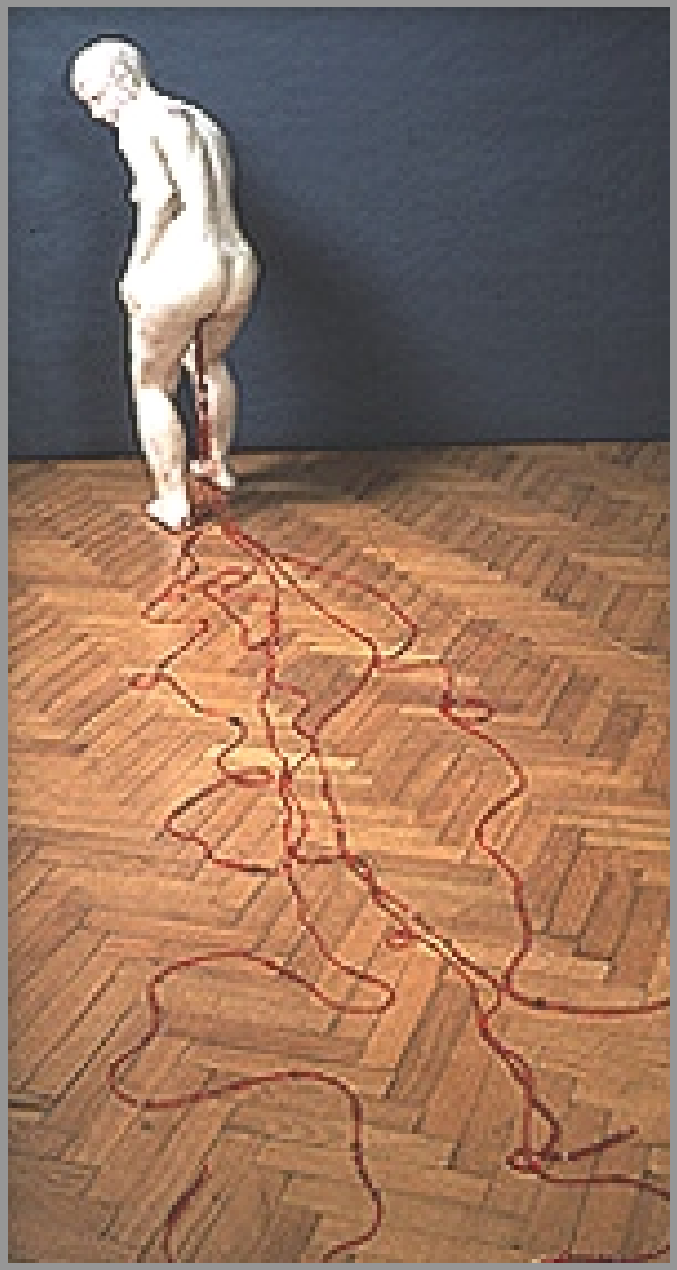
Together, they activate hormone secretion from the follicle.

The early antral stage is a ‘make-or-break’ time for each follicle.

It’s survival depends on adequate stimulation by FSH.

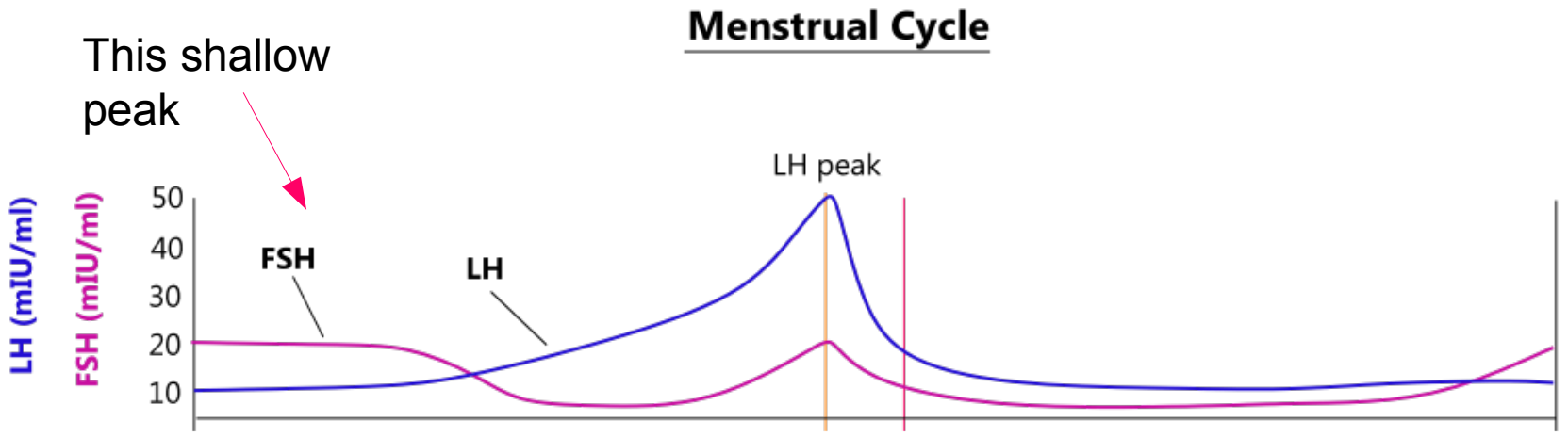
The menstrual cycle

menstrual cycle: *a process that is repeated ova and ova again* (R Saunders)

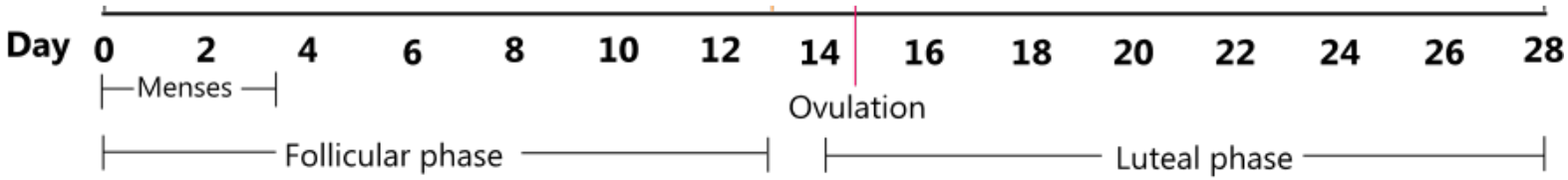


Installation art: Kiki Smith "*train*"

This shallow peak

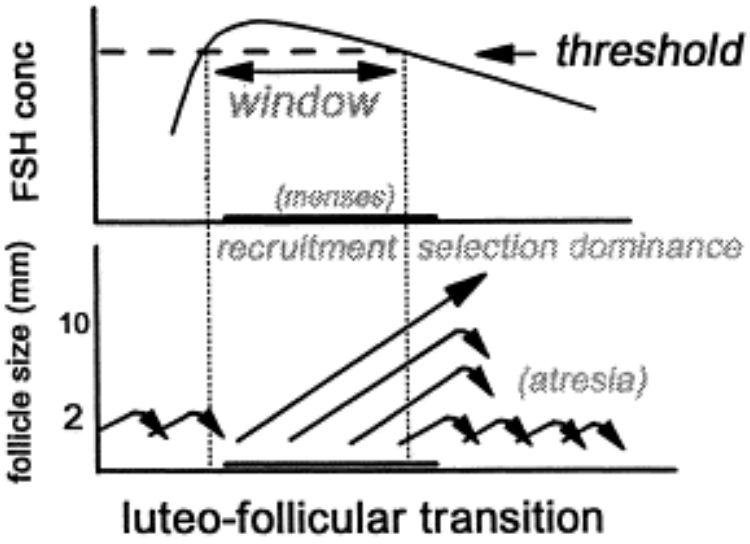


(other hormones blanked out for now)



Human follicle development

- FSH threshold/window concept -



The intercycle rise in serum follicle stimulating hormone (FSH) concentrations exceeds the threshold for recruitment of a cohort of follicles for further development. The number of follicles recruited is determined by the time (`window') in which the serum FSH is above the threshold at which recruitment occurs.

Source of figure: Macklon NS, Fauser BC. Follicle development during the normal menstrual cycle. Maturitas. 1998 Oct 12;30(2):181-8. doi: 10.1016/s0378-5122(98)00072-3. PMID: 9871911.

If it does receive enough FSH, the antral follicle matures further to become a Graafian follicle at the surface of the ovary.

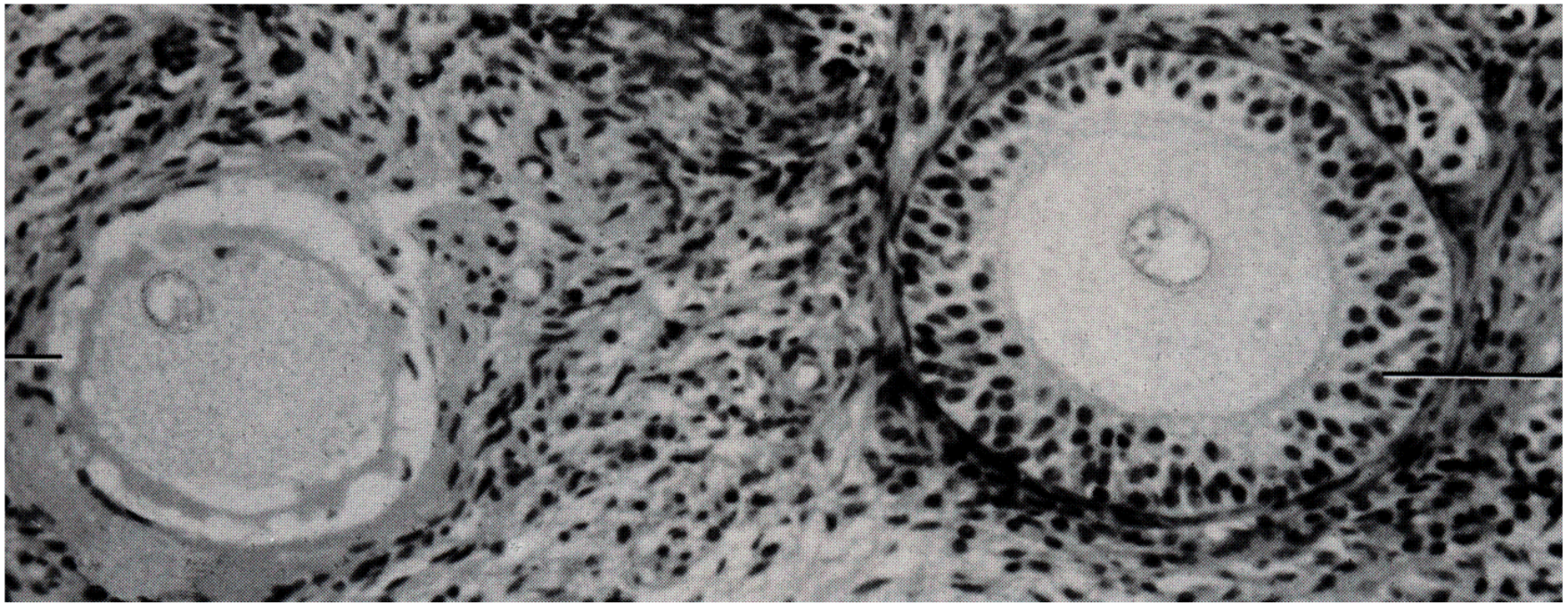
This makes it more sensitive to FSH, and makes it signal back to the pituitary, with oestrogen to reduce FSH levels.

Falling FSH levels prevent recruitment of further follicles in that cycle, but with increased sensitivity the dominant ('winning') follicle still has enough FSH stimulation even with lower serum levels.

>>> (Usually) only one follicle matures.

Drugs that block oestrogen detection by the pituitary drive higher and longer duration production of endogenous FSH, and more follicles to mature.

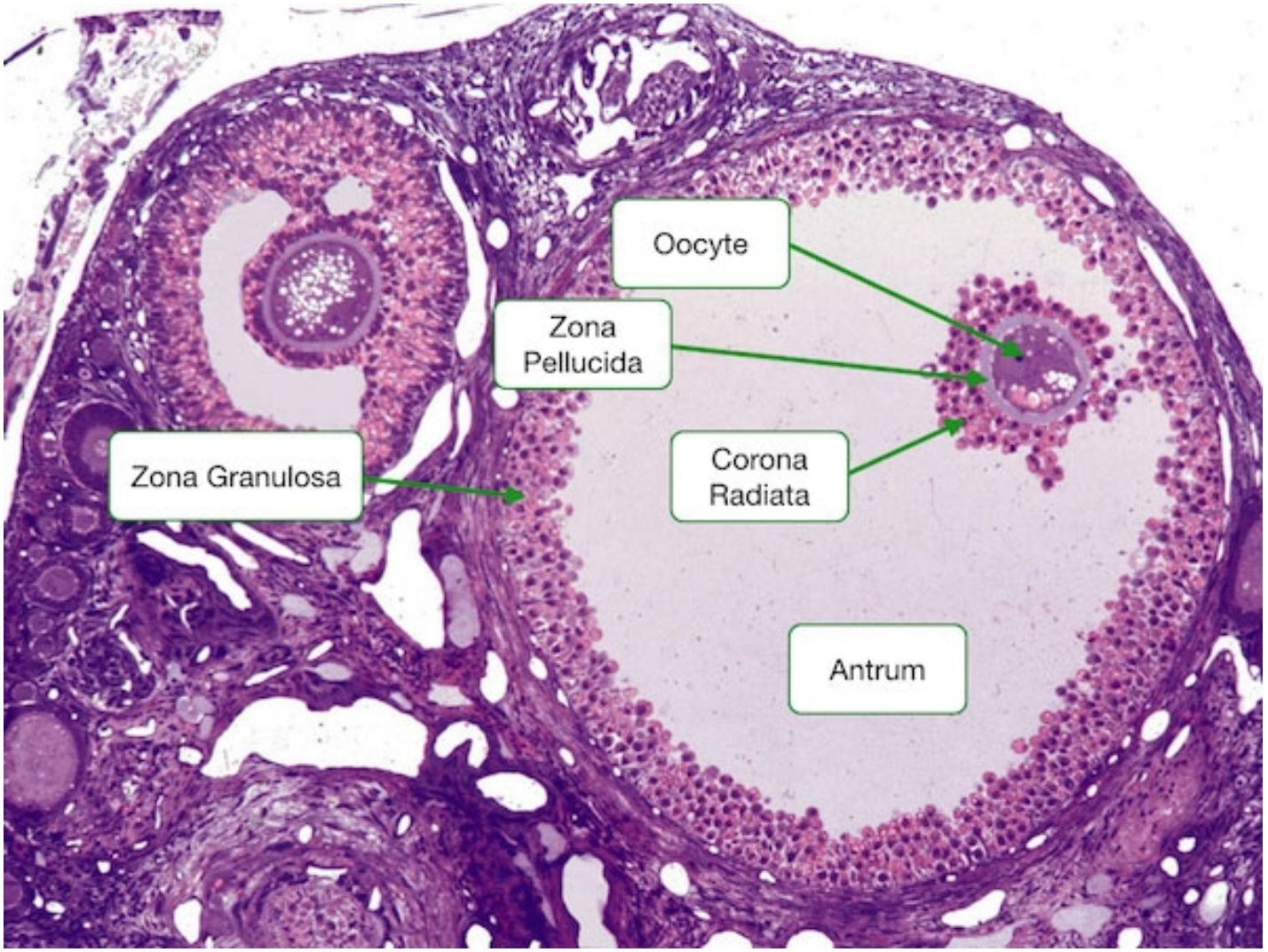
Follicles that do not get the FSH surge when they need it die (‘atresia’)

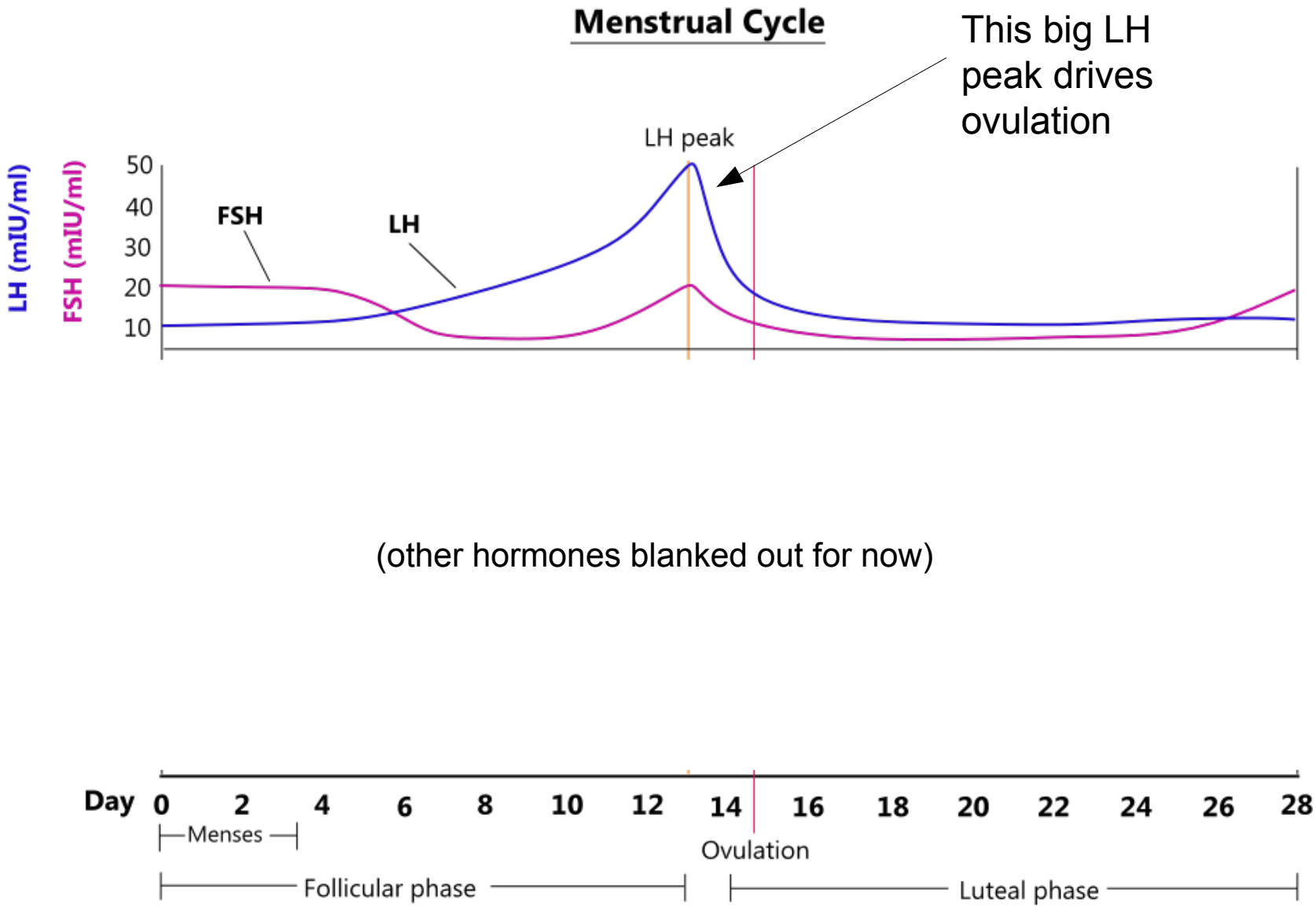


Atretic (from “atresia” - withering)

Normal

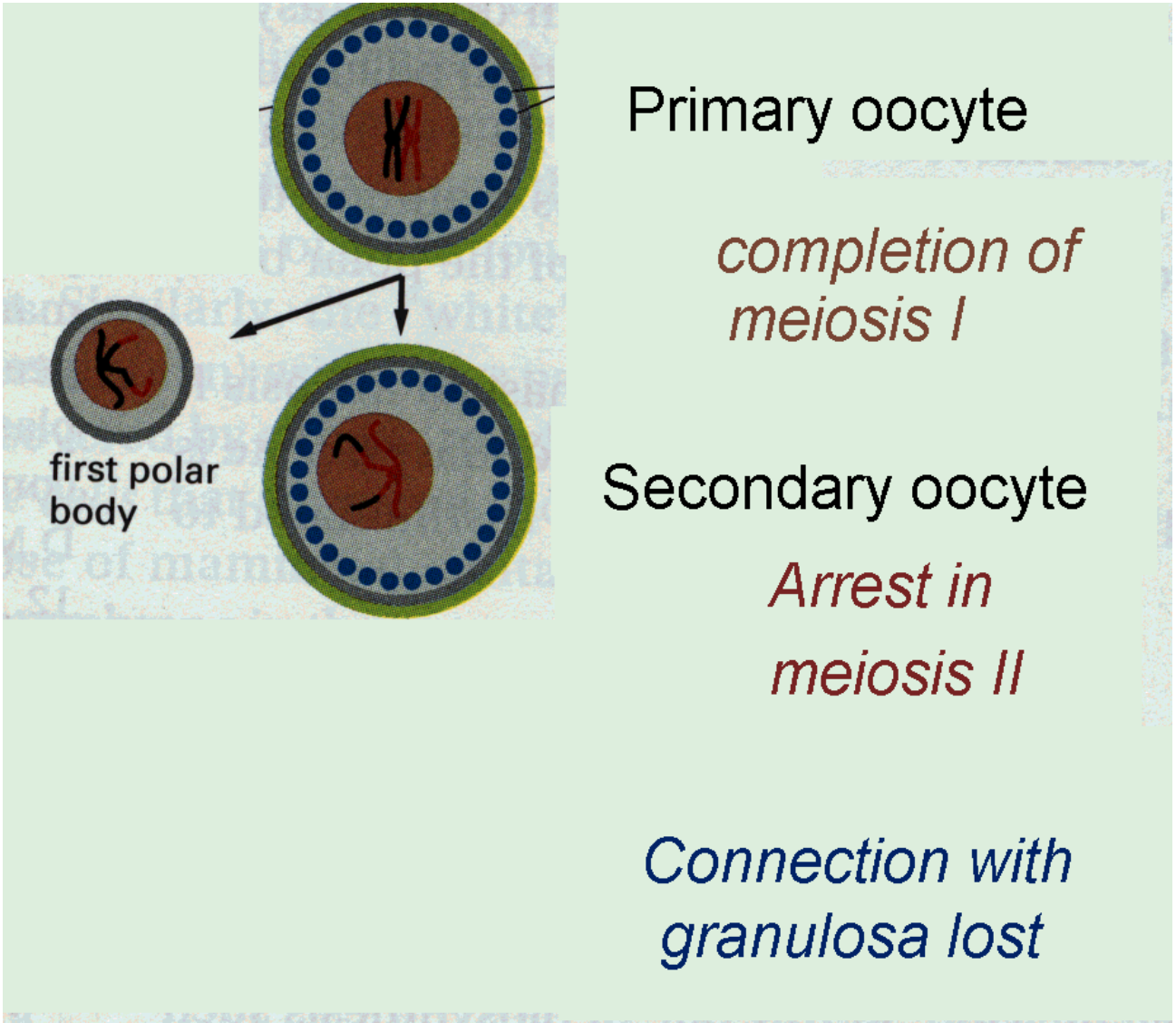
Maturing Follicle ("late antral stage")





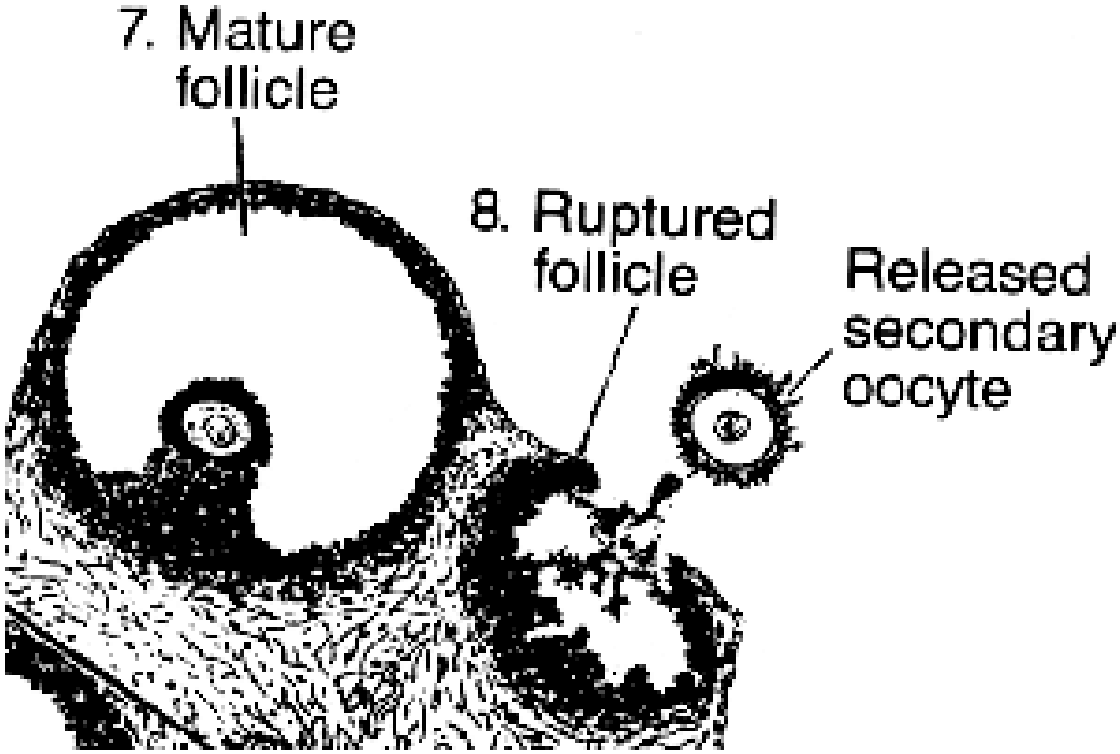
(other hormones blanked out for now)

Preovulatory growth following LH surge



Takes only about 12h

Then the mature oocyte digests its way out of the edge of the ovary;



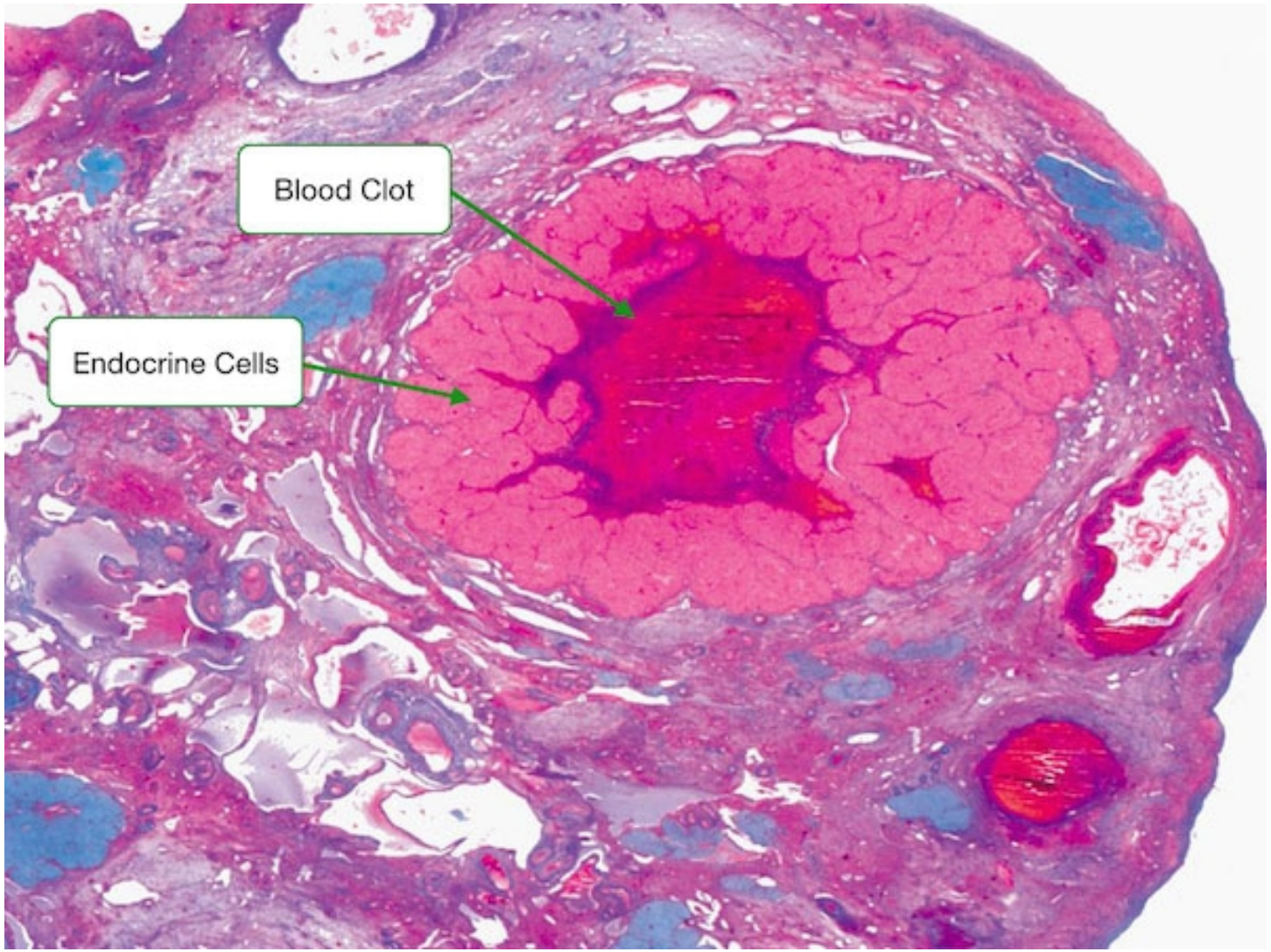
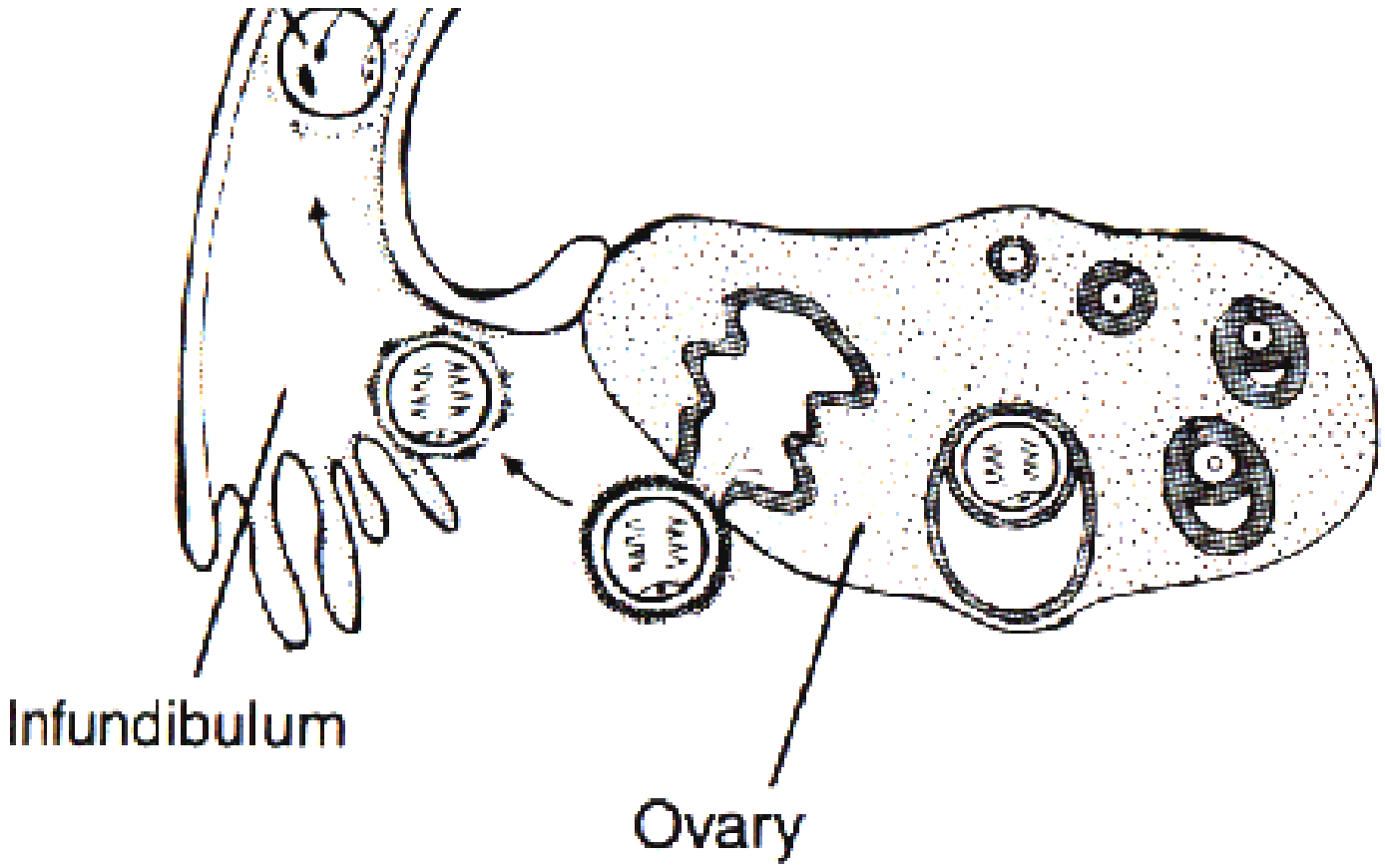


Image credit: Yale University, Pub Dom, via http://medcell.med.yale.edu/histology

And enters the fallopian tube;

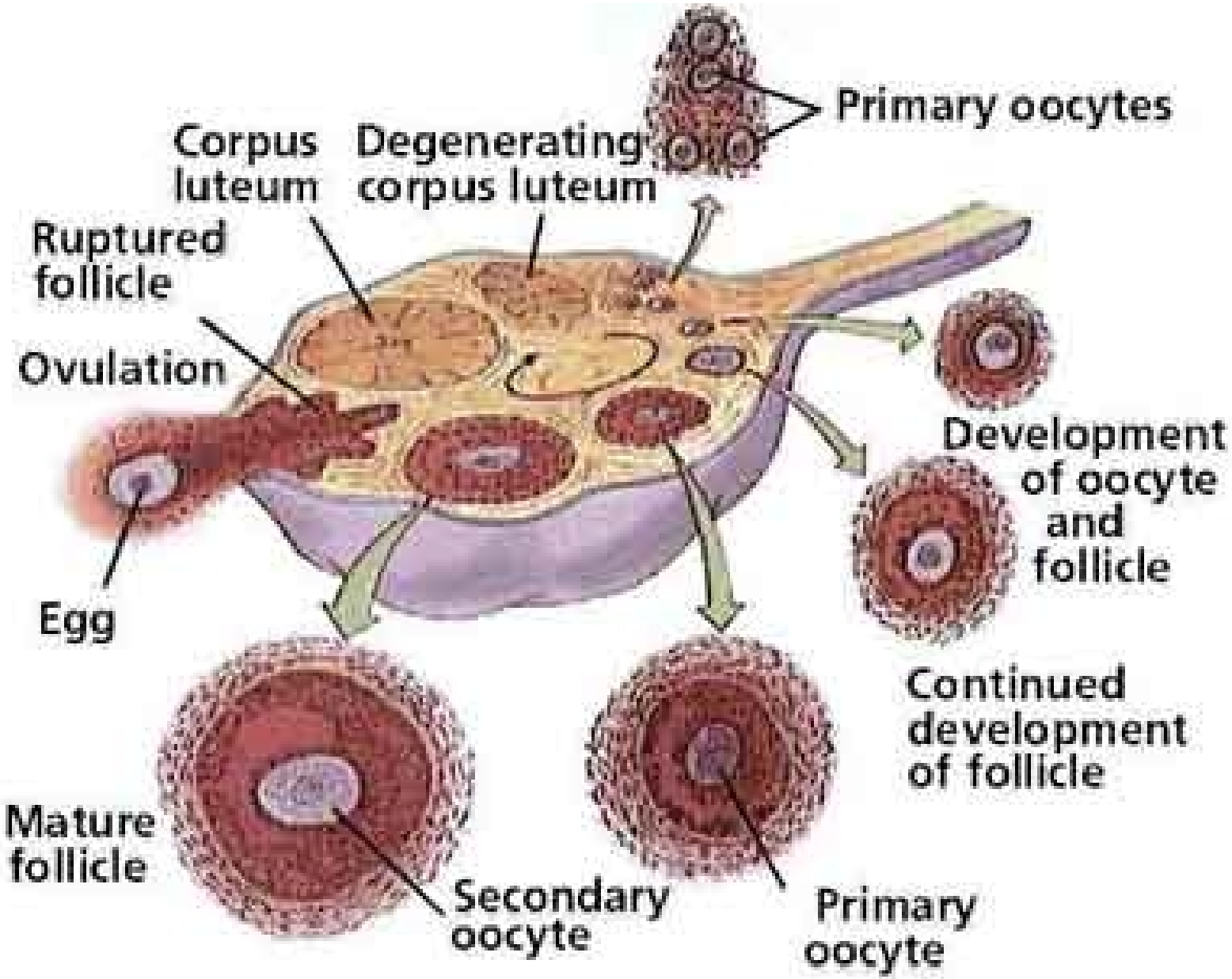


Meiosis II is never completed unless fertilization happens (see next lecture)

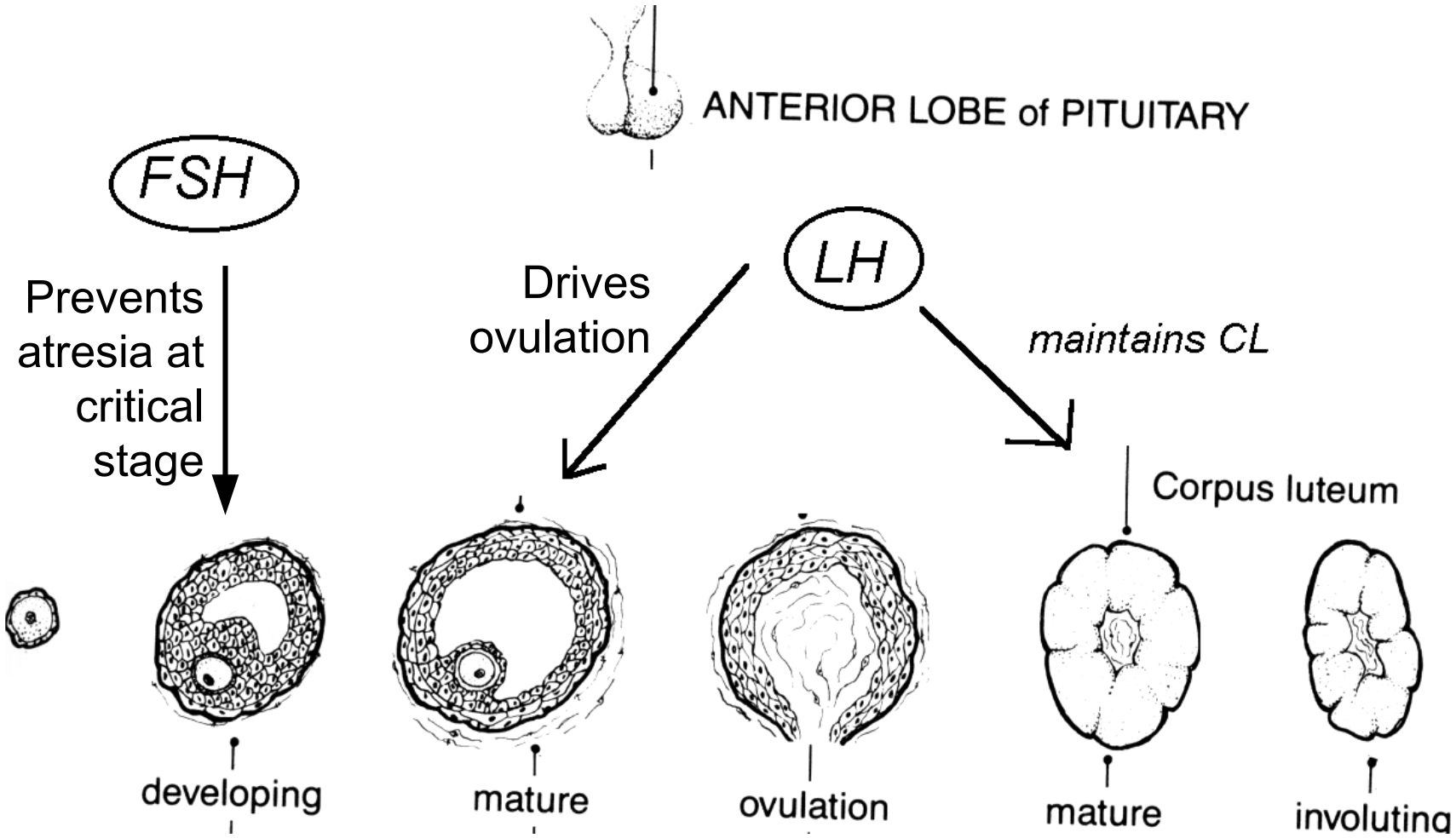
The remains of the ruptured follicle become the corpus luteum.

The Corpus luteum produces hormones (progesterone, oestrogen) that prepares the lining of the uterus to receive an embryo

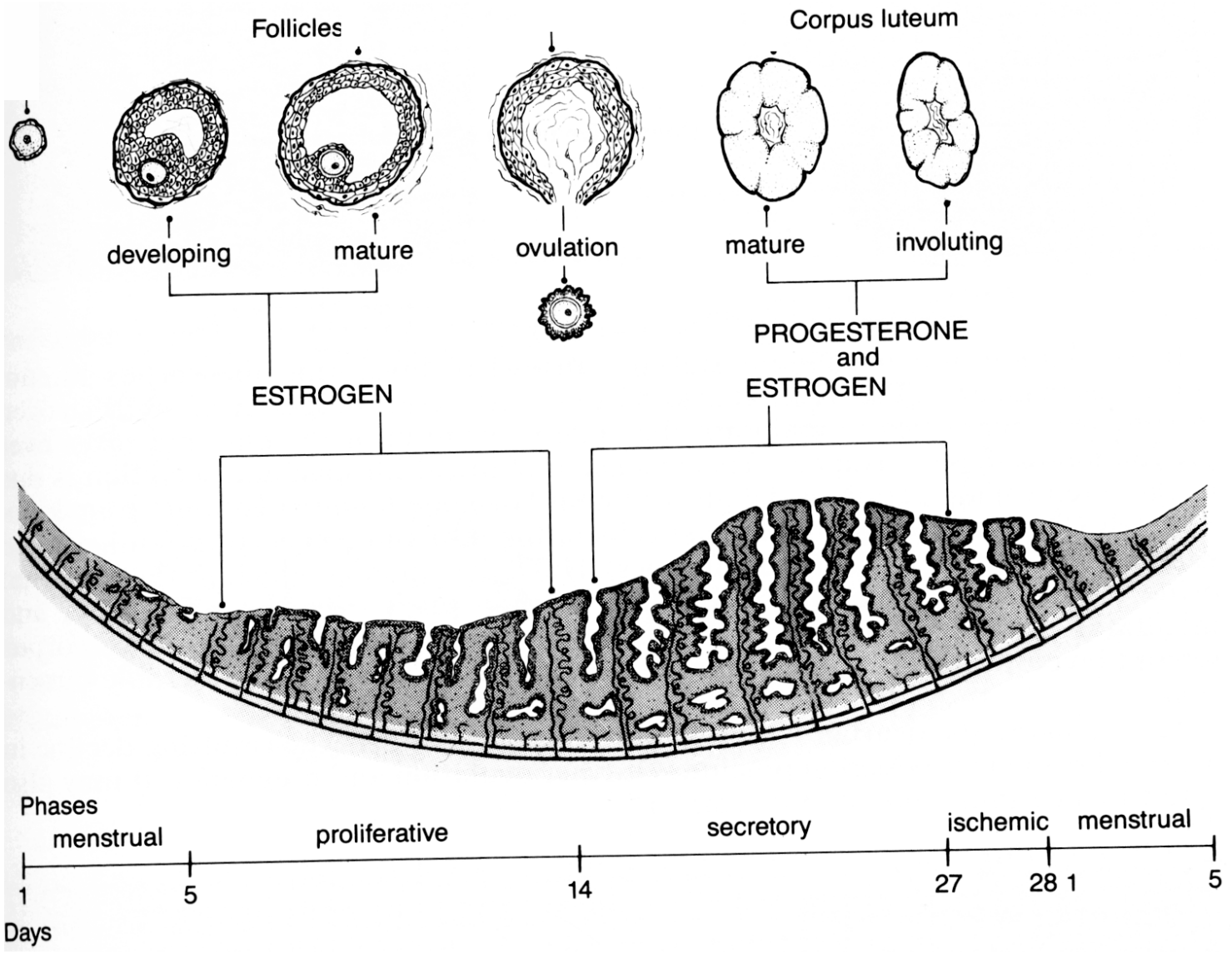
Unless the woman is pregnant, the CL dies after a week or so.

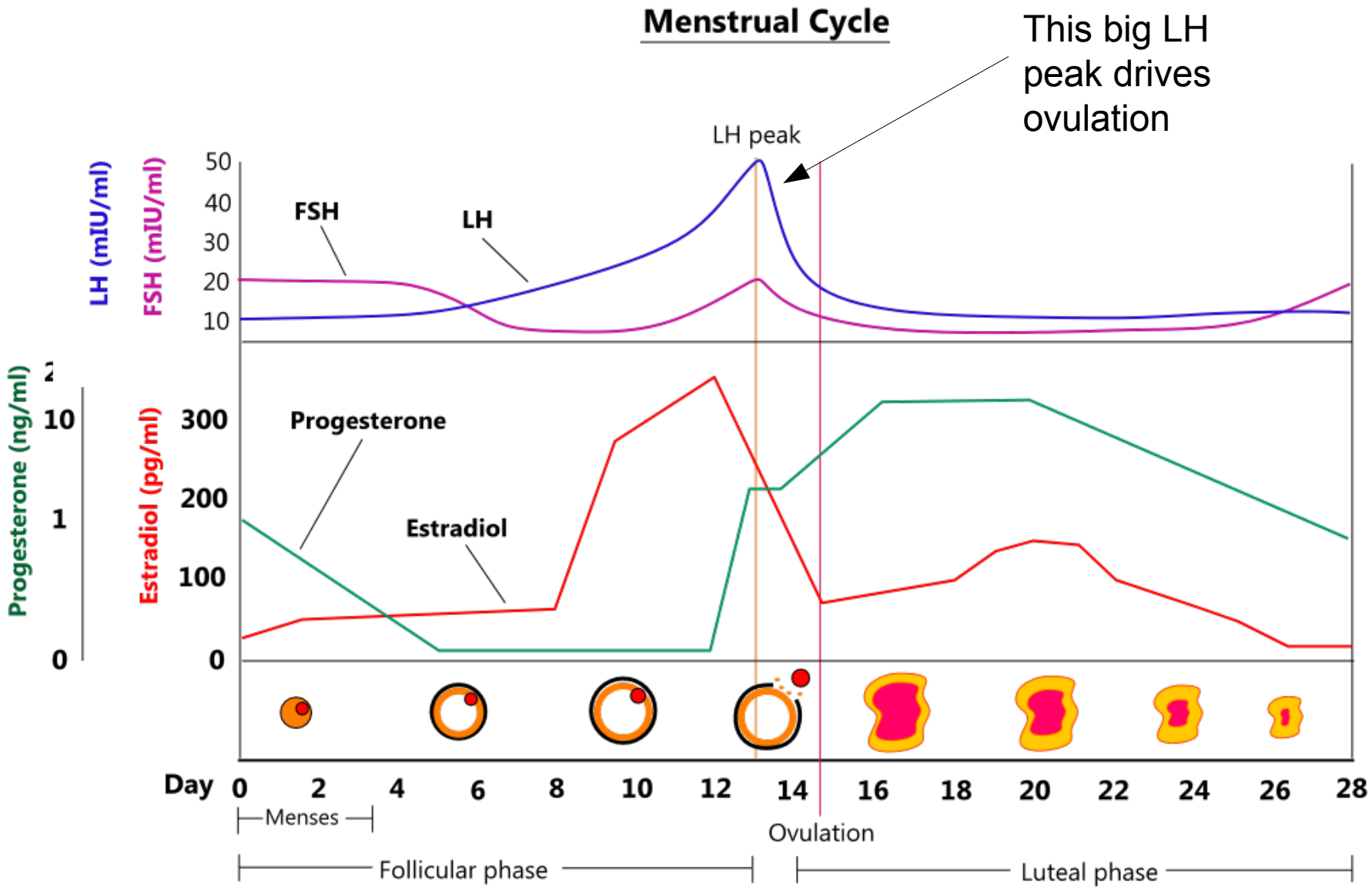

Primary oocytes
Corpus luteum
Degenerating corpus luteum
Ruptured follicle
Ovulation
Egg
Development of oocyte and follicle
Continued development of follicle
Mature follicle
Secondary oocyte
Primary oocyte

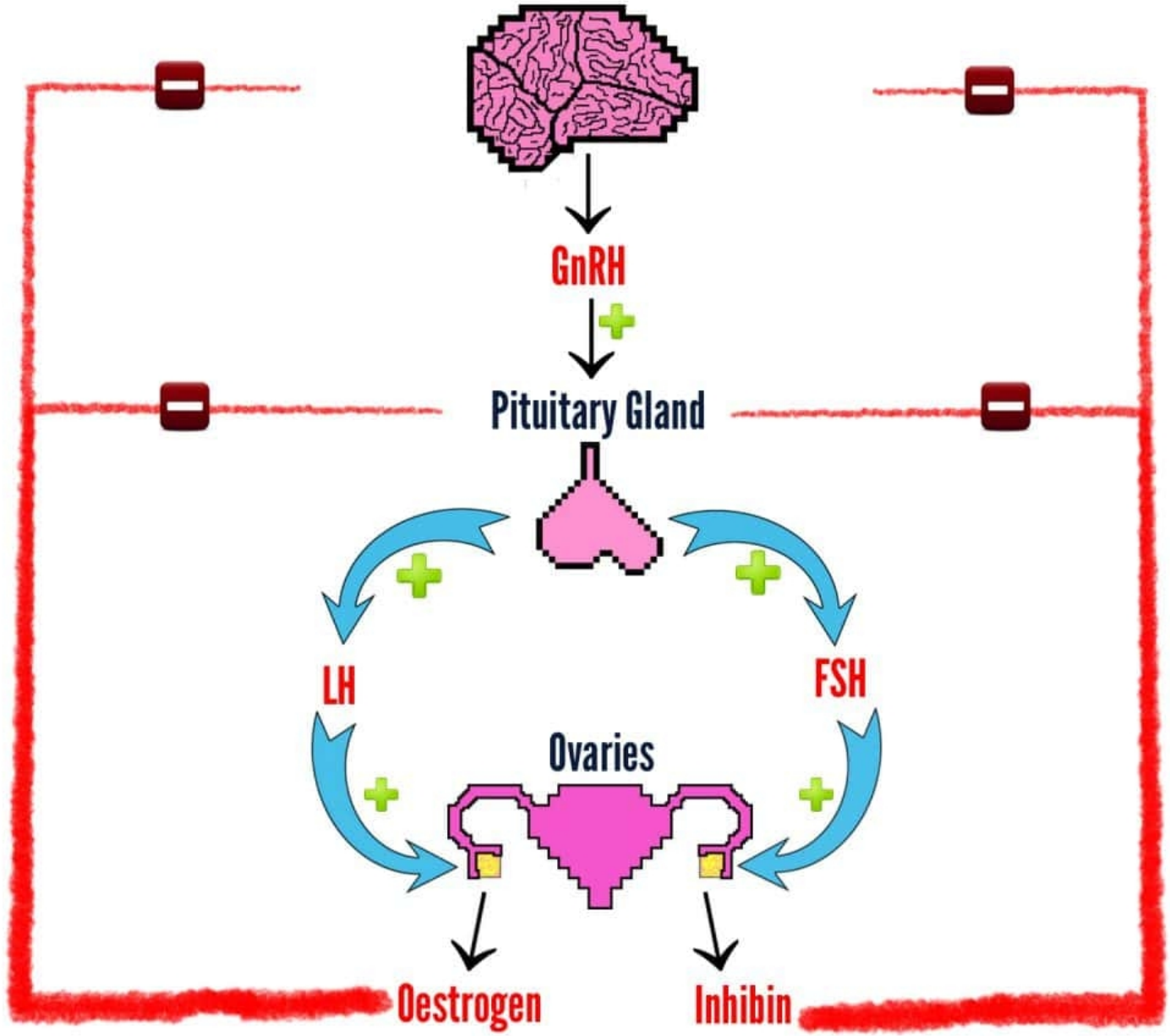
Summary of hormonal inputs to follicles



Hormonal outputs from the follicles (a little simplified)




Menstrual Cycle
This big LH peak drives ovulation
LH peak
LH (mIU/ml)
FSH (mIU/ml)
50
40
30
20
10
FSH
LH
Progesterone (ng/ml)
10
1
0
Estradiol (pg/ml)
300
200
100
0
Progesterone
Estradiol
Day
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
Menses
Ovulation
Follicular phase
Luteal phase



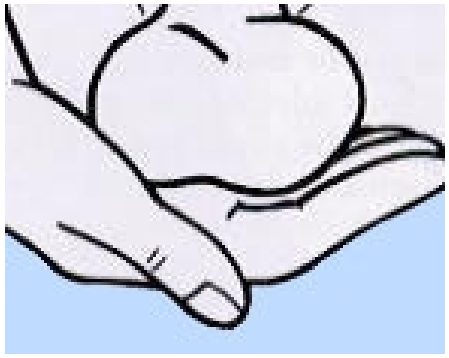
Positive Feedback

Negative Feedback

<this is not part of the course – but those with testes, please read it anyway>

Testicular self-examination

a good idea for all young men, and transwomen retaining testes – especially important if your testes descended late



Examine your testicles is after a warm shower or bath, when the skin of the scrotum is relaxed.

Whilst standing, support your testicles in the palm of your hand. Become familiar with the size and weight of each testicle**.** It is not unusual to have one testicle slightly larger or hang lower than the other. However, any recent changes in size or weight may mean that something is wrong.

Next, gently roll each testicle between the thumb and fingers, looking for any lumps, swelling or unexplained tenderness. Also, check the testicles for any change in firmness. It is normal to be able to feel the epididymis. If you are unsure, use the contralateral testicle as a control.

If you find any lumps, DO NOT PANIC (most will be things other than tumours) but do seek medical advice.

A partner can check you instead, but they must concentrate on examination rather than 'play'.