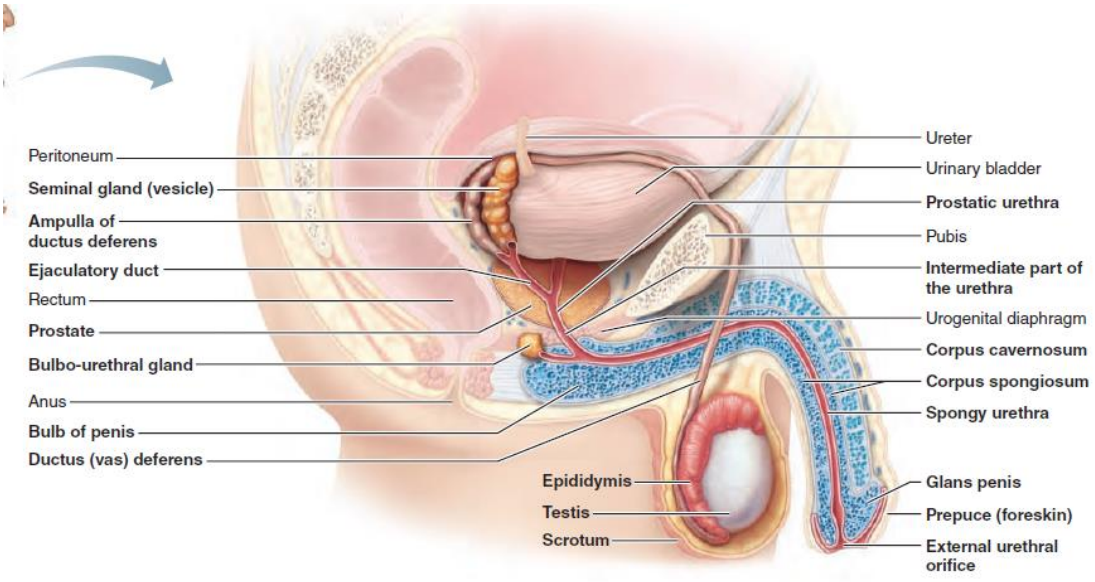
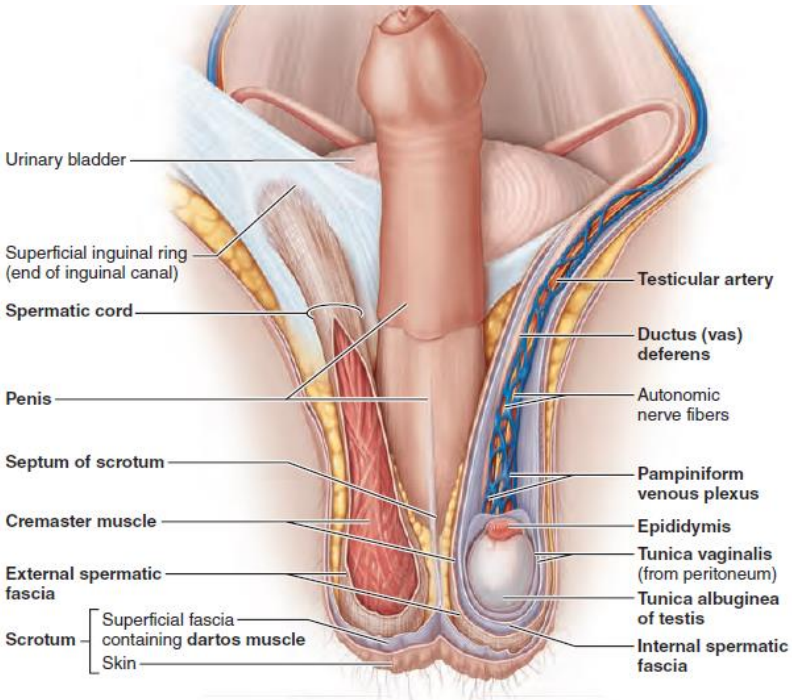
Topic 5: Reproductive system Part 1

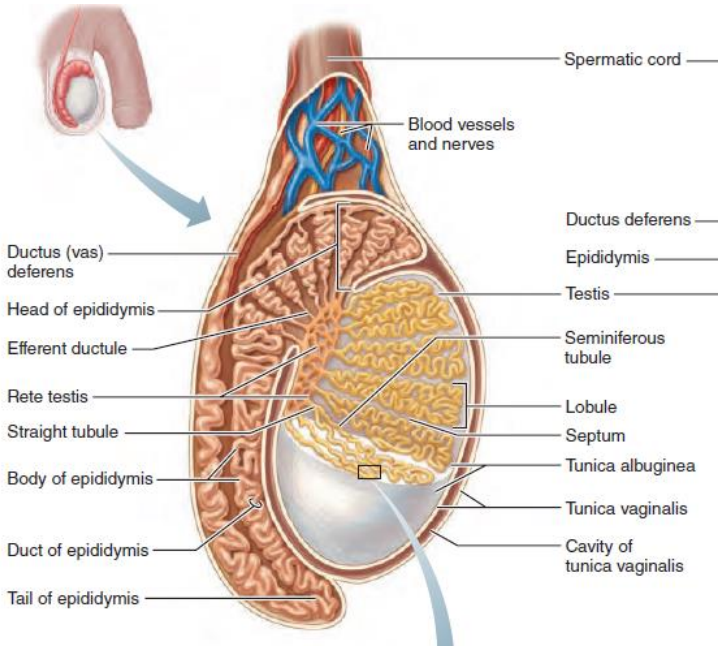
Anatomy and physiology of the male and female reproductive systems

- What are the purposes?
  - Creation of new individuals.
  - Genetic variability.
  - Allow for mixing of genetic info.
  - Production of male and female reproductive hormones that have important effects in the body.
- Things you need to understand before:
  - Endocrine system
  - Hypothalamic-pituitary-testicular and ovarian axis-→ regulate reproductive function.
  - Meiosis→ what are the steps to produce eggs/ sperm?
- **Cyclical system of the female, male isn't.**

Anatomy of the Male reproductive system

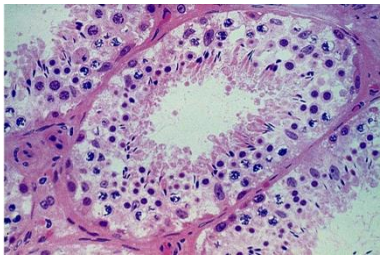






Gross and microscopic anatomy of the testes

- a lot of the anatomy of the male reproductive system is basically tubing to get the sperm outside of the body.
- Testes located in **scrotum**: sac of skin + superficial fascia outside abdominopelvic cavity at the root of penis.
- Midline **septum** provides one compartment/ testis.
- Exterior position provides essential temperature 3 degrees **lower** than core.
- Testes are located outside the abdominopelvic cavity because in males, spermatogenesis occurs at a lower than normal temperature that's why they're located exteriorly. The eggs are in the abdominopelvic cavity because ootogenis can happen at normal body temperature.
- **2 Tunics**
  - **Tunica vaginalis:** outer, 2 layer. Originates from the peritoneal membrane, as they descend some of the peritoneal membrane from the abdominopelvic cavity comes down with it.
  - **tunica (coat) albuginea (white):** white covering we see over the testis. Fibrous capsule of testis (white coat); septal extensions. Important that it subdivides testes into compartments because inside there are coiled tubules (**seminiferous tubules),** if you don't organize them they might become tangled with each other and they're important for making sperm. Within each lobule there are **1-4 of these coils**. Because there are so many of the seminiferous tubules you can make so much sperm.
  - **What are the roles of the dartos and cremaster muscles in testicular temperature regulation?**
    - Muscles control how close the testes is to the body
    - Cold day contracts → hold the testes close to the body
    - Warm day relaxes→ farther away from the body so they don't warm up too much
- **Pathway sperm follows from the seminiferous tubules:**
  - Stages of maturation of the sperm
  - Spermatogonium--> spermatocyte--> spermatid--> spermatozoan (sperm)
    - sperm is manufactured in the seminiferous tubules--> rese testes
    - sperm travels to the epididymis where it is stored for up to 6 weeks until it matures.
    - when it is time for ejaculation: sperm travels from epididymis to the vas deferens
    - from vas deferens up and out of the scrotum--> loops around the pelvic bone and goes does towards the prostate.
    - passes through prostate--> ejaculatory duct--> urethra
  - seminiferous tubules → tubulus rectus (straight tubule)→ rese testes → efferent ductules→ epididymis
- **Production of testosterone**
  - Happens in the Leydig cells
  - **Leydig cells:**
    - NOT inside the seminiferous tubules, they're outside but still within the structure of the testes. Interstitial→ in between tissues (the seminiferous tubules).
    - Interstitial cells that produce androgens (testosterone).
  - **Blood supply**
    - Innervation to the testes
    - Vas deferens carries sperm away from the scrotal side.
    - Testicular arteries (branch from abdominal aorta).
    - Testicular veins form pampinoform plexus
      - a network of small veins that also help with temperature regulation.
      - Close physical association between the testicular artery and the pampinoform plexus, so that the blood has started to cool down because you have communication.
      - If you have an arrow→ pampinoform plexus (network) not just a vein.
    - Spermatic cord: blood and lymph vessels, nerves, vas deferens.
      - Nerves and lymphatic vessels travel through there, enclosed in a connective tissue sheath (spermatic cord).



Pathway followed by sperm from the epididymis to the exterior of the body

- **Epididymis (~3.8cm)**
  - **Head** caps superior part of testis (receives sperm from the efferent ductule)
  - **Body** and **tail** contain highly coiled duct of epididymis; (uncoiled ~6m!)
  - Sperm that enter epididymis are **immature, nonmotile**
  - ~20 days to traverse epididymis → gain ability to swim.
    - If you stretch out the epididymis it's about 6m so lots of surface area! Sperm travels through all the complicated tubing. By the time they arrive in the epididymis they have undergone meiosis but they're not able to swim yet. As they spend 3 weeks making their way through the epididymis they will develop receptors for the egg membrane and gain ability to swim.
  - Epididymis wrapped in an entire membrane. Packaged in a very compact way.
  - **What happens to the epididymis during ejaculation?**
    - Smooth muscle in the wall of epididymis will propel the sperm.
    - During ejaculation the sperm will be pooled down at the tail of the epididymis.
    - Sperm are viable for 2-3 months, after that they'll start to be broken down and taken up by the walls of the epididymis.
- **Ductus (Vas) Deferens (1/testis)**
  - No need to remember numbers
  - Pathway taken by the vas deferens to the point where it becomes the ejaculatory duct:
    - Vas deferens merges with a duct, when they merge together it's the ejaculatory duct.
    - Vas loops around the pelvic bone and goes toward the prostate where it merges with the seminal gland and becomes the ejaculatory duct.
    - Each vas deferens propels sperm out during ejaculation.
  - Not a great structure because enlargement of the prostate gland makes it harder to empty the bladder. There is only one prostate gland.
  - When ejaculatory duct merges with urethra, all the rest of the pathway is the urethra.
  - **Vasectomy:**
    - They snip the lower part of the vas deferens. Sperm can't get anywhere. It can be reversed, not 100% that it can be successful but you go back in and connect the two tubes again.
    - Way of birth control.
- **Urethra**
  - Terminal portion, serves both urinary and reproductive functions.
  - **Prostatic urethra**: the urethra as it's passing through the middle of the prostate gland.
  - **membranous urethra**: As it's crossing the urogenital
  - **Spongy (penile) urethra:** erectile tissue: can become engorged or penile: because it goes through the length of the penis.
  - If she points at the different parts of the diagram label each section of the urethra specifically.

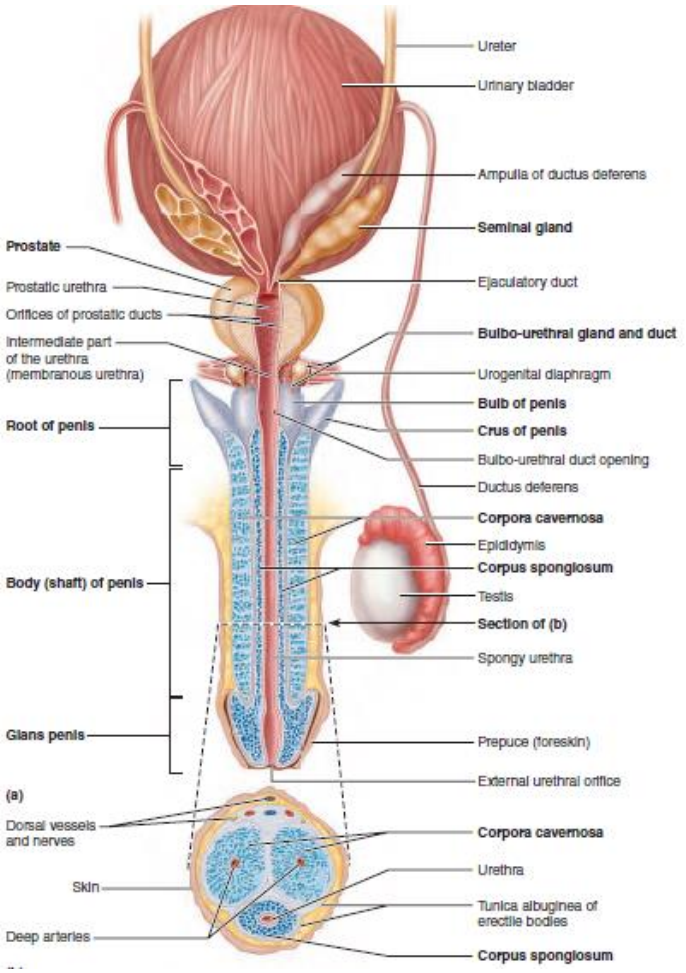
Structure of the male reproductive accessory glands

- Produce secretions that, along with sperm, make up **semen.**
- **Seminal vesicles (2)**
  - Posterior wall of bladder, about size and shape of little finger.
  - Contribute ~70% of semen volume
    - (yellow, viscous, alkaline; fructose, citric acids, coagulating enzyme, prostaglandins)
    - Uses fructose→ used in the seminal fluid instead of glucose
    - Once semen is deposited, it coagulates a bit so it can hold them at the entry point so the sperm can start swimming to the vaginal.
    - Prostaglandin→ helps the sperm move in the right direction using reverse peristalsis stimulated by the prostaglandins.
  - Flavin proteins coming from the seminal fluid cause the yellow colour
    - fluoresce under UV light.
  - Once sperm comes via the vas deferens then the material is in the ejaculatory duct.
    - Sperm + seminal fluid in **ejaculatory duct.**

- **Prostate gland (1)**
  - Single gland, size and shape of chestnut; encircles urethra inferior to bladder.
  - Milky secretion (close to 1/3 semen volume; contains enzymes; role in activating sperm when it is ejaculated; also contains PSA (prostate specific antigen))
  - Prostatic cancer is common, slowly developing cancer so usually nothing much is done about it. Many men die with prostatic cancer, but not because of it (If they're already old). But if a young man gets it, it has to be addressed because it's something you have to deal with.
    - It's a tricky area to do surgery, risk you will interfere with the ability to excrete urine.
  - There are several ducts that secrete several things to the prostatic urethra during ejaculation.
- **2 bulbourethral glands (2)**
  - Pea-sized, inferior to prostate
  - Secrete thick, clear mucus to spongy urethra before ejaculation
    - Secretion helps with lubrication.
    - To clear out the pathway so that the seminal fluid can make it.

Structural organization of the penis as a copulatory organ

- Delivers sperm into female reproductive tract: Vas deferens→ ampulla→ urethra
- External genitalia= penis + scrotum
  - the parts of the reproductive system that you can see from outside the body.
- Penis= attached **root** + free **shaft** or body; enlarged tip= **glans penis**
  - Erectile tissue makes up most of the structure of the penis
  - Penis is attached at the roots, the arrow head area is the glans penis
- **Foreskin or prepuce**= cuff of skin around glans **(circumcision)**
- Bulbourethral glands on either sides
- The 2 small red dots are blood vessels. The one in the middle is the urethra
- Internally, penis contains;
  - **Spongy urethra**
  - 3 corpora of erectile tissue
  - **2 corpora cavernosa:** two bodies that are most important for erection in the male.
  - **Corpus spongiosum** is the thinner one and gives the penis the arrowhead: glans. From the outside it's called the bulb but the tissue is the glans penis.
- **Good diagram and it's a good one to have on the exam**

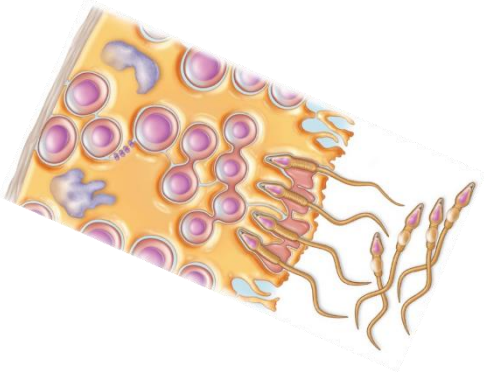


Composition of the semen

- Secretions provide:
  - transport medium: Sperm are carried along in a fluid as they're moving through the system, aren't really swimming yet because they're not yet activated.
  - nutrients (eg. fructose, citrate)
  - chemicals (eg. PGs)- protect/ activate sperm. Both sperm and egg are fragile because they're haploids. They need to be protected as much as possible.
- For semen slightly alkaline, pH of the entry to the vagina is acidic so you need to neutralize that a little.
- Single ejaculate is between 2-5 mL and there are around 50-100 million/mL sperms. Many lost along the way.

Regulation of male reproductive function

Differentiate functionally between Sertoli and Leydig cells



- Normal rate of sperm production is $2x10^8$ sperm/ day.
- Testis is a source of both **germ cells** and **hormones**
- Testis is composed of:
  - **Seminiferous tubules= Sertoli cells** (make up the walls of seminiferous cells) + **spermatogenesis intermediates**; 80% of testicular mass
  - **Leydig cells:** synthesize androgens **(testosterone)**
- This is a wedge taken from the wall of the seminiferous tubules.
  - Yellow: Sertoli cells: tall columnar cells. The nucleus is the white thing.
  - The little dots are gap junctions
  - The circles are developing sperm cells→ going through meiotic division then they go through a shape change to mature.
  - Developing spermatozoa are not inside the Sertoli cells but they're in between membranes.

What is testosterone?

- They are steroid hormones that come from cholesterol.
- When making steroid hormones you go through steps.
  - Always start with cholesterol then enzymes catalyze steps to steadily convert cholesterol into various intermediates until you get to the testosterone.
  - Cholesterol (27C) → progesterone→ androstenedione→ testosterone (19C)
  - Ring structure is retained and gives it the lipid like property.
- **What cell type in testis synthesizes testosterone?** Leydig cells

Actions of Testosterone

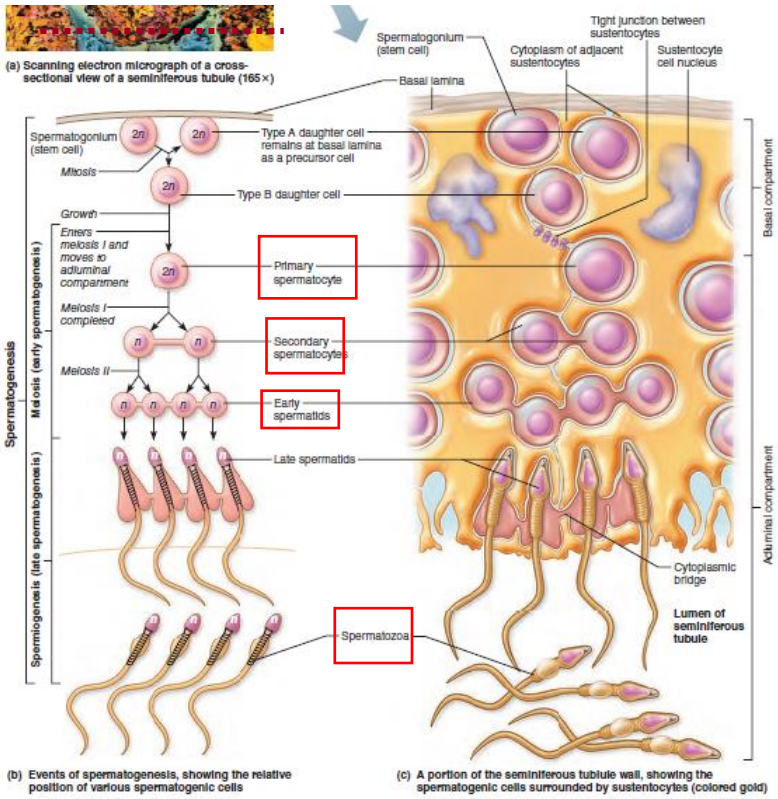
- **Gonadal:**
  - when a male is going through puberty→ growth and maturation of the maturation of gonads and accessory organs
  - Essential for spermatogenesis
- **Somatic**
  - Stimulates growth spurts. Starts and stops→ when the levels get high enough it stops by closing the epiphyseal plates
  - Growth of larynx and vocal cords
  - Secretion of sweat
  - Hair (face, chest, armpits, groin)
- **Metabolic**
  - Anabolic: hematopoiesis, BMR
- **CNS**
  - Maintenance of libido
  - Aggression
- Which of the events begins first?
  - Activation of the testis begins first because you need testosterone to stimulate the rest of the events to kick in.
- **Steroid hormones are lipids- significance in terms of their interaction with cells:**
  - Steroid hormones don't need a surface receptors, they can easily get into and out of cells and act directly on the nucleus.
  - If they are in the plasma they most likely need to be associated to a binding protein. Will move into the nucleus, interact with the DNA and increase transcription.

Describe the hypothalamic and pituitary regulation of steroidogenesis in the male

- **Anterior pituitary hormones:**
  - **Gonadotropins** are glycoproteins
  - **Water soluble**- significance: **cell surface receptors, 2nd messengers**
    - Regulate activity of enzymes
  - **Follicle stimulating hormone (FSH):** stimulates Sertoli cells to support spermatogenesis (T required)
  - **Luteinizing hormone (LH):** stimulates Leydig cells to secrete testosterone.
- Testosterone synthesis stimulated by LH (luteinizing hormone) from the anterior pituitary
  - Gonadotropin releasing hormone→ luteinizing hormone→ testosterone
  - Hypothalamic-pituitary-testicular axis
- cAMP second messenger mechanism of water-soluble hormones:
  - hormone (1st messenger) binds receptor
  - receptor activates G protein
  - G protein activates adenylate cyclase
  - Adenylate cyclase converts ATP to cAMP
  - cAMP activates protein kinases (triggers responses of target cell by activating enzymes, stimulating cellular secretions, opening ion channels, etc..)
- **GnRH:** gonadotropin releasing hormone
  - Pulsatile secretion by **hypothalamic** neurons.
    - By varying the frequency of pulses, it can separate the stimulatory effect of the release of LH and the rate of release of GnRH. Single hormone regulating these two hormones so this is the way to separate them a little.
  - **Stimulates** secretion of FSH and LH from the anterior pituitary
  - **Inhibin:** released by **Sertoli** cells, inhibits secretion of ONLY **FSH.**
    - Why? To prevent the sperm count from getting too high.

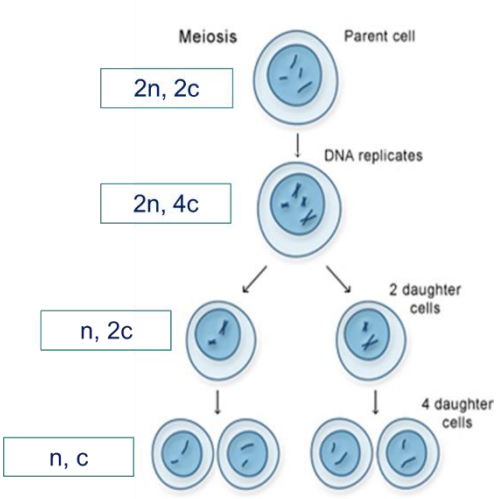
Main steps in spermatogenesis

- At puberty, 6 x10^6 spermatogonia per testis; self-perpetuating→ when the cell is produced in mitosis, one of the products stays behind to maintain the stem cell population so that there are constantly new cells available for this meiotic pathway.
- Dotted line is the gap junction, most tight junctions have to temporarily open.
- **Blood-testes barrier:** cut off from blood supply and immune system (avascular environment).
  - to prevent the sperm (new genetic material from meiosis) to be attacked by the immune system because they might express different antigens.
- **spermatogonium (diploid 2N)**
  - starting point; supply constantly maintained
  - first step: spermatogonium undergoes 2 mitotic divisions→ 4 primary spermatocytes
- **Primary spermatocyte (2N)**
  - Starting point of meiotic divisions
  - First round yields 2 **secondary spermatocytes/** primary spermatocyte.
- **Secondary spermatocyte**
  - 2 copies of each of 23 chromatids (eg. if male would have 2 Y chromatids)
  - 2nd division→ 2 haploid (N) **spermatids**
- **Spermatid:** haploid
  - 22 autosomal chromatids + X or Y- still a **round cell**
- **Sperm/ spermatozoa:** mature sperm cell.

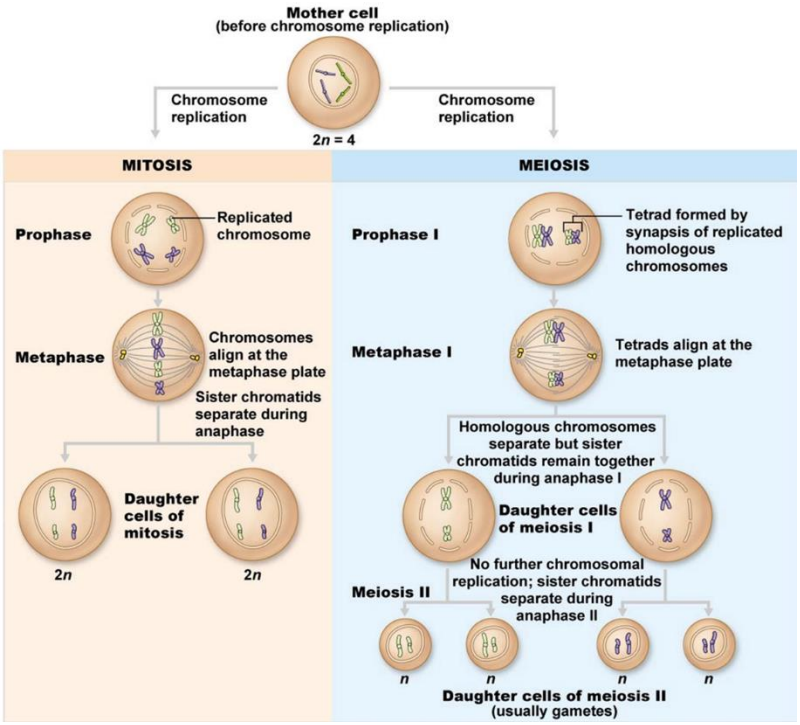


Snapshot of meiosis (2n=4)

- N= ploidy (# of chromosomes)
- C= # of DNA molecules

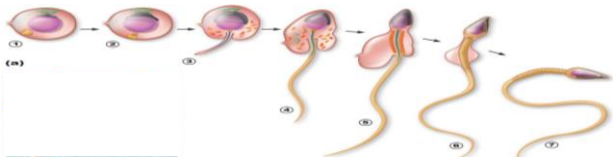


Comparison of mitosis and meiosis



Spermiogenesis

- **From primary spermatocyte to spermatozoan, takes ~70 days**
- **Spermatozoan:**
  - Conversion of spermatid to spermatozoan requires structural reorganization
    - **Reorganization of nucleus and cytoplasm**
      - A lot of the cytoplasm is discarded
      - Mitochondria pile up in the middle region to fuel the movement of the flagellum
    - **Development of flagellum**
  - Spermatozoa then released into lumen; still not completely mature
  - In epididymis, will acquire ability to:
    - Express receptors for the egg membrane.
    - Gain motility.



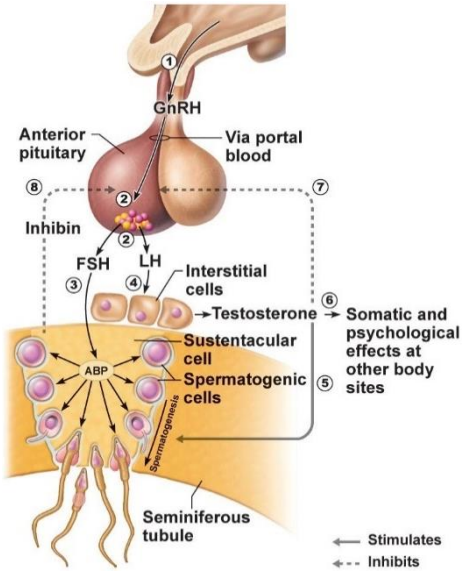
Blood Testis barrier and the functions of Sertoli and Leydig cells in supporting spermatogenesis

- **Role of Sertoli Cells**
  - Spermatids and spermatocytes at various stages embedded in Sertoli cells
  - Sertoli cells sit on basement membrane; tight junctions create 2 compartments:
    - **Basal compartment:** from basal lamina to their tight junctions. Contain spermatogonia and earliest primary spermatocyte.
    - **Adluminal compartment:** internal to tight junctions and includes meiotically active cells and the tubule lumen. Site of maturation.
  - **Tight junctions create blood testis barrier;** all stages after initiation of meiosis occur in avascular environment. This way, the products of meiosis are protected from the immune system because the different genes might trigger the immune system to destroy it.
  - **Sertoli cells:**
    - Nourish developing spermatozoa
    - Secrete fluid into seminiferous tubule lumen
    - Digest cytoplasm discarded by spermatozoa
      - Bind FSH and testosterone
      - Produce inhibin→ negative feedback on production of FSH.

- **Role of Leydig cells**
  - Located **between** seminiferous tubules
  - **Vascularized**- why? Because they receive cholesterol from the blood which is the precursor for testosterone which is important for supporting accessory organs.
  - Receptors for **LH**- stimulated by LH to secrete testosterone to:
    - Support spermatogenesis
    - Support accessory organs

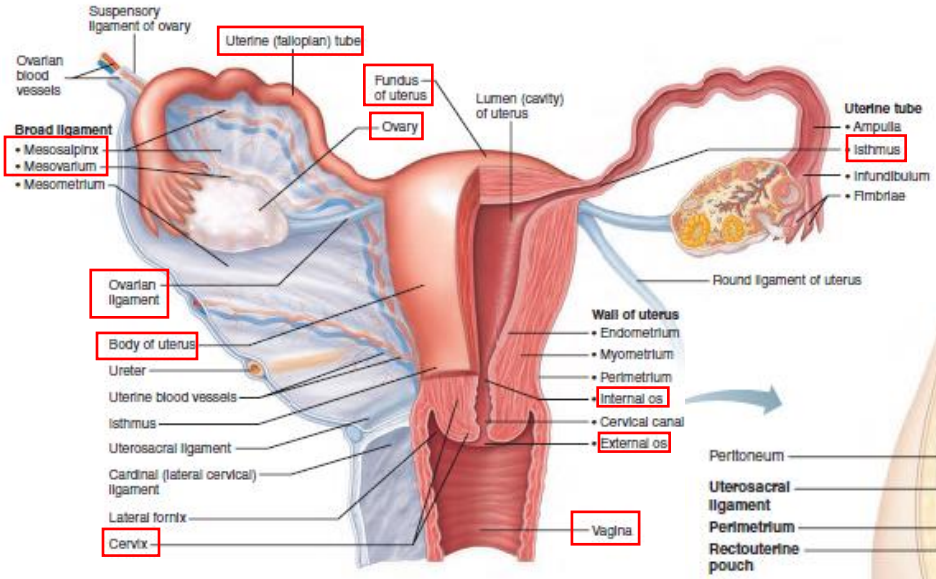
Functional contributions of the epididymis and the accessory organs to the production of semen

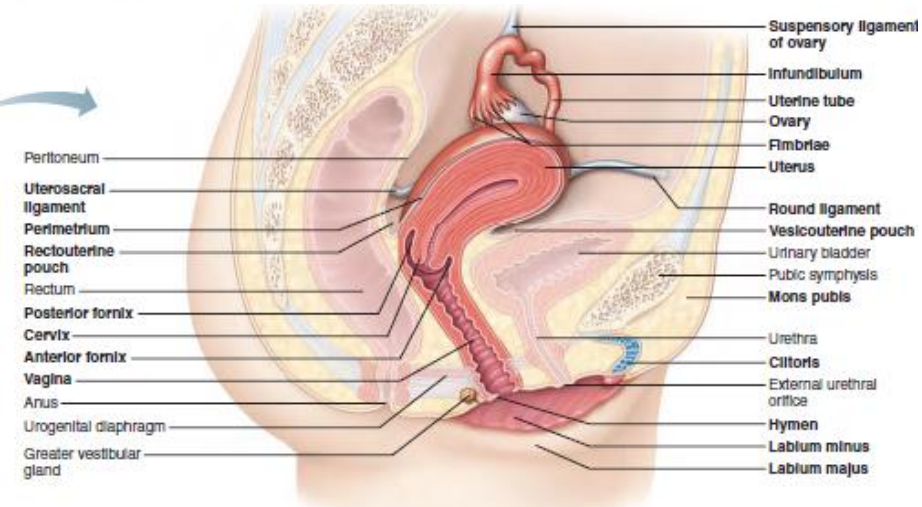
- **Epididymis**
  - Sperm spend ~20 days here
  - Further maturation- membrane and enzyme changes to permit:
    - Sustained motility
    - Binding to egg
- **Seminal vesicles**
  - Secrete viscous, yellow fluid rich in **fructose**
  - Why fructose? Because it is the sugar used by the seminal vesicles.
  - Also contains **prostaglandins**→ stimulate reverse peristaltic contractions in the woman to help propel the sperm.
- **Prostate gland**
  - Secrete thin, milky fluid to neutralize acidity of male urethra and female vagina
- **Bulbourethral glands**
  - Thick, clear mucus
  - Neutralizes traces of acidic urine in urethra.



- Androgen binding protein: binding protein for testosterone in Sertoli cells. When test comes in, it binds to ABP and is then conveyed to the nucleus where it can influence transcription.

Anatomy of the female reproductive system





Gross and microscopic anatomy of the ovaries

- Female reproductive system is more complex. Must:
  - Produce gametes
  - Prepare to nurture developing embryo
    - **Internal genitalia:** ovaries
    - **Accessory ducts:** uterine tubes (aka fallopian tubes aka oviducts), uterus, vagina
    - **External genitalia:** vulva
- **Ovaries**
  - Anchored by ligaments
    - **Ovarian ligament**
    - **Suspensory ligament:** attaches laterally to the body wall to prevent the lumen from closing.
    - **Mesovarium:** part closest to the ovary
  - Suspensory/ Mesovarium ligaments are part of the **broad ligament** that supports uterine tubes, uterus, vagina.
  - Ovarian arteries (branches of abdominal aorta) and ovarian branch of uterine arteries.
  - External surface covered by **tunica albuginea**
  - Final outer covering is **germinal epithelium**
    - Single layer of cuboidal epithelial cell, needs to be broken to let the egg out
    - Possible source of ovarian cancer since every time there is ovulation need to activate mitotic divisions to close the gap, it is possible when you activate mitotic activity for it not to be activated in a controlled manner and for mitotic division to go out of control.
  - Ovarian **cortex** contains **follicles** at all stages of development
    - **Oocyte**
    - **Granulosa cells**
    - **Theca cells**
  - **Corpus luteum** formed from ovulated follicle each month.
    - Inside the ovary there is a time course, primordial follicles get larger and the wall of the follicle left behind forms the corpus luteum.
    - Follicular cells surround the egg→ follicle regulated by FSH.
    - Towards the inside: granulosa cells, towards the outside are the theca cells.

Gross and microscopic anatomy of the oviducts

- Receives egg and provide site for fertilization ~10cm long.
- **Fimbriae → infundibulum → ampulla:** oocyte released into peritoneal cavity, fimbriae direct it to ampulla of oviduct.
  - Ampulla is the expanded end of the oviduct where fertilization happens in the enlarged part.
- Structure of wall of oviduct also helps oocyte move toward uterus:
  - Fimbriae is a thin like process, tries to create current to get it swept in the ova duct.
  - Area that narrows is the **isthmus:** bridge is where the ova duct connect to the uterus. If the oocyte gets fertilized there it will be terminated.
- Exit covering= visceral peritoneum; supported by **mesosalpinx**

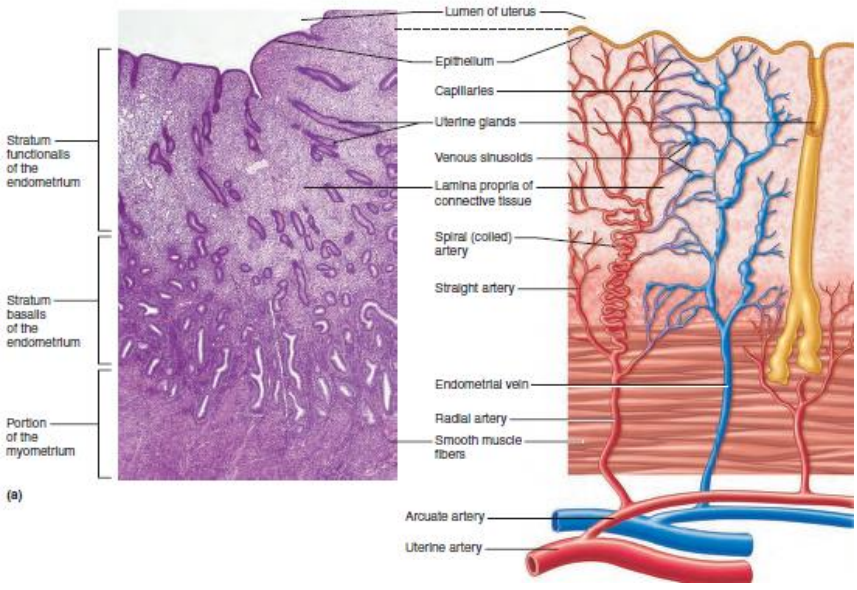
Gross and microscopic anatomy of the uterus

- Anterior to the rectum and postero-superior to bladder
- Receives, retains and nourishes embry
- Inverted pear in **nulliparous** women (never been pregnant).
  - **Internal os:** uterus→cervix
  - **External os:** cervix→vag.
- **Cervical glands**: mucus fills cervical canal and covers ext os→ prevents infection; less viscous at midcycle. Why?
  - To block the spread of bacteria from the vagina into the uterus
  - Blocks sperm entry except at midcycle, when it becomes less viscous to allow sperm to pass through.
- **Supports of the uterus:**

- **Mesometrium:** supports uterus laterally (broad ligament)
- **Lateral cervical ligaments:** inferiorly; from cervix and upper vagina to lateral wall of pelvis.
- **Uterosacral ligaments:** to sacrum posteriorly
- **Round ligaments:** to anterior body wall
  - Supports allow mobility (eg. During labor)
  - Principal support by muscles of pelvic floor (urogenital and pelvic diaphragms).

- **Uterine wall: 3 layers**
  - **Perimetrium:** visceral peritoneum, outermost serous layer
  - **Myometrium:** middle, interlacing bundles of smooth muscle. Contracts rhythmically during childbirth.
  - **Endometrium:** simple columnar epithelium + thick lamina propria
    - if fertilization occurs, the young embryo burrows into the endometrium and resides there for the rest of its development.
    - There are glands embedded in the endometrium that secrete glycogen rich secretions to provide nourishment if an embryo arrives.
    - **Stratum functionalis:** undergoes cyclic changes in response to blood hormone levels and is shed during menstruation.
    - **Stratum basalis:** thin, deeper layer. Forms the new functionalis after menstruation ends. Not affected by ovarian hormones.
- **Vascular supply**
  - **uterine arteries** (from internal iliacs in pelvis)
    - **arculate arteries**
      - **radial arteries** within myometrium
        - **straight arteries** (stratum basalis) + **spiral arteries** (stratum functionalis)
  - when menstruation happens, the straight arteries cut off the blood supply to the stratum functionalis so the cells die without oxygen and that layer is shed.

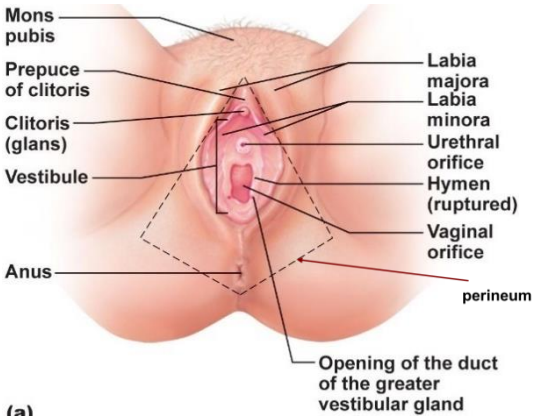
The anatomy of the vagina



- thin-walled tube, 8-10cm long
- urethra embedded in anterior wall
- passageway for:
  - entry of sperm
  - exit of menstrual flow → lining discarded
  - delivery of infant
- 3 layers:
  - **Adventitia:** outer, fibroelastic (very well attached to accommodate for the pressure of labour
  - **Muscularis:** smooth muscle
  - **Mucosa:** inner, transverse **rugae**. Stratified squamous epithelium to accommodate for wear and tear during intercourse and labor.
- no glands, lubrication provided by cervical glands.
- Epithelial cells store glycogen→ metabolized to lactic acid by resident bacteria→ acidic pH deters infection but it hostile to sperm.
- Hymen extends out to the entry point in a vagina.

External genitalia

- **Vulva:** mons pubis, labia, clitoris, structures associated with vestibule.
- **Mons pubis:** fatty, rounded area overlying pubic symphysis, covered with hair
- **Labia majora:** elongated, hair-covered fatty skin folds (homologue of scrotum).
- **Labia minora:** thin, hair-free skin folds enclosed by labia majora.
- **Vestibule:** recess between labia minora- contains external opening of urethra and vaginal opening; greater vestibular glands.
- **Clitoris:** erectile tissue (homologous to penis); hooded by skin fold, richly innervated; corpora cavernosa but not corpus spongiosum.
- Large area is the vestibule, small area is the perineum.
- **Good diagram → be asked to label this.**



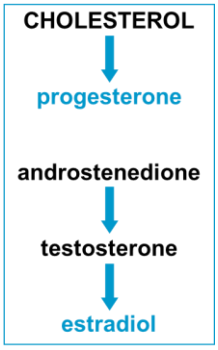
The regulation of female reproductive function

Ovarian steroidogenesis as a compartmentalized process

- General information
  - Ovaries have two key functions:
    - Produce oocytes
    - Produce reproductive hormones (eg. **estradiol, progesterone)**
  - Remember: the hormones a cell can produces depends on the enzymes it has + steroids are lipids and can easily transverse the plasma membrane.
  - Granulosa cells make estradiol from testosterone

Hypothalamic and pituitary regulation of steroid hormone production in the female

- There are 3 types of steroid hormones produced in the ovarian follicle
- **Progestins (eg. progesterone- all have 21 carbons)**
  - Produced by all major ovarian cell types: follicular **granulosa** cells, **theca** cells, **corpus luteum.**
  - Most important as a product of the corpus luteum- during luteal phase of menstrual cycle and for maintenance of pregnancy.
- **Androgens (eg. testosterone- all have 19 carbons)**
  - Most important as a precursor for synthesis of estradiol in developing follicle.
  - Synthesized by follicular theca cells and by corpus luteum→ goes to granulosa cells and gets converted to estradiol
  - Too much testosterone is associated with follicular atresia. (degeneration)
    - Either theca are making too much or granulosa not taking it up quickly.
  - Most testosterone gets converted to estradiol
- **Estrogens (eg. estradiol- all have 18 carbons)**
  - Synthesized by follicular granulosa cells and corpus luteum
  - Essential for stimulation of follicular development, onset of puberty etc.



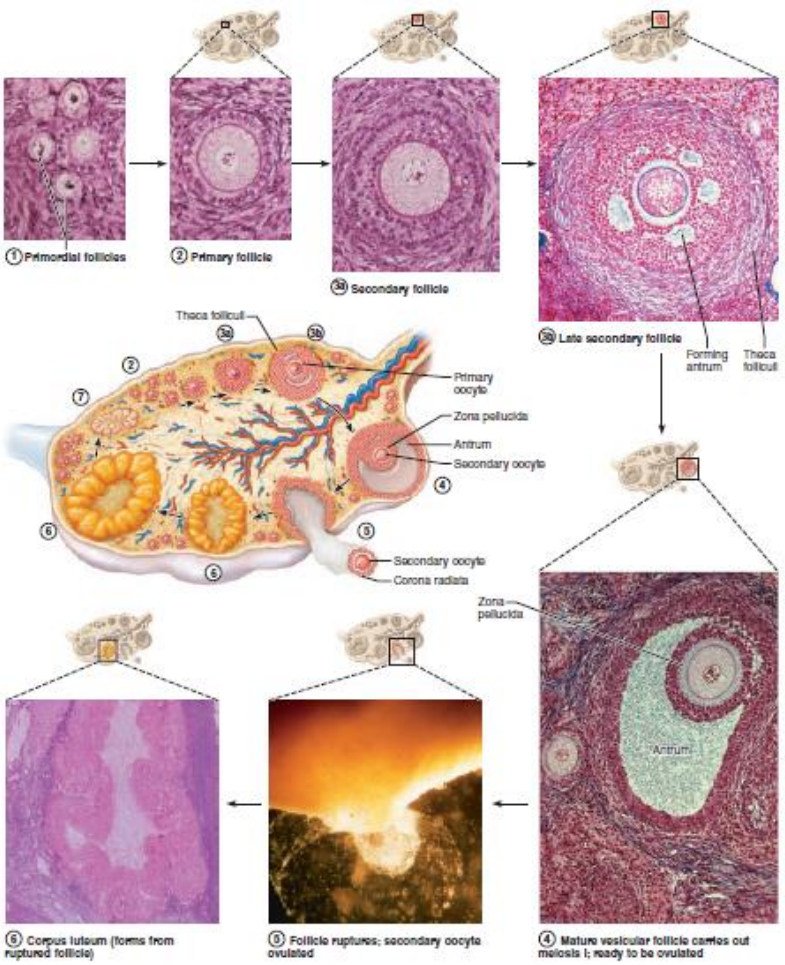
- **Hypothalamic-pituitary axis: Anterior pituitary hormones**
  - **FSH**
    - Stimulates ovarian follicles to grow and produce estradiol (targets granulosa cells).
  - **LH**
    - Stimulates testosterone production by theca cells (like Leydig cells in males)
    - Stimulates ovulation, secretion of steroid hormones by corpus luteum.
    - Becomes very important mid-cycle and the second half of the menstrual cycle.
- **Hypothalamus:**
  - The secretion of both FSH and LH is stimulated by GnRH.

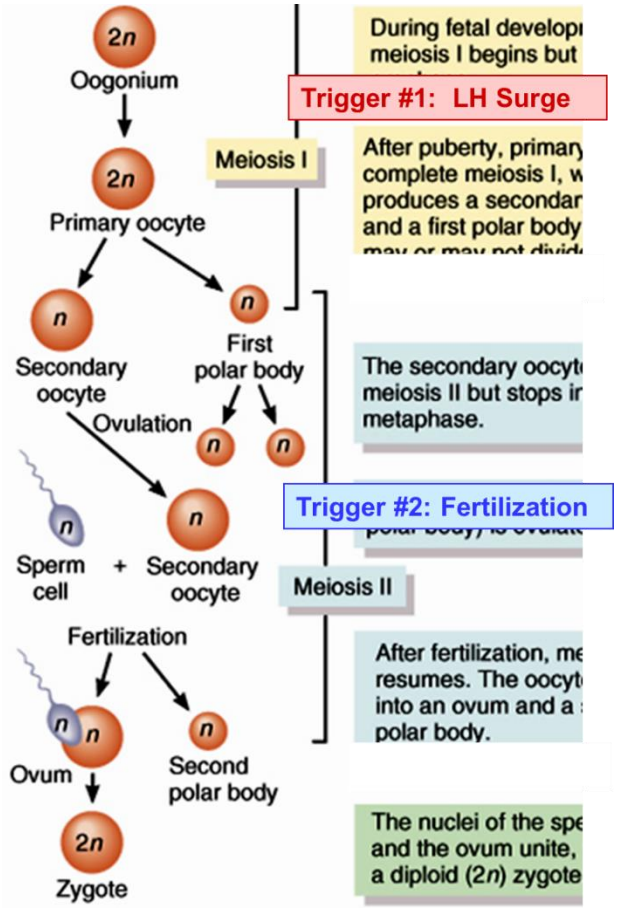
Ovarian follicular development and hormonal regulation

- What is the goal of each menstrual cycle?
- **Primordial follicle**
  - starting point= oocyte surrounded by a single layer of flattened follicular cells (will become granulosa cells).
  - Oocyte (primary oocyte) **arrested** at prophase of meiosis I.
    - This is how eggs get old, all eggs are stuck in meiosis I so the longer it remains in meiosis the more chances there are for mistakes to happen.
  - By 6 months postpartum, ovary has full complement of primordial follicles.
  - ~2 milion at birth; gradual loss (degeneration): ~400,000 remain by puberty.
    - They don't need FSH or LH to start developing so they'll grow but they won't get the support they need from the hormone and will undergo atresia.
  - Primordial follicle= oocyte + single layer of flattened granulosa cells.
  - **Initiation of development of primordial follicles does NOT require gonadotropic stimulation- some follicles can and do begin developing at any time.**
  - Oogonia to primary oocytes accomplished at birth.
    - At what stage are oocytes arrested? Prophase I of meiosis
    - What would they look like under the microscope? Condensed and meiotic spindle starts to form.
    - What triggers the resumption of meiosis? First trigger LH surge, second trigger fertilization.
    - Fate of most primary oocyte? They never resume meiosis
    - Fast of most oocytes in which resumption of meiosis was initiated by trigger 1? Not to complete meiosis.
    - ¾ of the genetic info is discarded as polar bodies and only one quarter is kept for ovulation.
- **From primordial to primary follicle**
  - **Gonadotropin independent**
    - Oocyte increases in size and acquires **zona pellucida** → important protective barrier to prevent fertilization by more than one sperm. Thick, transparent extracellular layer.
    - **Granulosa** cells start to divide and form several layers outside oocyte, connect to oocyte through gap junctions.
    - Outside bm ovarian interstitial cells closest to growing follicles differentiate to form **theca cells.**
    - Now called a primary follicle- **continued maturation of this follicle requires LH and FSH.** FSH to stimulate the granulosa cells and LH to stimulate theca cells.
- **Antral follicle:**
  - What is an **antrum?** Why is it important to have an **antrum** in a maturing follicle?
    - Clear liquid begins to accumulate between the granulosa cells.
    - When six to seven layers of granulosa cells coalesces to form a large fluid-filled cavity its called the antrum.
    - Antrum continues to expand with fluid until it isolates the oocte, along with its surround capsule of granulosa cells called a **corona radiata.**
  - Antral phase (late secondary follicle)
  - Follicle reaches preovulatory stage and all granulosa cells bear FSH receptors.
  - Basement membrane divides follicle into two compartments:
    - Inner **granulosa cell** compartment
      - Non-vascularized
      - FSH- responsive
        - Granulosa cell proliferation (E)
        - Granulosa cell estradiol production from testosterone and androstenedione.
        - More FSH receptors
    - Outer **theca cell** compartment
      - Vascularized
      - LH-responsive
        - Androstenedione and Testosterone production for use by granulosa cells.
        - Too much androgen and granulosa cant keep up → cell atresia.
- Timing is everything!

- If development of follicle coincides with **rising FSH levels** at the beginning of cycle→ development will be supported- otherwise: **atresia!!**
  - FSH stimulates granulosa cells to make lots of enzymes that convert testosterone into estradiol.
- For one follicle to become **dominant,** must convert potentially androgenic environment to estrogenic environment- otherwise: **atresia!!!**
  - A few follicles have the right receptors and the right cell populations but only one will go to be populated.

- **Emerging dominant follicle becomes the preovulatory follicle**
  - Estradiol levels continue to rise- FSH switches to **inducing receptors for LH**
    - LH stimulates further estradiol and progesterone production.
    - Stage is set for **LH surge** to trigger ovulation.
    - Both cell populations respond to LH.

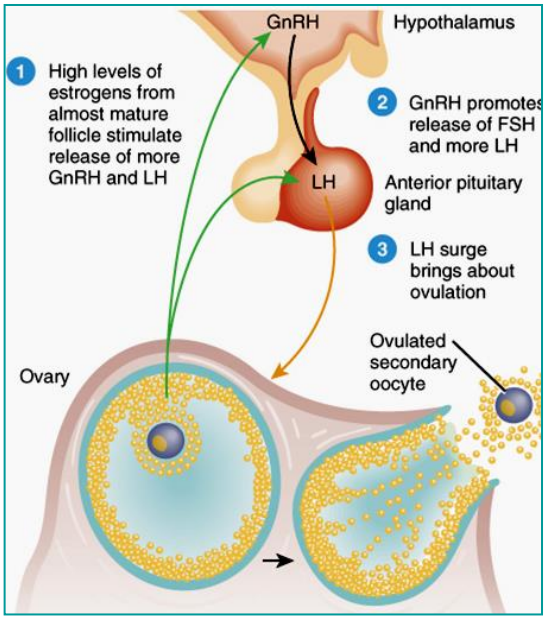




Ovulation and its regulation

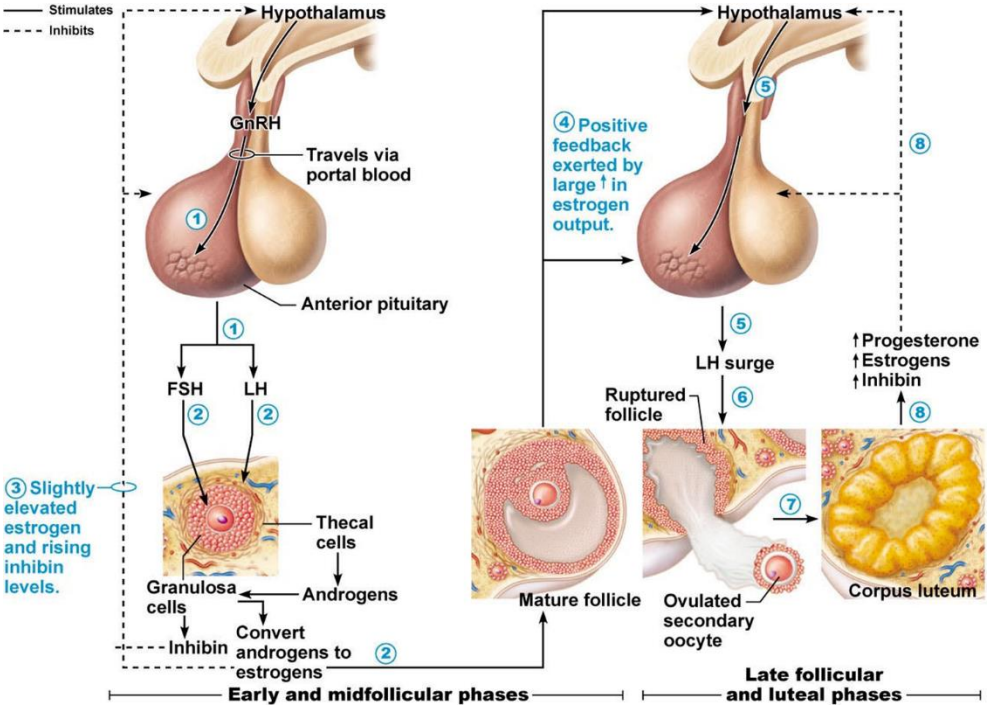
- **LH stimulates:**
  - Resumption of meiosis- extrusion of polar body 1
  - Progesterone production by granulosa cells→ progesterone is the pregnancy hormone.
  - Increase in antral fluid volume→ so that when the balloon breaks the fluid will rush out and carry egg.
  - Release of hydrolytic enzymes→ make a whole in the wall of the membrane.

- **Minor FSH surge**
  - Ensures efficient LH receptors on granulosa cells for luteal phase.
  - there's a stock of granulosa cells surrounding oocyte to keep it attached to the wall of the follicle, this must detach so the oocyte can rush out of the ovary. Stimulation of synthesis of **hyaluronic acid**- important in **cumulus expansion**.
    - Cumulus expansion are the series of transformations of the follicle in the pre-ovulatory phase. After the cumulus expansion, a hole in the follicle will form and the secondary oocyte will leave through the whole.
  - Cumulus granulosa are granulosa cells right next to the oocyte and they are involved in attaching the oocyte to the wall of the follicle.
  - What is the cumulus-oocyte complex (COC)?
    - In order to loosen the attachment, the whole attachment becomes looser and wobbly, so when the fluid rushes out, the COC complex rushes out as well.
    - Granulosa loosely attached to the oocyte that leaves.

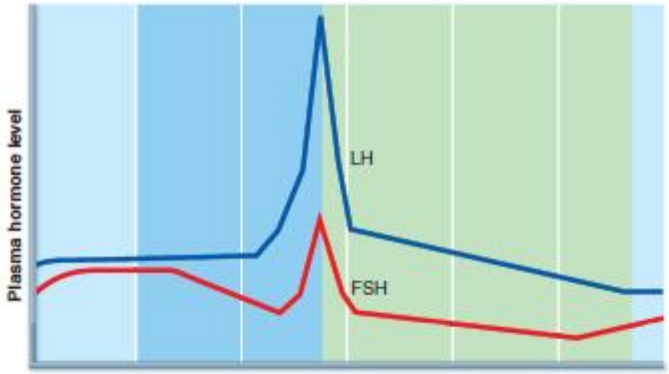


Corpus luteum as a transient endocrine structure

- Corpus luteum= yellow body
- Capillaries bring cholesterol to follicle
- Corpus luteum= luteinized granulosa + theca cells + capillaries
  - Remaining granulosa cells enlarge and they have receptors for LH, with internal theca cells already expressing receptors for LH → come together to form the corpus luteum.
  - Pregnancy does not occur: corpus luteum starts degenerating in about 14 days.
  - Oocyte fertilized and pregnancy ensues, corpus luteum persists until the placenta is ready to take over.
- Unless a pregnancy intervenes, lifespan of CL is <14 days- what is required to maintain CL?
  - Human chorionic gonadotropin→ not identical to LH, structurally similar enough that it can bind to LH receptors on the corpus luteum and extend its lifespan. Otherwise, the lining of the uterus is shed and you go through menstruation.
  - Hormone produce by the placenta after implantation→ detected by pregnancy tests.

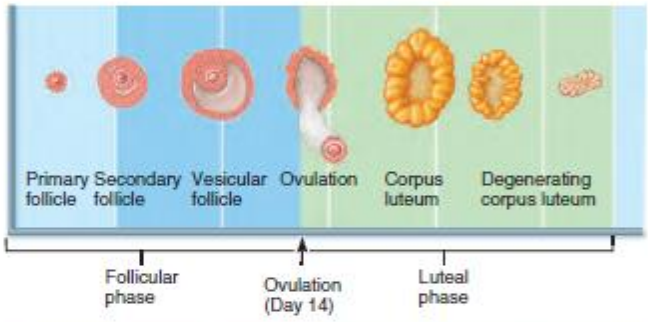


This diagram summarizes what is mentioned above.
Inhibin is made by the granulosa cells and has a negative influence on the release of FSH from the anterior pituitary (same as in the males).



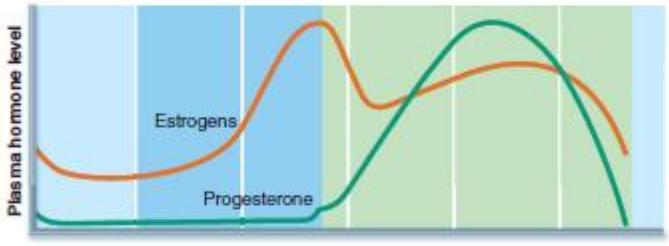
(a) Fluctuation of gonadotropin levels: Fluctuating levels of pituitary gonadotropins (follicle-stimulating hormone and luteinizing hormone) in the blood regulate the events of the ovarian cycle.

- Ovulation day at day 14
- Minor FSH surge and LH surge
- Decline in FSH levels means death for all the follicles
- Luteal phase: corpus luteum only has receptors for LH so the FSH levels drop lower.
- Less LH= menstruation.
- Drop in estrogen level due to menstruation.
- **When does the embryo arrive in the uterus and try to implant? Around day 21.**



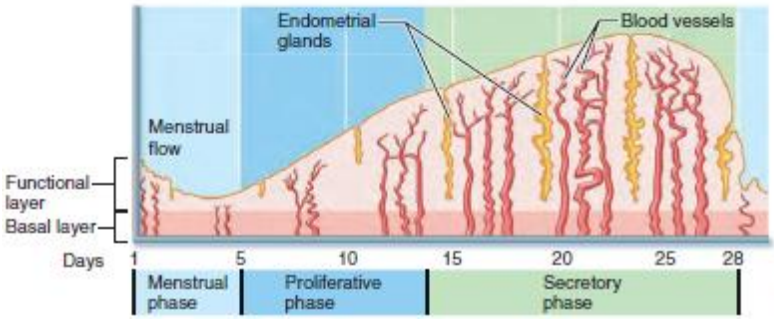
(b) Ovarian cycle: Structural changes in the ovarian follicles during the ovarian cycle are correlated with (d) changes in the endometrium of the uterus during the uterine cycle.

- **Very first day of cycle is the first day of menstruation, it will go on for about 5 days.**
- **Stratum functionalis is being shed and soon after that it has to be replaced to prepare for the arrival of the embryo at day 21.**



(c) Fluctuation of ovarian hormone levels: Fluctuating levels of ovarian hormones (estrogens and progesterone) cause the endometrial changes of the uterine cycle. The high estrogen levels are also responsible for the LH/FSH surge in (a).

Ovary	Uterus
Follicular phase	Menstruation & Proliferative phase
Luteal phase	Secretory phase



(d) The three phases of the uterine cycle:

- Menstrual: The functional layer of the endometrium is shed.
- Proliferative: The functional layer of the endometrium is rebuilt.
- Secretory: Begins immediately after ovulation. Enrichment of the blood supply and glandular secretion of nutrients prepare the endometrium to receive an embryo.

Both the menstrual and proliferative phases occur before ovulation, and together they correspond to the follicular phase of the ovarian cycle. The secretory phase corresponds in time to the luteal phase of the ovarian cycle.

The cyclical regulation of the uterine endometrium

- **Proliferative phase:**
  - Resurfacing of epithelium (regrow the stratum functionalis).
  - Cell **proliferation** in response to ovarian estradiol.
  - Development of **spiral arteires** and **uretine** glands
  - Cervical mucus becomes thin; forms channels that facilitate sperm passage.
- **Secretory phase**
  - Thickening of the whole layer due to cell **growth** and **fluid retention.**
  - Why is called the secretory phase? if no embryo arrives, steroid hormone levels drop and the endometrium is shed. AS LH levels decline, Coprus luteum begins to degenerate (~D24) in absence of progesterone secretion, uterine endometrium is shed and cycle starts again.
  - Cervical plug: deters microorganisms from coming up to the uterus.
  - when is the endometrium maximally receptive to embryo implantation? Day 21.
- If it was a 32 day cycle, what day would ovulation occur? Not in the middle, luteal phase has a fixed duration of 14 days. The first half is the one that matters. If a cycle is longer or shorter it's due to variations in the follicular phase.

- **If oocyte is fertilized:** hCG is produced in increasing amounts beginning D9-13 after ovulation; hCG **rescues** corpus luteum until placental progesterone can maintain pregnancy.
    - Human chorionic gonadotropin (hCG)→ structurally similar to LH that it can bind to LH receptors and keep the corpus luteum going until it is replaced by the placenta.
    - If the corpus luteum shuts down too quickly it might result in a miscarriage, it has to be a gradual decline and a gradual increase with an overlap in between. This is why the end of the third month is complicated for pregnancy.

Hormonal regulation of puberty

- Initial hormonal events are the same in males and females→ need to get the hypothalamic pituitary axis activated.
- In females, FSH stimulates E secretion by granulosa cells to make estradiol (LH stimulation provides T precursor from theca cells)
- **Estradiol responsible for:**
    - Growth and maturation of breasts, reproductive organs
    - Fat redistribution
    - Bone maturation (growth until closure of epiphyseal plates).
    - **(All processes gradually completed over a ~4 year period) → age depends on person.**
- Cycles of proliferation and regression until sufficient growth occurs that withdrawal of steroid support (due to atresia of follicle) results in first menstruation (**menarche).**
    - Follicular development will get a bit farther and maybe an LH surge doesn't occur but the follicle grows a little bit more and it starts to degenerate (atresia).
    - If corpus luteum isn't formed, the cycle will not have its normal length. Cycles could be quite irregular but eventually it should fall into regular patterns.
- First ovulatory cycle often may not occur until a few months later.
- Concept of **critical weight** to reach before menarche:
    - Specifically, a critical **ration of fat to lean- why?** Once a girl goes through puberty, she can become pregnant so the body needs to be big and strong enough to endure a pregnancy.
    - Physical activity will delay the onset of puberty.

Menopause and its effects on female physiology

- Definition: **cessation of menses for at least 12 months**
- IN north America, occurs at mean age of 51.4
- Primary cause is **depletion of ovarian follicles→** women start off with all the eggs they have.
- **Perimenopause:**
    - Extends from early 40s onward- <<transitional years>>
    - Ovarian function begins to wane- deprivation of estrogen (and its effects on FSH/LH secretion) can result in: **hot flushes, insomnia, irritability, fatigue, headaches, depression/mood changes, loss of libido, poor mental performance/ nervousness, loss of skin elasticity.**
    - Loss of effects of estradiol to maintain adequate bone density. Keep bones healthy through exercise.
- **Menopause**
    - Median age of 51.4 years; can live 1/3 of life after ovaries have ceased functioning.
- Loss of ovarian Estrogen affects all tissues that have **estrogen receptors**
    - **Genital tissues:** atrophy, vaginal dryness, high incidence of vaginal infections
    - **Urinary tract:** lining of bladder and urethra have E receptors→ urinary frequency, urgency and even inconsistence.
    - **Breasts:** some atrophy
    - **CV system:** atherosclerosis, stroke
    - **Skeleton:** osteoporosis
        - Compression fractures of the thoracic vertebrae
        - Lower ribs rest on iliac crests.

Process of oocyte fertilization and the main features of early embryonic development up to implantation

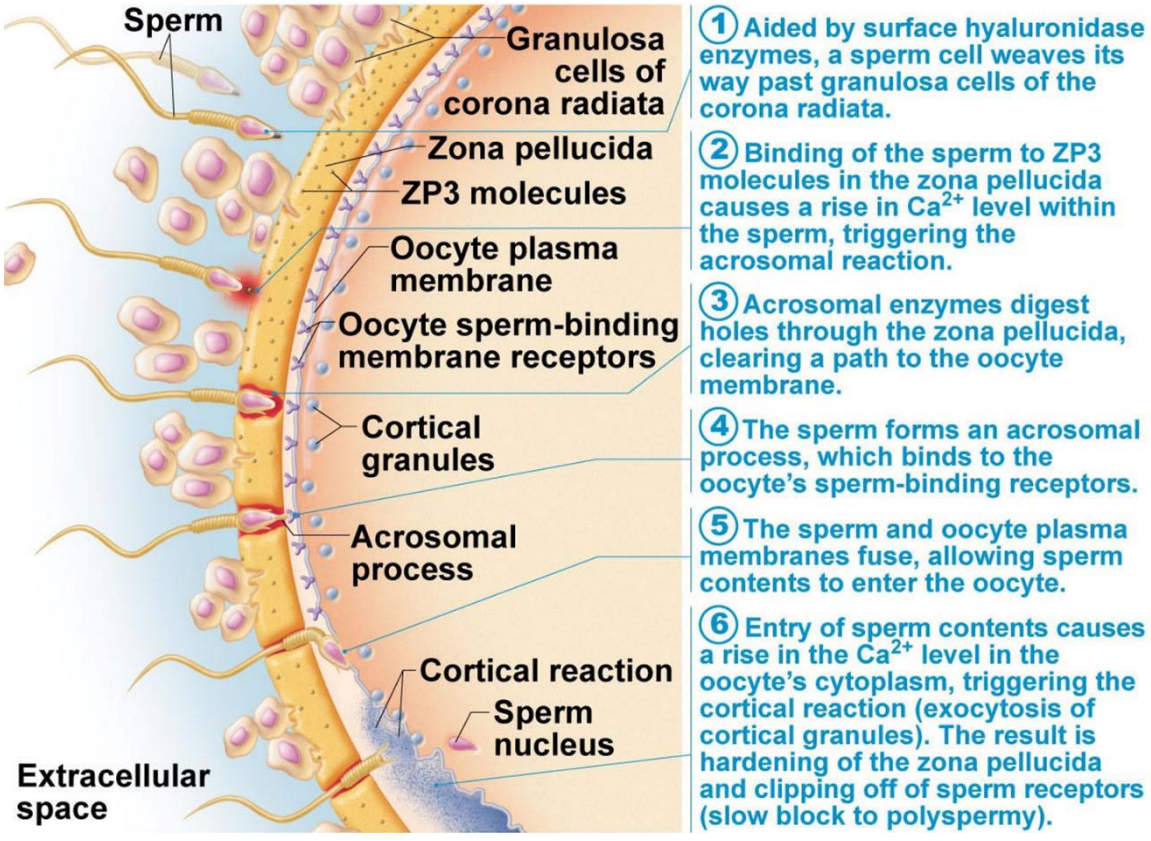
- For how long after ovulation is an egg capable of being fertilized? 24 hours
- How long do sperm remain viable in the female reproductive tract? About 3 days

Sperm capacitation and it's relevance to fertility

- A further maturation sperm must undergo to be capable of fertilizing the egg.
- Occurs following ejaculation once sperm is in the female tract
- Seminal fluid contains **capacitation inhibiting factors**
- **After capacitation, sperm:**
  - Have increased rate of flagellar beat and accelerated motility pattern
  - Plasma membranes are more fragile→ facilitates **acrosome reaction**
- **IVF:** can induce capacitation by washing sperm or running them through a Percoll gradient.
  - Sperm is put with the egg and is taken through a gradient to try and get them away from the capacitation inhibiting factors.

Acrosome reaction

- Acrosomal cap on top of the sperm, inside the acrosome are enzymes to get through the zona pellucida of the egg. The enzymes in the cap want to be kept in until it encounters the egg and it makes holes so the enzymes are released.
- Zona pellucida can bind many sperm but only 1 sperm fertilizes the egg
- Of ~300 M sperm in ejaculate, only few hundred get close to oocyte (where? ampulla of oviduct)
- Binding of sperm to zp induces **acrosome reaction:** what happens and why is this important?
  - Very important that the eff has a way from protecting itself against polyspermy, there is a fast block and a slow block.
  - Acrosome reaction allows for the tunneling of a pathway for the sperm.
  - If a sperm arrives at the egg with no acrosomal cap, it won't have enzymes that can make a hole in the zp and the sperm won't be able to bind to the egg.



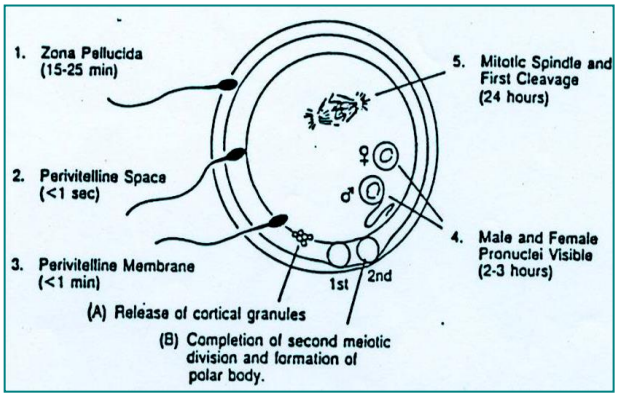
Fertilization is the trigger for the resumption of meiosis. The depolarization is the trigger.

Fast block to polyspermy happens when the sperm binds to the ZP, rise in calcium causes a depolarization which keeps other sperms from entering right away.

At the same time, cortical granular reaction happens where enzymes that chemically change the structure of the ZP ensure that nothing can get through it. This is a permanent change for that egg.

Polyspermy and the fast and slow blocks to polyspermy

- As soon as first sperm penetrates perivitelline membrane:
  - **Fast block to polyspermy:** depolarization that immediately follows
  - **Slow block to polyspermy:** release of the cortical granule that have the enzymes to chemically modify the zp to change its chemical structure permanently.
  - **resumption of meiosis:** extrusion of 2nd polar body, formation of female **pronucleus**
    - polar bodies get trapped in between the egg and the surround zp.
  - sperm nuclear material forms male **pronucleus**, male and female pronuclei fuse to form **2N** nucleus of **zygote**.



Zygote and the developmental steps that occur while the embryo is traversing the oviduct

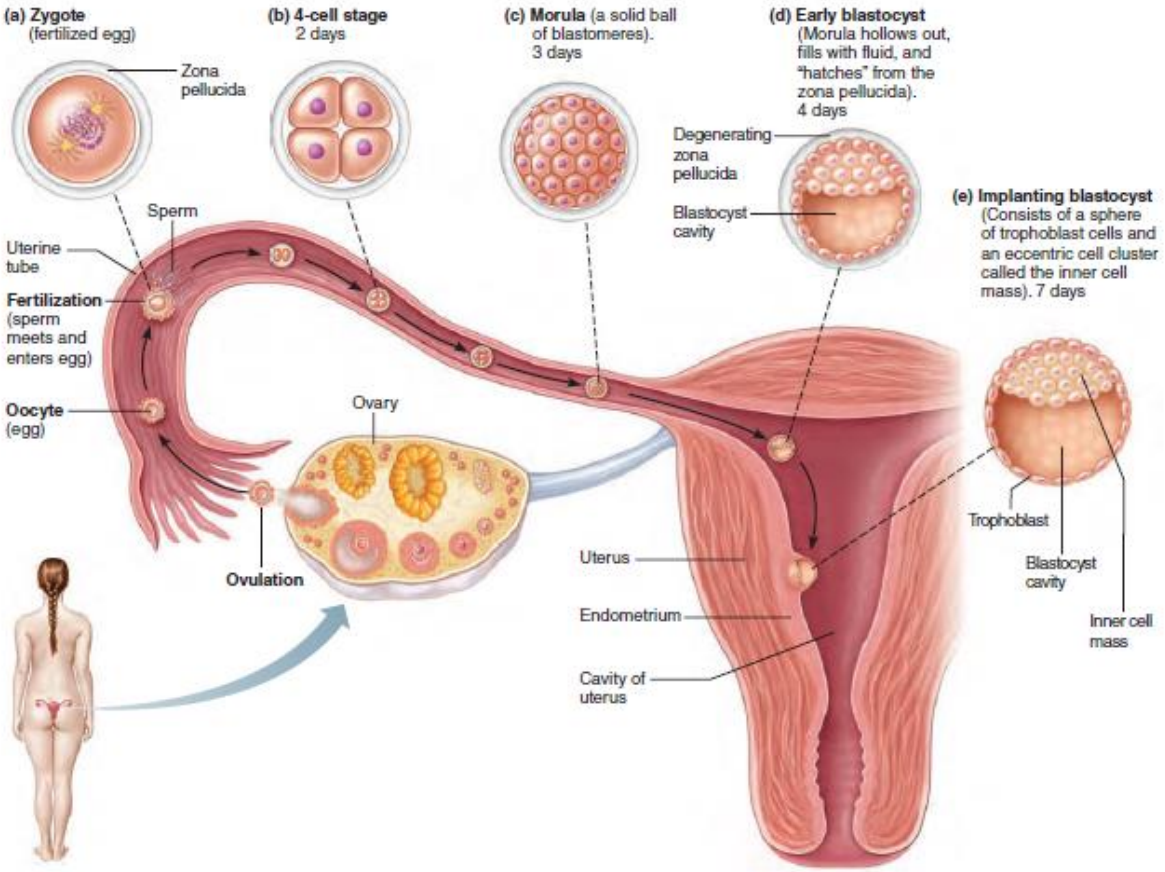


Figure 28.4 Cleavage: From zygote to blastocyst. The zygote begins to divide about 24 hours after fertilization, and continues the more rapid mitotic divisions of cleavage as it travels down the uterine tube. Three to four days after ovulation, the embryo reaches the uterus and floats freely for two to three days, nourished by secretions of the endometrial glands. Because there is little time for growth between successive cleavage divisions, the resulting blastocyst is only slightly larger than the zygote. At the late blastocyst stage, the embryo implants into the endometrium; this begins at about day 7 after ovulation.

Fertilization in ampulla.

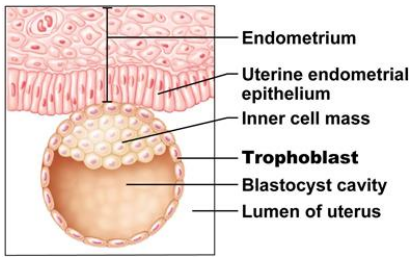
Zp prevents embryo from getting larger to prevent an **ectopic pregnancy.**

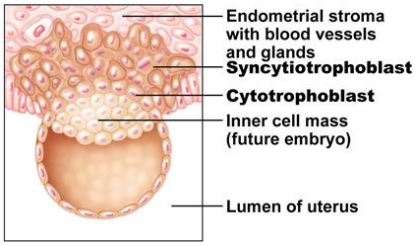
d) ones on the inside make the new human while outer ones will become the placenta.

Morula, blastocyst, hatching

- morula: solid ball of cells.
- Blastocyst: inside cells get pushed and fluid accumulates in the middle to spate the two cell populations.
- **Implantation** begins on ~6th day following fertilization:
  - **Blastocyst** burrows into endometrium
  - **Trophoblast** cells grow toward mat blood vessels.
- Zp has bene lost and now the blastocyst comes out of the zp and leaves it behind, has to do that first before the trophoblast cells can do that.

- **Hatching:** the blastocyst is crowded and gets expanded and streatches out and then some of the trophoblast cells get latched to the endometrium in the uterus. Hatching refers to the process of getting rid of the ZP which must happen.
- First one shows the initial attachment, a single later of columnar epithelial cells. The trophoblast start to digest a little place until they become entirely embedded in the endometrium.
- As implantation proceeds, you get the two cell populations: inner are called the **cytotrophoblast**, the cells incading the endometrium are the **synctiotrophoblast.**
- **trophoblast cells** differentiate into the placenta. This is the beginning of the umbilical cord which will carry blood to and from the lining of the uterus.
- Placenta is really large and blood vessels travelback and forth to deliver oxygen, nutrients and get rid of wastes.





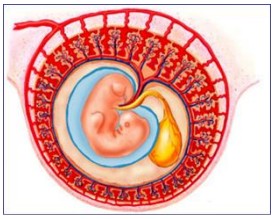
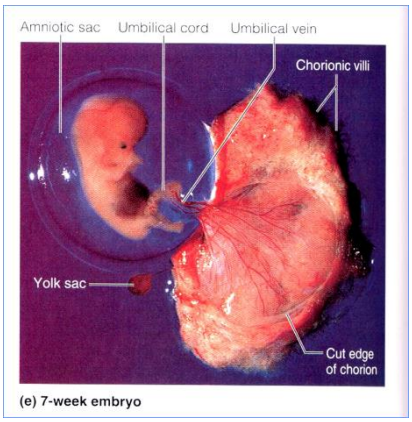


Fig. 28.7d. 4.5 weeks



(e) 7-week embryo

- Conception to 2 weeks- germinal period
- 3-8 weeks- embryonic period: embryo is most susceptible to any medication the woman might be taking. It's a very critical period since all the major organ systems are laid down.
- 9 weeks to term- fetal period: not as dangerous a period for interfering with development.

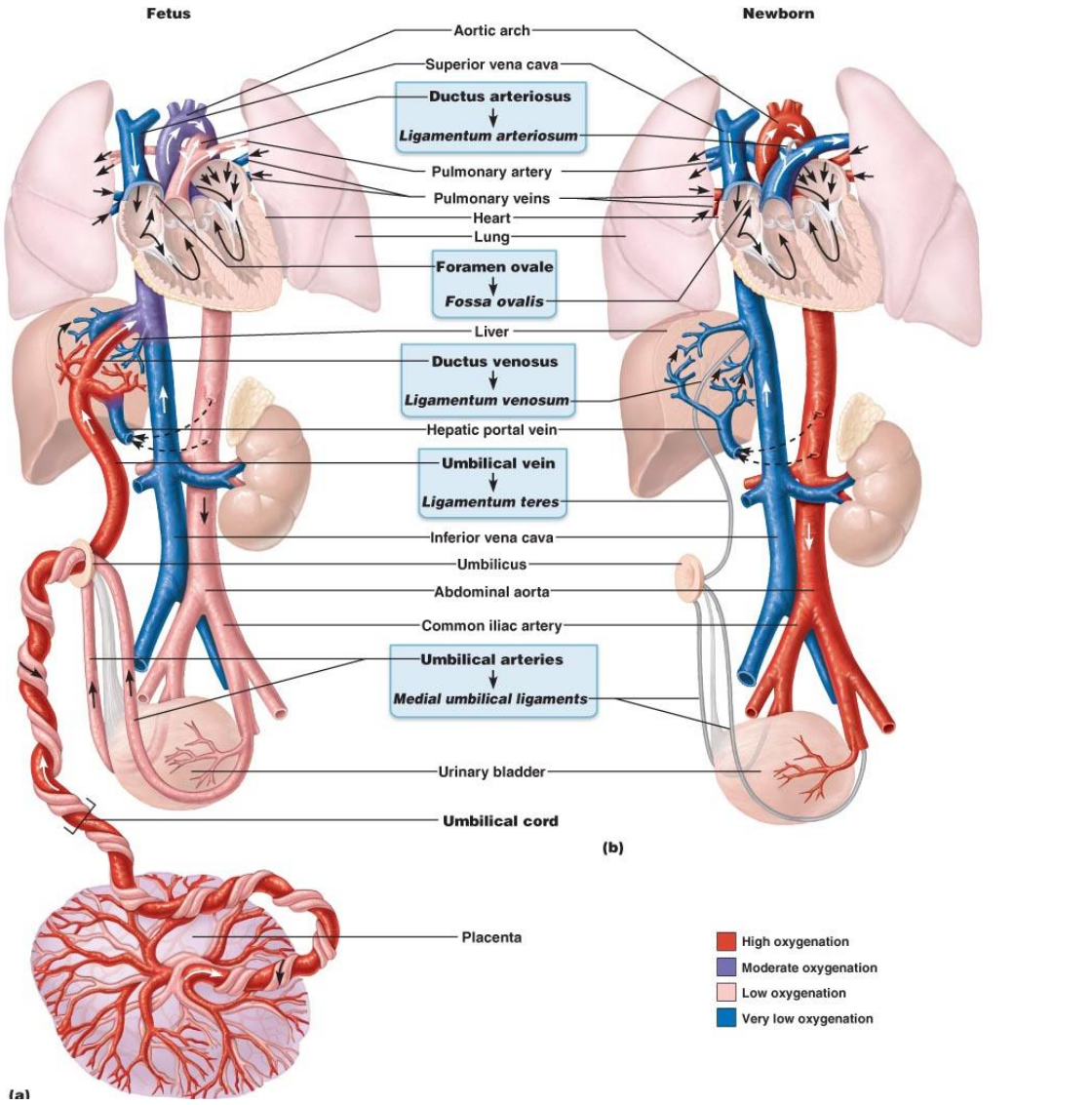
The hormonal regulation of pregnancy, parturition and lactation

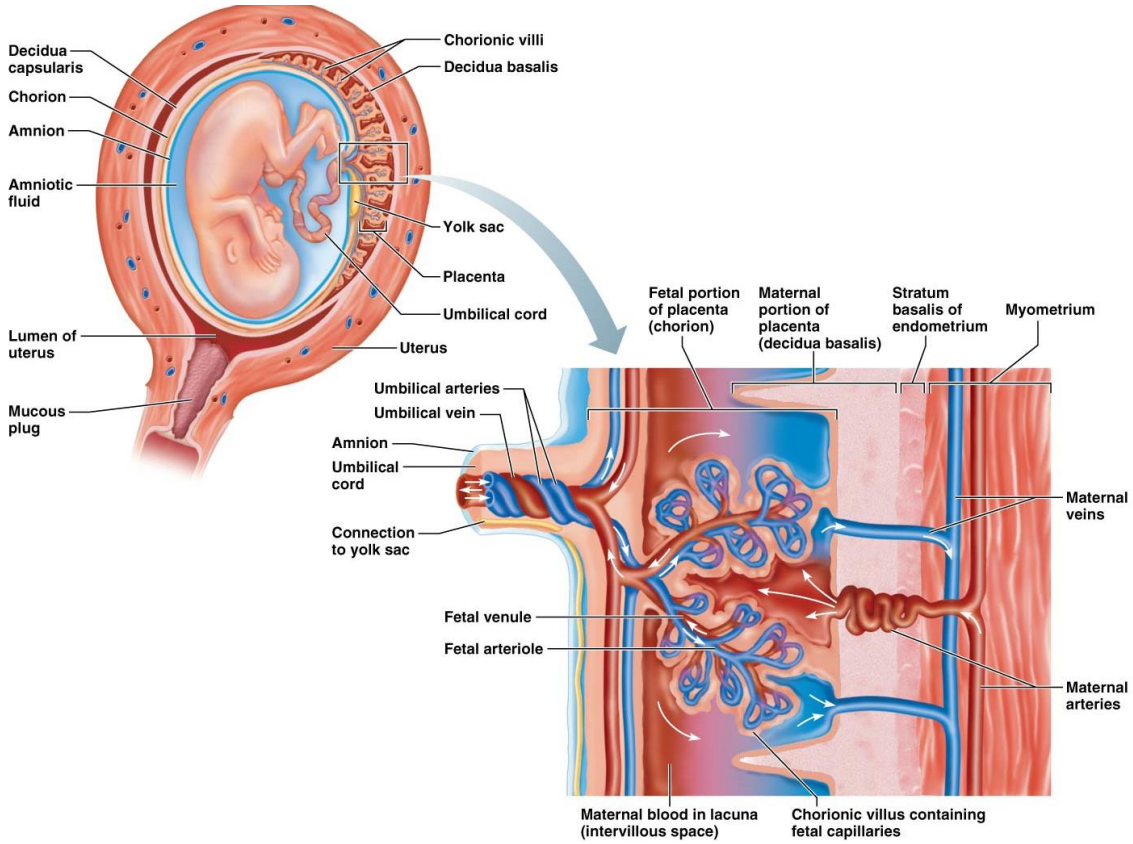
Placentation

- Maternal and fetal blood supplies NOT in direct contact; nutrients, gases, wastes diffuse through:
  - Trophoblast
  - Mesenchyme
  - Fetal capillary endothelium
- Three layers of tissues through which diffusion occurs. All of them are of fetal origin.
- Normal term placenta is ~500g, measures 15-20cm diam, 2-3cm thick.
- Umbilical cord usually 50-70cm in length; contains 2 umbilical arteries, 1 umbilical vein.
- placenta has two critical functions during pregnancy:
  - source of important hormones
  - place of exchange
- There are bypass pathways that have to be closed after:
- What is the **foramen ovale?** Direct communicating pathway between the left and the right atrium. You don't want the blood mixing between the two chambers of the heart. It's not present until after birth when it closes since the oxygen is coming from the placenta.
- what is the **ductus venosus?** No incoming food, GI system is not a source of nutrients for the fetus, the placenta is. There is no portal system going to the liver and this also has to change after birth. It shunts a portion of the left umbilical vein umbilical vein blood flow directly to the inferior vena cava; it allows the oxygenated blood from the placenta to bypass the liver.

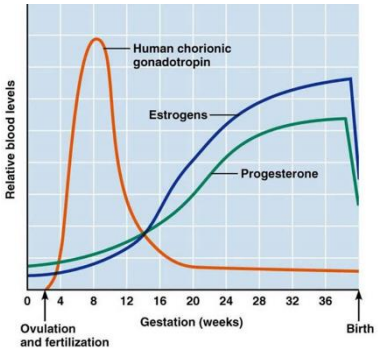
Dual functions of the placenta: endocrine and exchange

- even though the developing fetus is completely embedded in one side of the uterus as it grows, it involves the entire uterus.
- Placenta concentrates itself on a disk shape structure on one side that leads into the umbilical cord in the uterus.


Fetus
Newborn
Aortic arch
Superior vena cava
Ductus arteriosus
Ligamentum arteriosum
Pulmonary artery
Pulmonary veins
Heart
Lung
Foramen ovale
Fossa ovalis
Liver
Ductus venosus
Ligamentum venosum
Hepatic portal vein
Umbilical vein
Ligamentum teres
Inferior vena cava
Umbilicus
Abdominal aorta
Common iliac artery
Umbilical arteries
Medial umbilical ligaments
Urinary bladder
Umbilical cord
(b)
Placenta
High oxygenation
Moderate oxygenation
Low oxygenation
Very low oxygenation
(a)


Decidua capsularis
Chorion
Amnion
Amniotic fluid
Chorionic villi
Decidua basalis
Yolk sac
Placenta
Umbilical cord
Lumen of uterus
Uterus
Mucous plug
Fetal portion of placenta (chorion)
Maternal portion of placenta (decidua basalis)
Stratum basalis of endometrium
Myometrium
Umbilical arteries
Umbilical vein
Amnion
Umbilical cord
Connection to yolk sac
Maternal veins
Fetal venule
Fetal arteriole
Maternal arteries
Maternal blood in lacuna (intervillous space)
Chorionic villus containing fetal capillaries

Hormones



- **Human chorionic gonadotropin (hCG)**
  - Present in maternal serum by 8th day after fertilization; levels peak by ~60-80 days, then begin to decrease
  - What is the primary function of hCG? How does this relate to the timing of its production and secretion by the developing embryo/fetus?
    - Maintains the corpus luteum
    - It's similar enough to LH to bind to LH receptors and is secreted by the trophoblast cells.
    - Bypasses hypothalamic-pituitary-ovarian controls at this critical time and prompts the corpus luteum to continue secreting progesterone and estrogen.
    - the chorion(develops from trophoblast after implantation) continues this hormonal stimulus.
    - hCG also has protease activity and is an autocrine growth factor that promotes placental development.
    - Blood levels of hCG continue to rise until end of the second month. After that the placenta produces the hormones necessary for pregnancy (estrogen and progesterone).
  - Can detect pregnancy by 3 days after missed period
  - Based on detection of **hCG** in blood or urine.
- **Human placental lactogen (hPL)**
  - Structurally similar to **GH** and **prolactin (**human chorionic somatomammotropin, hCS)
  - Placenta begins to secrete hPL during first trimester; levels increase until delivery.
    - Stimulates breast development in preparation for postnatal lactation
    - Supports fetal bone growth
    - Makes glucose available to fetus= **diabetogenic or anti-insulin effect.**
- **Estrogens**
  - Initially come from corpus luteum; function gradually assumed by placenta
  - Placenta converts circulating androgens (fetal and maternal adrenal glands) to estrogen.
  - Initially estrone and estradiol-17-b, then **estriol**
    - Maintains uterine endometrium
    - Contributes to breast development
- **Progesterone**
  - Initially from corpus luteum; function gradually assumed by placenta
  - Levels gradually increase over the course of pregnancy
  - A **relaxing** effect on smooth muscle:
    - **Uterus:** cope with the stretching pressure, accommodate fetus
    - **Blood vessel walls:** relax and open up so to accommodate increasing blood volume.
    - **Ureters:** more urine produced→ more frequent and urgent urination and increased risk for urinary tract infections.
    - **GE sphincter:** heartburn because the esophagus is displaced and baby is taking up space in abdominopelvic cavity.
    - **Intestines:** constipation because things stay longer in the GI tract.

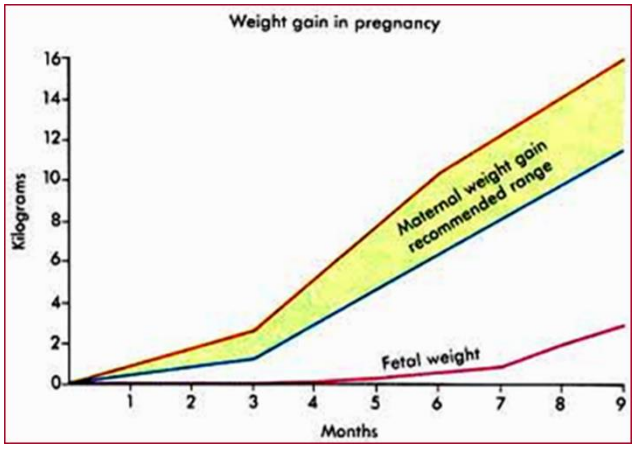
Influences of pregnancy on the CV, Digestive, urinary and reproductive systems of the mother

- **Cardiovascular**
  - **Bp** decreases slowly to nadir @24 weeks; then slowly back up to NP levels.
    - Decreases because the walls of blood vessels relax and dilate to accommodate bv. Heart has to work harder as the workload increases with the increasing size of the baby.
  - **Pulse** slowly increases to max of 15-20 beats/min above NP in third trimester.
  - **Myorcardial hypertrophy**, increased contractility (increase size and strength in pumping), increased cardiac output, these will go back to non-pregnant values after you get rid of the infant.
  - **Overall increase** in **blood volume** (~40%) and RBC by 20-30%--> **physiological anemia of pregnancy**
    - Greater amount of plasma for RBC so the anemia is normal. This Is protective to accommodate blood loss during labor.

- **GI tract:**
  - **Nausea:** increased progesterone, hCG, both??
  - when severe: **hyperemesis gravidarum;** if untreated can lead to dehydraton, ketosis, electrolyte derangements, liver and kidney damage.
  - Mostly in embryonic period when the developing embryo is more susceptible. Thalidomide was once used to cure morning sickness but it caused a lot of births of children with no appendages. For most women, it goes away by the third month.
  - There are no medications that can help with morning sickness.
- **Urinary tract**
  - Kidneys increase in length by 1-1.5cm **(**increased renal blood flow)
  - Bladder tone decreases; bladder capacity nearly doubles
  - Glomerular filtration rate (GFR) increases by 30-50% in first trimester
  - High **progesterone** promotes renal Na (and water) loss; but increased **aldosterone and estrogen** promote salt and water retention.
    - Mix of the hormones, some women will have problems with fluid retention, other women will not have as much of a problem. Variable because of the relative levels of those hormones and their interactions with one another.
  - Increased risk of urinary tract infections- due to problems with blood glucose levels.
- **Cervix**
  - Softening and increased vascularity from early in 1st trimester
  - Increased production of mucus by **endocervical glands.**
  - Eventually cervix has to completely open up to allow for the passage of the baby .
  - Mucus plug→ prevent bacteria from going up the cervix.
- **Vagina:**
  - Cervical secretions increase in quantity; decrease in pH (high estrogen)
  - Increased susceptibility to vaginal candiadiasis (lots of glycogen so susceptible to yeast infections)
    - Fungal infection; high estrogen, high glycogen.)
- **Uterus**
  - Enlarges by hypertrophy from 50-70g (NP) to ~1000g at term (effects of progesterone and estrogen).
  - During 2nd trimester, uterus moves out of pelvis and begins to displace intestines up.
  - By 36th week, intestines pushed up to just beneath the diaphragm→ discomforts experienced by mother include GI reflex (heartburn), constipation, musculature more relaxed, shortness of breath because less area for the diaphragm to descend.
  - Blood flow to uterus at term ~500-750ml/min (10x NP level)= 10-20% total CO.
  - Contracts every 5-20min during pregnancy; irregular contractions that are not coordinated= **Braxton hicks contractions.**
    - They are not as strong and are unorganized. They are more isolated little areas of tightening.
    - May or may not occur often.

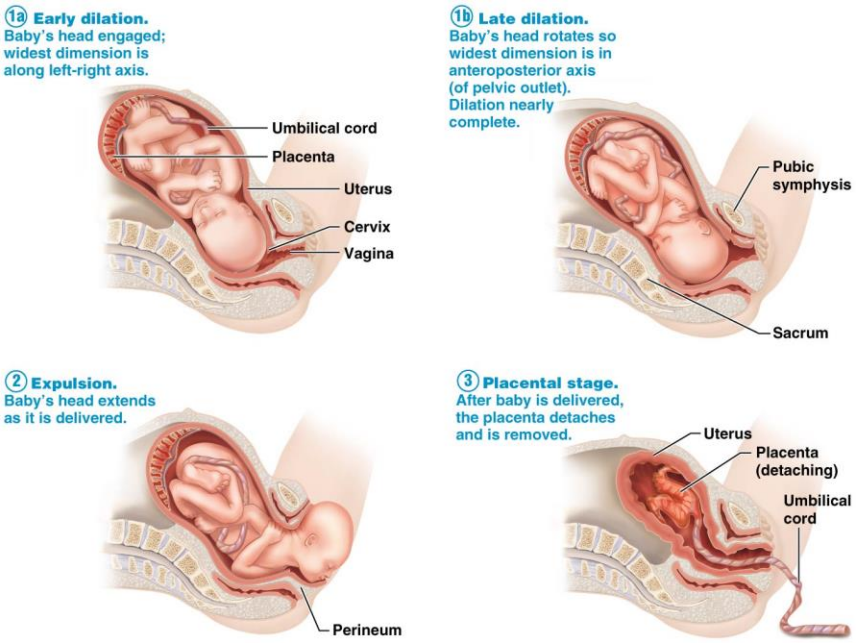
Importance of good nutrition during pregnancy

- Not more food, but balanced diet and more nutritional molecules important (p, c, f, vitamins, minerals, fiber)
- Important vitamins include **vitamin D (**important for absorption of calcium→), **folic acid** (neural tube development→ women encouraged to increase folic acid and its protective against spine epifeda), **vitamin K (**blood clotting, important for labor and delivery).
- Important minerals include **iron** (baby's blood system), **calcium** (development of fetal skeleton, stimulation of muscles, cell signalling, etc..)



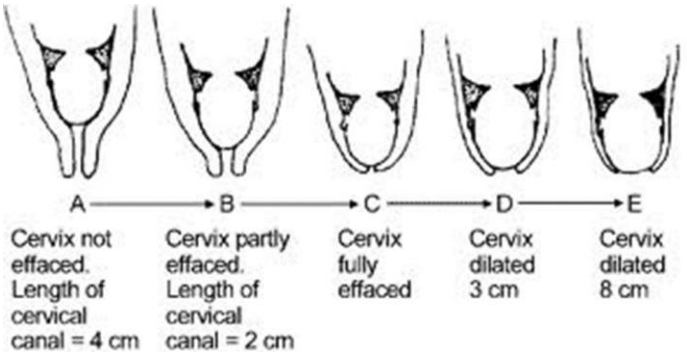
Stages of parturition

- Whole process is not completely understood- especially what is the signal to initiate parturition and how can we **stop premature** labor and delivery?
    - What initiates going into labor? Important to keep the baby in the uterus for as long as possible so development is done.
- Estrogen levels highest toward time of parturition
    - Make sure that there are lots of **oxytocin** receptors on myometrial cells
    - Antagonizes relaxing effect of **progesterone**
- two hormones important during labor and delivery:
    - **oxytocin**- from the posterior pituitary
        - important for lactation and delivery
        - targets smooth muscle in the wall of the uterus and stimulates the cells directly
    - **prostaglandins**- from the walls of the smooth muscles of the uterus itself
        - stimulate contractions as well, myometrial cells (smooth muscles) to contract.
- **Stages:**
    - **Dilation**- uterine contractions dilate cervix up to 10cm; variable in duration. Longest stage. Especially the first time takes longer.
    - **Expulsion-** complete cervical dilation to birth (minutes to few hours).
    - **Placental-** delivery of placenta; 15min after birth. Placenta will detach from the wall of the uterus, important to get it out because it is very mitotic tissue and if it stays behind it can become cancerous.



Cervix is quite long and skinny, the cervix will shorten first and it has to open to give a pathway for the baby's head to come through. The rest of the body is softer and easier to get out after the head and the shoulders come out. The uterus will be continuing to contract down and expel the placenta.

Effacement, then dilation.



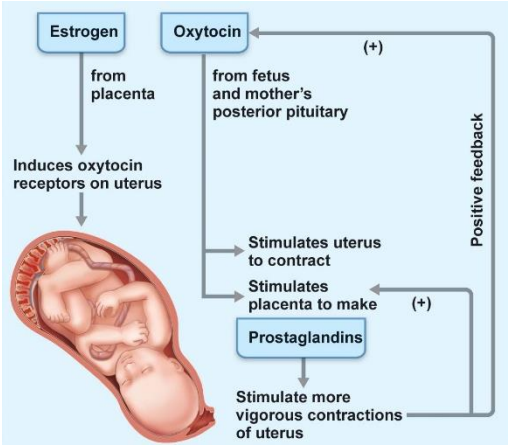
- **effacement:** process by which the cervix prepares for delivery. Cervix will shorten, gradually soften and become thinner.
- **Dilation:** baby's head drops down to pelvis, puts pressure on cervix and the pressure causes release of oxytocin which causes contractions, combination of hormones and pressure from the baby's head causes dilation.

Neuroendocrine regulation of the onset and completion of parturition

- Baby moves into birth canal; pressure of head on cervix→ **neuroendocrine reflex**→ stimulate hypothalamus to release of oxytocin from the posterior pituitary→ causes contractions→ more pressure on cervix→ stronger neural stimulation and more hormones released→ positive feedback until the baby comes out.
- Oxytocin stimulates uterus to **synthesize prostaglandins-** stimulate contractions in uterus wall.
- Oxytocin levels are high during latter part of pregnancy by labor not initiated because:

- **Progesterone** levels are also high.
- Insufficient oxytocin **receptors.**

- Stimulate myometrial cells to contract.
- Once the baby gets expelled, there is no longer pressure on the cervix.
- The sucking of nipples also stimulates the release of oxytocin.



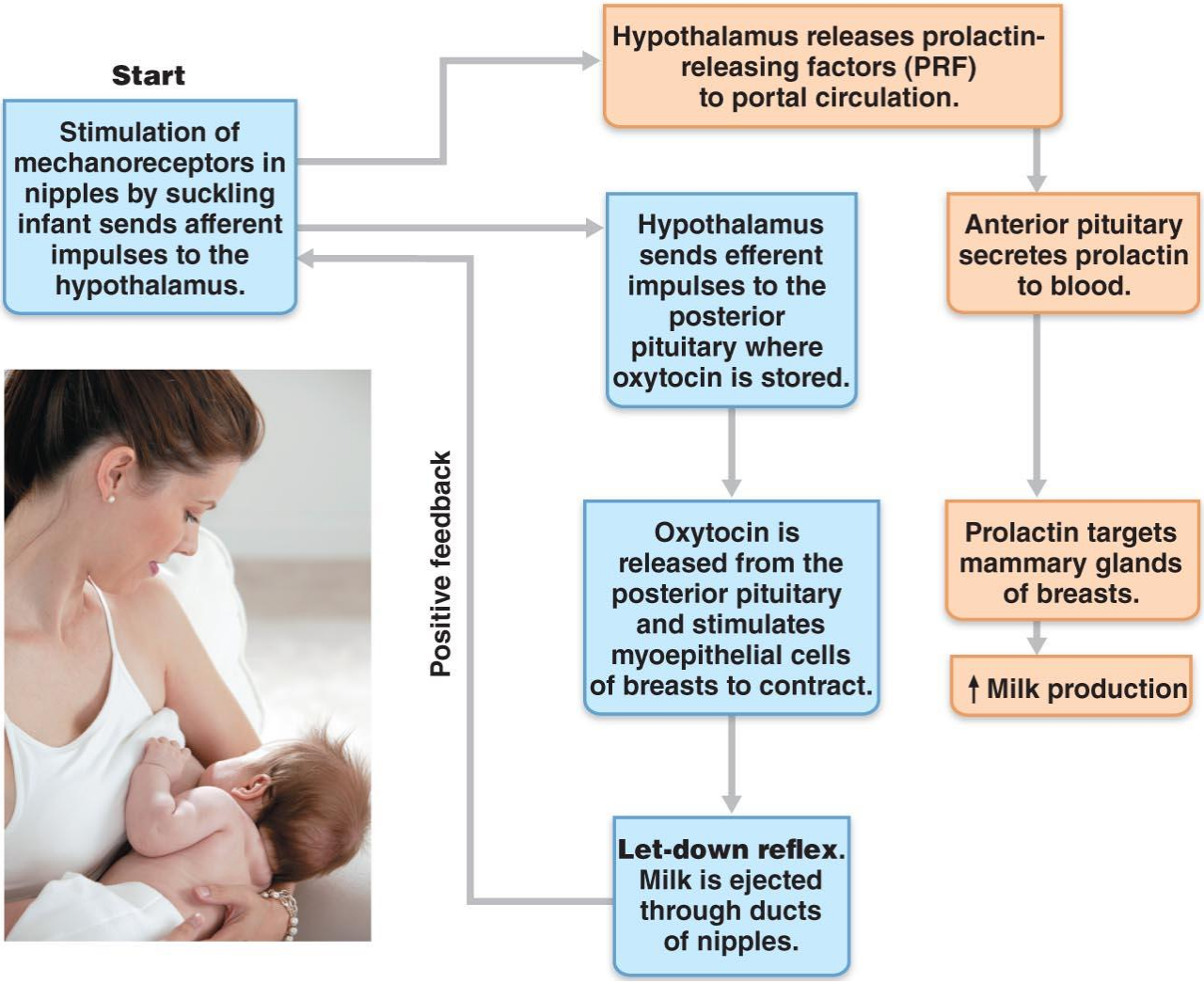
Pregnancy-associated preparation for lactation and the roles of prolactin and oxytocin in supporting milk production and milk let-down

Hormonal regulation of breast development

- **During pregnancy**
  - **Alveolus:** glandular structure involved in milk production; lined by a single layer of milk-secreting epithelial cells. (tiny milk producing gland, epithelial cells will push all the milk constituents into the lumen and the ducts will travel through breast tissue conveying the milk to the exist point (the nipple)).
  - Each mammary gland divided into 15-20 **lobes**; subdivided into **lobules**; basic component of each lobule is the **alveolus.**
  - in preparation for lactation, glands have to become active in the production of milk. Lots of preparation during pregnancy, then the level of milk production will increase.
  - Neuroendocrine pathway driving this process.
  - **Estradiol** and **progesterone** levels increased during pregnancy→ stimulate futher growth and development of alveloli and ducts.
  - also **permissive** actions of **glucocorticoids, prolactin, human chroionic somatomammotropin.**
  - **Prolactin** stimulates milk **production**; actual **secretion** during pregnancy **inhibited** by high levels of estrogen and progesterone.
- **Postpartum:**
  - levels of estradiol and progesterone decrease, allowing full expression of prolactin and oxytocin?
  - Now can have production (by prolactin) and secretion (milk let-down by oxytocin).

How lactation is maintained

- Classical Milk Let-down reflex and hormonal maintenance of lactation
  - 2 important hormones:
    - **Prolactin:** secretion of casein, lactose, fatty acids
      - basal levels will start to drift down and three months after delivery the levels might be down at baseline until the mom starts feeding. When the baby feeds, oxytocin stimulates the release of prolactin so there's a lift and the mom is ready to feed the baby again.
      - Every time the infant suckles, it will stimulate prolactin release
    - **Oxytocin:** contraction of myoepithelial cells
      - if the mom doesn't breastfeed the oxytocin levels will decrease and so will the prolactin levels.
      - Some of the oxytocin will simulate the release of prolactin.
  - Both of these hormones are required for continued lactation.



Define:

Corpus albicans: As the **corpus luteum** is being broken down by macrophages, fibroblasts lay down type I collagen, forming the **corpus albicans**. Regressed form of the corpus luteum.

Inhibin: hormone released by sertoli cells in male and granulosa cells in females that has a negative feedback on the release of FSH.

Diploid: has 2 sets of chromosomes.

Theca cells: produce testosterone in the female, endocrine cells associated with ovarian follicles. Make up the outer compartment of the basement membrane of the follicle.

Sertoli cells: tall columnar cells that make up the walls of seminiferous cells.

- Nourish developing spermatozoa
- Secrete fluid into seminiferous tubule lumen
- Digest cytoplasm discarded by spermatozoa
    - Bind FSH and testosterone
    - Produce inhibin→ negative feedback on production of FSH.

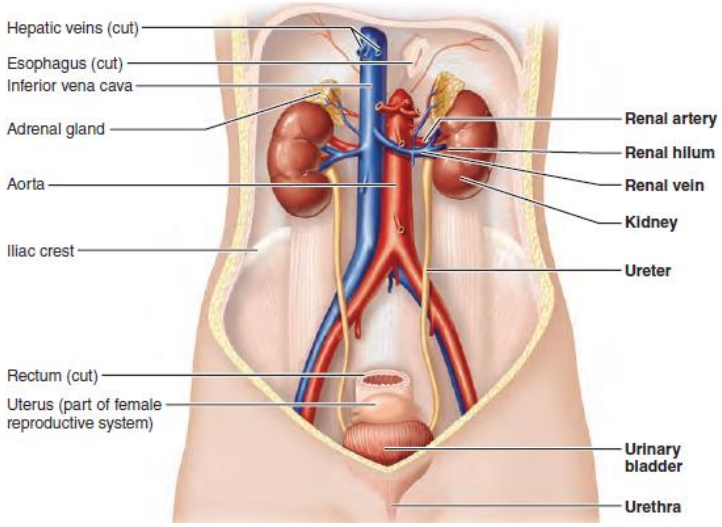
Androgen: sex hormone, Most important as a precursor for synthesis of estradiol in developing follicle.

Ovulation: process by which a mature oocyte is expelled from the ovaries.

Topic 4: Renal System

Overview of Kidney Functions

- Primarily responsible for maintaining stability of Extracellular fluid volume, electrolyte composition of the blood, and plasma osmolarity
- Main route for eliminating potentially toxic metabolic wastes and foreign compounds from the body.
- Maintain water balance in the body
- Maintain proper osmolarity of body fluids, primarily through regulating water balance.
    - Osmolarity: concentration of a solution expressed as the total number of solute particles per liter.
- Regulate the quantity and concentration of most ECF ions
- Maintain proper acid-base balance in the body.
- Excreting (eliminating) the end products (wastes) of bodily metabolism
- Excreting many foreign compounds.
- Producing renin.

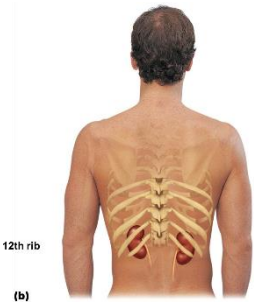


Urinary system organs

- **Kidneys-** major excretory organs- form the urine
    - Outer, granular appearing cortex
    - Inner, striated medulla
    - Renal pelvis in inner core of kidney collects urine after its formed.
    - Each kidney has a million nephrons.
- **Ureters-** transport urine from kidneys to urinary bladder
- **Urinary bladder-** temporary storage reservoir for urine
- **Urethra-** transports urine out of body.

Gross Anatomy of Kidneys

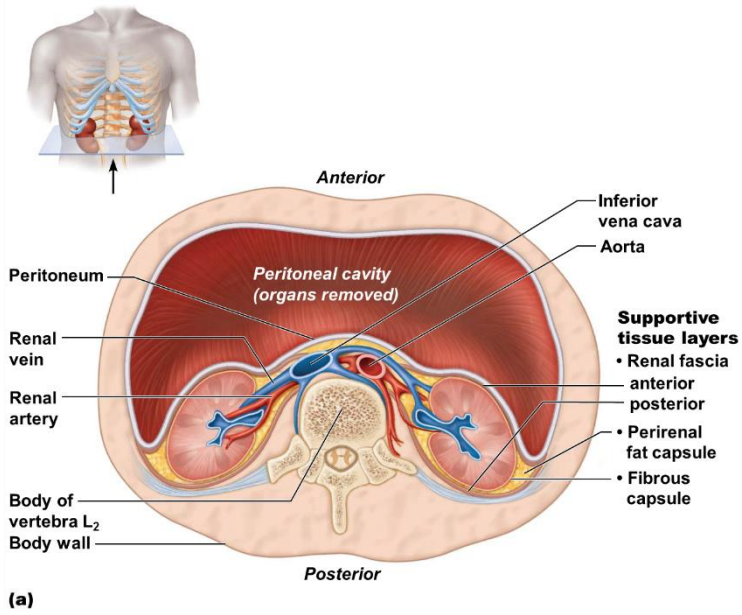
Location and external anatomy



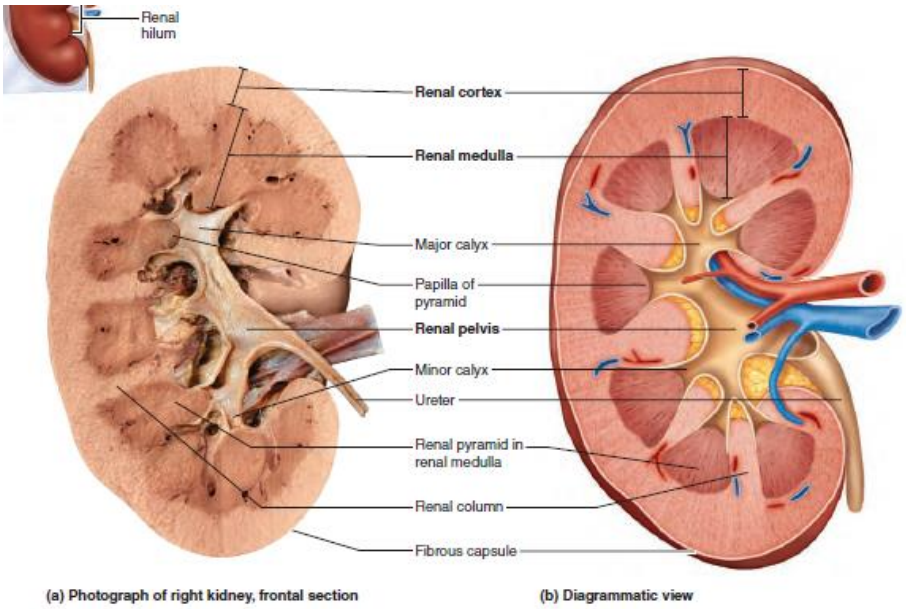
- Retroperitoneal, in the superior lumbar region (Located between T12 and L5)
- Right kidney is crowded by liver, so it's lower than the left kidney.
- Adrenal (suprarenal) gland sits atop each kidney: secrete aldosterone
- Convex lateral surface
- Concave medial surface with vertical **renal hilum** leads to internal space, renal sinus.
    - Ureters, renal blood vessels, lymphatics and nerves enter and exit at hilum.
- Concave medially: **renal hilus to renal sinus**

3 layers of supportive tissue

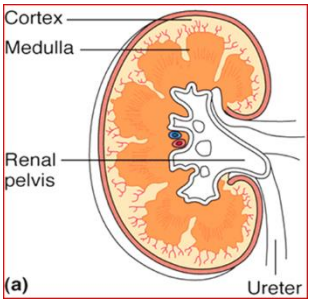
- **Renal capsule:** fibrous, adheres directly to kidney surface, strong barrier to prevent infections from the surrounding regions from spreading to the kidney.
- **Adipose capsule:** cushions, helps hold kidney in place.
- **Renal fascia:** dense CT surrounds adrenal gland and kidney, anchoring role.



Internal Anatomy



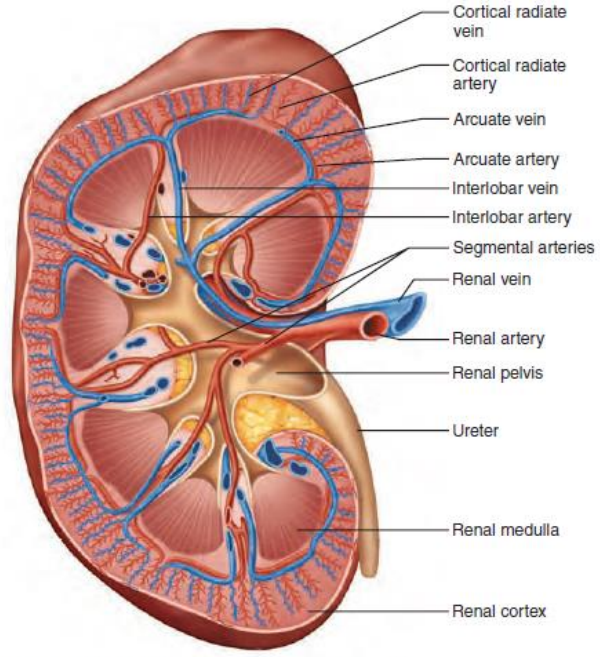
- **Cortex:** contains the renal corpuscules and the renal tubules except for the loop of Henle. Part of the kidney where ultrafiltration occurs.
- **Medulla:** darker colour; **medullary or renal pyramids (**containing nephrons)
    - why do they appear striped? Because they are formed almost entirely of parallel bundles of microscopic urine-collecting tubules and capillaries.
    - Apex (papilla aka nipple) points internally.
    - Separated by **renal columns** (cortical tissue); each medullary unit= ~1/8 of kidney
- **Pelvis:** flat, funnel-shaped tube
    - Continues with ureter; **major and minor calices**
        - Minor calices enclose papillae of pyramids; calices collect urine
    - calyces collect urine which drains continuously from the papillae, and empty into the renal pelvis.

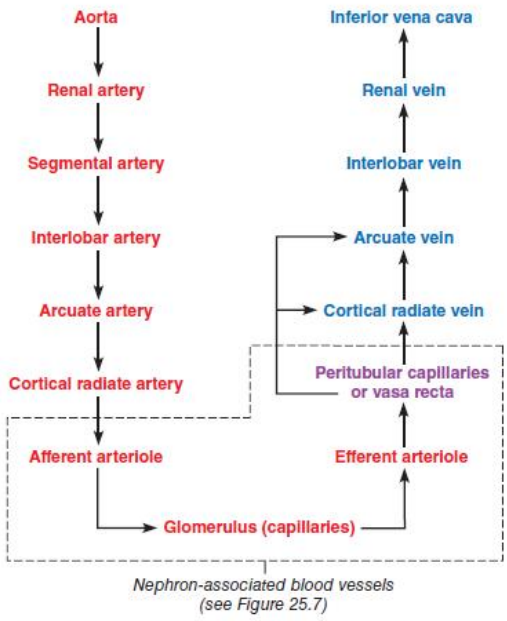


- walls of calyces, pelvis, and ureter contain smooth muscles, propel urine by **peristalsis**
- **what is pyelitis?** Infection of the renal pelvis and calyces.
- **What is pyelonephritis?** Infections that affect the entire kidney. Kidney swells, abscesses form and the pelvis fills with pus. Untreated, the kidney may be severely damaged but usually can be treated using antibiotics. Mostly cause by eschera coli.
- **Path of urine drainage:**
    - Papillary duct in renal pyramid→ minor calyx→ major calyx → renal pelvis→ ureter → urinary bladder.

Blood and Nerve supply

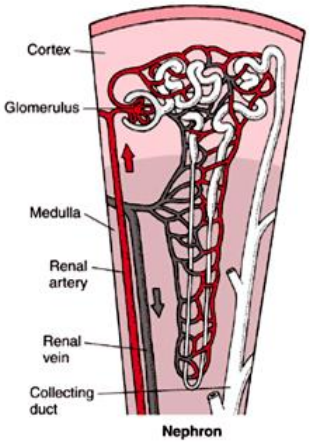
- 20% of cardiac output goes to the kidney (1/5); about 1200ml/min.
- When it goes inside glomerulus, 95% of the liquid is reabsorbed.





5 segmental arteries
No segmental veins.
Left renal vein longer (2x)
Renal plexus : network of ANS fibres and ganglia, provide the nerve supply for the kidney and the ureter. Most sympathetic fibres. SNS vasometer fibres regulate renal blood flow by adjusting the diameter of renal arterioles and influence the formation of urine by the nephron.

- renal arteries~ 1/5 total systemic CO (~1.2L) to kidneys/min.
- Arterial branches pass up between medullary pyramids to reach cortex; venous branches drain back via same route.
- Nerve supply provided by **renal plexus** of primarily **sympathetic** fibres→ regulate renal blood flow by adjusting diameters of renal arterioles



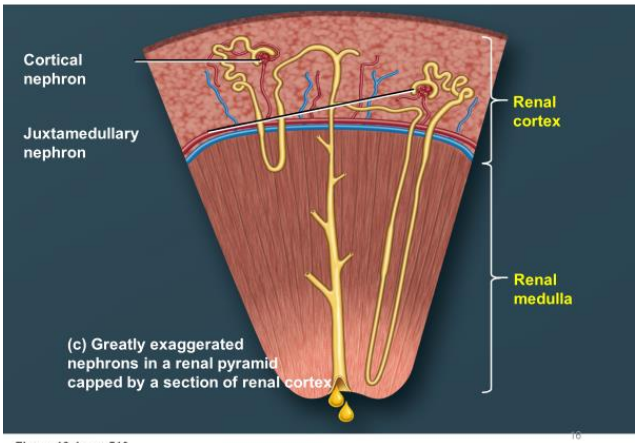
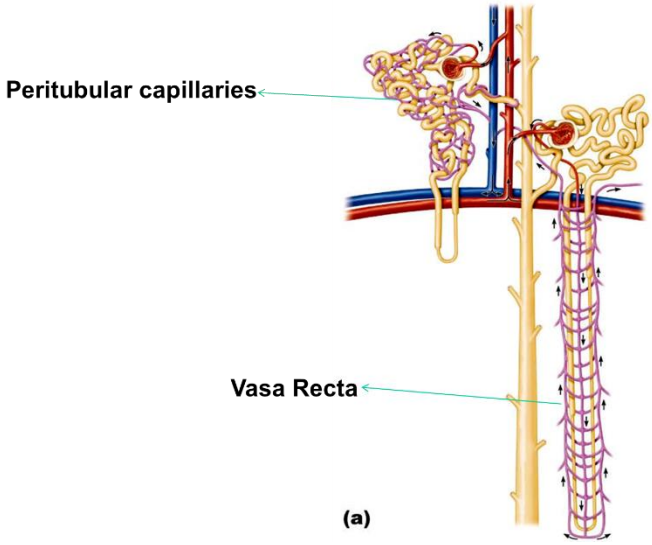


Figure 12-1c, p. 513

Nephron Capillary Beds

- **Peritubular capillaries**
  - Low pressure, porous capillaries adapted for absorption of water and solutes
  - Arise from efferent arterioles- these drain into renal venules
  - Cling to adjacent renal tubules in cortex
  - Empty into venules
  - **Surround the cortical nephrons**
- **Vasa recta**
  - Long, thin-walled vessels parallel to long nephron loops of **juxtamedullary nephrons.**
  - Arise from efferent arterioles serving juxtamedullary nephrons
    - Instead of peritubular capillaries
  - Function in formation of concentrated or diluted urine (like in kangaroos)
  - Found in outer medulla and inner medulla.

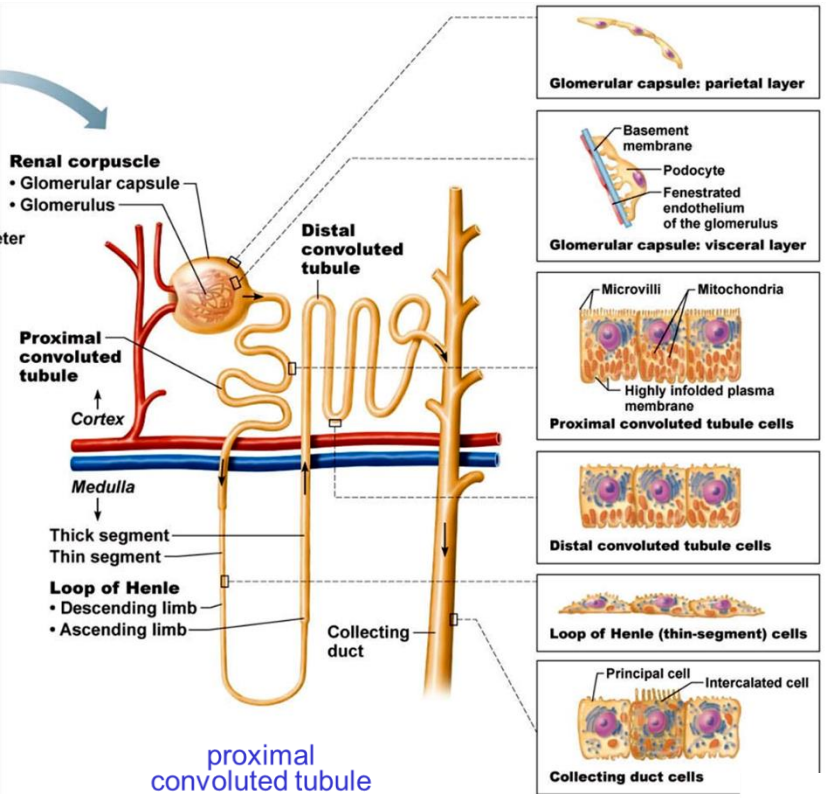


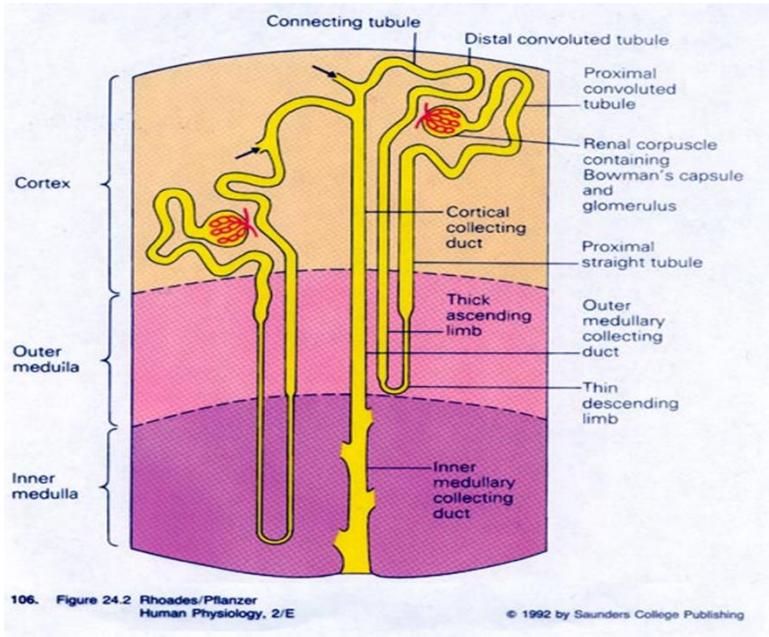
Nephrons

- Structural and functional units of the kidneys that form urine
- > 1million per kidney
- There are thousands of collecting ducts, collects fluid from several nephrons and conveys it to renal pelvis.
- **2 types of nephrons:**
  - **Cortical (85%)**: located entirely in the cortex except for the Loop of Henle.
  - **Juxtamedullary (15%)**
    - Role: concentration/ dilution of urine according to the situation→ adaptive. EXAM
- Each nephron consists of a renal corpuscle (in cortex) and a renal tubule (start in cortex and pass into medulla)
- **Renal Corpuscle consists of:**
  - **glomerulus** (tuft of capillaries)
    - specialized for filtration→ both fed and drained by arterioles
      - arterioles are high resistance vessels
      - afferent arteriole has larger diameter.
    - endothelium of glomerular capillaries is fenestrated (penetrated by many pores)→ very porous.
    - Allows for large amounts of solute-rich fluid to pass from the blood into the glomerular capsule.
    - Plasma-derived fluid that renal tubules process to form urine: **filtrate**
  - **glomerular capsule (aka Bowman's capsule).**
    - Cup shaped hollow structure surrounding glomerulus
    - Two layers:
      - external **parietal layer** (simple squamous epithelium→ just structure, no firltration)

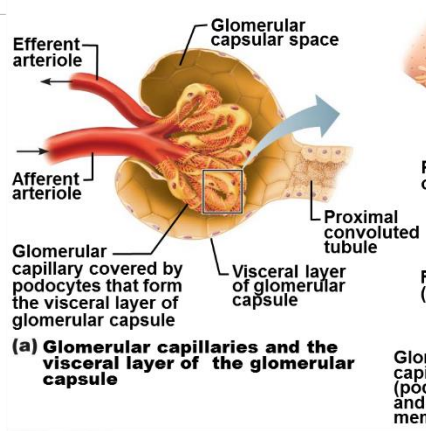
- **visceral layer** that clings to glomerular capillaries (highly modified epithelial cells called **podocytes)**.
    - Octopus like podocyte terminate in **foot processes,** which interditate aas they cling to the basement membrane of the glomerulus.
    - Clefts or openings between the foot processes are the **filtration slits (**filter enters **capsular space).**

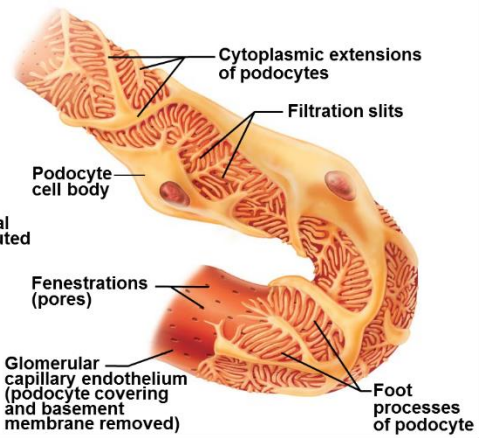
- **Renal Tubule and Collecting duct**
    - **Renal tubule** is about 3cm long.
        - Consists of a single later of epithelial cells, but each region has its own unique histology and function.
        - Four major parts:
            - **Proximal convoluted tubule:** closest to renal corpuscle→ 2/3 of filtrate is reabsorbed.
            - **Thin descending and ascending loop of Henle and thick ascending loop of Henle**
            - **Distal convoluted tubule-** cuboidal epithelial cells,
    - Distal convoluted tubule drains into the collecting duct which is made of three parts: **cortical collecting duct, medullary collecting duct and inner medullary collecting duct.**
    - Collecting duct runs through the medullary pyramids and fuse together as they approach the renal pelvis to deliver urine into the minor calyces via papillae of the pyramids.
    - **Collecting duct has two cell types**
        - **principal cells**: lack microvilli, maintain water and Na balance
        - **intercalated cells**: cuboidal cells with lots of microvilli, acid-base balance.





proximal convoluted tubule
↓
loop of Henle
↓
distal convoluted tubule
↓
collecting duct
↓
papillary duct
↓
minor calyx

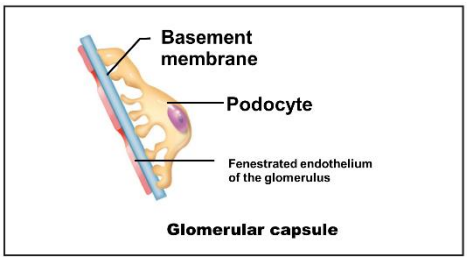




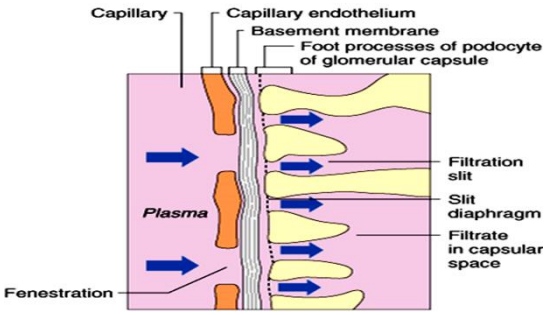
Kidney Physiology: Mechanisms of Urine Formation

Glomerular Filtration

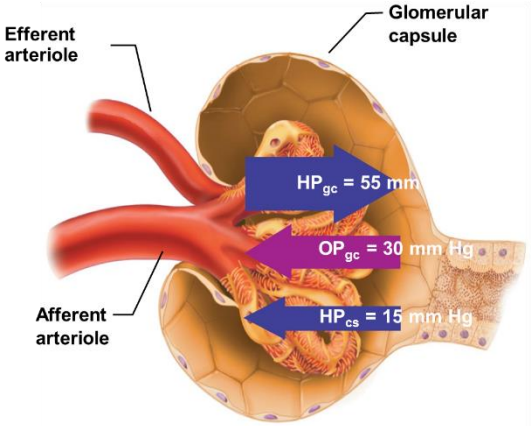
- Passive, selective (**size and charge**), fluids and solutes forced through by **hydrostatic pressure** (from heart).
- Glomerulus very efficient filter because:
  - Filtration membrane 1000x more **permeable** than other capillary membranes
  - Glomerular bp **higher** than in other capillary beds (55mm Hg vs. <18mm Hg)
  - **What allows this bp to maintained at such a high level?** The shape of the glomerular capillaries.



- 180L filtrate formed by kidney capillaries vs. 3-4L by all other capillary beds combined.
- **The filtration membrane**
  - Between blood and interior of glomerular capsule- 3 layers:
    - **Fenestrated capillary endothelium**
    - **Basement membrane** (negatively charged)
    - **Visceral membrane of glomerular capsule= podocytes**



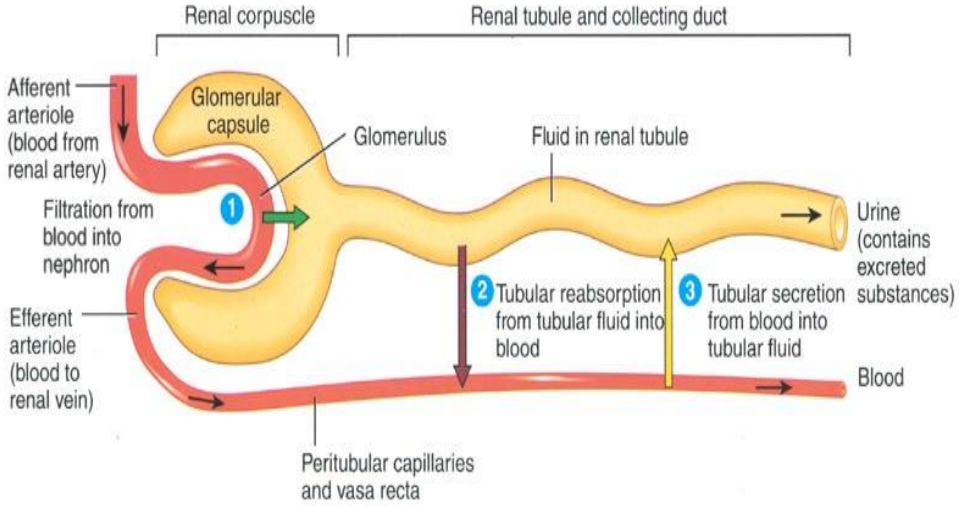
  - Molecules <3nm (water, glucose, a.a., N-wasters) pass easily
  - Molecules 3-6nm pass, but with difficulty
  - Molecules > 7nm are not filtered (proteins and RBCs).
  - Basement membrane restricts passage of most larger proteins; aided by negative charges on most basement membrane proteins
  - Retention of plasma proteins maintains colloid osmotic pressure, blood flow. Presence of proteins or RBCs in urine suggests filtration membrane damage.
- **Pressures that affect filtration**
  - Outward pressures:
  - **Hydrostatic pressure in glomerular capillaries (HP_{gc})**
    - Glomerular blood pressure.
    - Favor filtration- Very high: 55 mm Hg.
    - Remains high throughout capillary bed because efferent arterioles have a smaller diameter.
  - **Colloid osmotic pressure in the capsular space**
    - Would pull filtrate but since there are no proteins in the capsule, it's 0.
  - Inward pressures:
  - **Hydrostatic pressure in the capsular space (HP_{cs})**
    - Pressure exerted by filtrate in the glomerular capsule.
    - Opposes filtration – 15 mm Hg
  - **Plasma- Colloid osmotic pressure in glomerular capillaries (OP_{gc})**
    - Pressure exerted by proteins in the blood.
    - Opposes filtration – 30 mm Hg



NFP = Net filtration pressure
= outward pressures – inward pressures
= (HP_{gc}) – (HP_{cs} + OP_{gc})
= (55) – (15 + 30)
= 10 mm Hg

- **Glomerular filtration rate**
  - Volume of filtrate formed each minute by both kidneys (normal 120-125ml/min)
  - directly proportional to:
  - **Net filtration pressure** (most importantly the hydrostatic pressure in the glomerulus, can be controlled by changing the diameter of afferent arterioles).
  - **Total surface area available for filtration:** Mesangial cells contract to adjust total SA available for filtration
  - **Filtration membrane permeability:** more permeable because of fenestrations.
  - 180L of filtrate produced daily with a normal GFR of 120-125ml/min.
- **General definitions:**

Relation of a nephron's structure to its three basic functions (Figure 26.7)

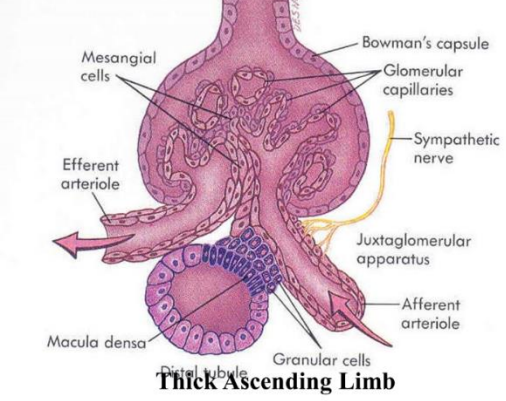


- Amount excreted= amount filtered- amount reabsorbed + amount secreted

- **Calculation of the GFR using Inulin**
  - Use inulin to figure out the GFR because it is freely filtered at the glomerulus and is neither absorbed nor secreted by the nephron. The amount filtered per unit of time equals its plasma concentration (P_{IN}) multiplied by GFR.
  - Plasma inulin concentration is known and they measure how much is excreted and how much remains in the blood. Inulin is not metabolized, synthesized or stored by the kidney tubules, so filtered and excreted amounts are equal.
  - Therefore: amount filtered (Plasma inulin concentration x GFR)= amount excreted (urine inulin concentration x V)
  - GFR is equal to the inulin **clearance (C_{IN})**
    - Clearance is the volume of plasma from which all the substance has been completely removed and excreted into the urine.
    - GFR is the glomerular filtration rate.
  - $$GFR = \frac{U_{IN} \times \dot{v}}{p_{IN}} = C_{IN}$$
    - Plasma inulin P_{in} and urine inuline (u_{in}) are in mg/ml.
    - V is the urine flow rate in ml/min.
    - Rate of appearance in urine= rate of appearance in filtrate
    - Amount excreted in urine per unit of time= amount filtered by the glomerulus per unit of time.
    - Amount filtered= amount excreted
    - V x uin= GFR x pin
    - **GFR is 125ml/minb**

- **Calculation of the GFR using creatinine**
  - Creatinine is freely filtered across the glomerulus and not reabsorbed, secreted or metabolized by the nephron. Unlike inulin, creatinine is produced by the body through dephosphorylation of phosphocreatinine in the muscles. In many clinal settins, creatinine is used to estimate or measure GFR.
  - Creatinine can be used to measure GFR in man and it is routinely performed in suspected cases of renal disease by nephrologists.
  - All the creatinine coming to the kidney in the renal artery does not get filtered in the glomerulus (15-20% of plasma creatinine is filtered)
  - The portion not filtered is returned to systemic circulation in the renal vein.
  - Amount filtered (plasma creatinine concentration x GFR)= amount excreted (Ucr x V)
  - Clearance for inulin provides a mean for determining the GFR.
  - $$GFR = \frac{U_{cr} \times \dot{v}}{p_{cr}} = C_{cr}$$
  - **GFR is in ml/min- 135ml/min**

- **Plasma inulin and creatinine as an estimate of GFR in renal failure**
  - In a perfectly healthy patient, urine concentration is 130 times higher than plasma. Plasam and urine concentrations must be in the same units.
  - What happens if GFR decreases by 50%? The plasma creatinine concentration increases as GFR decreases in chronic kidney disease (CKD). It is clear that plasma creatinine concentration is a good index of GFR when GFR has decreased to less than half of normal.
  - The value of 135ml/min is the volume of plasma which has been completely cleared of its creatinine to account for the amount appearing in the urine. This volume is also known as the plasma clearance of creatinine.
  - Can calculate plasma clearances for other substances as well. How?
    - Ex. Since there is no glucose in the urine of a normal person the plasma clearance of glucose is 0ml/min. Plasma clearances are calculated from plasma and urine concentration and urine flow rate.
- **Plasma Urea Clearance:**
  - We can use plasma clearance to determine how certain substances are handled by the kidney.
  - If plasma clearance is less than the GFR, we know the substance was reabsorbed.
  - If plasma clearance is greater than the GFT, we know the substance was secreted.
  - Blood urea nitrogen is influenced by protein intake, GFR and metabolic rate. Urea excretion is determined by GFR and urine flow rate. For these reasons, BUN **cannot** be used as the only index of GFR.
- **Regulation of Glomerular filtration**
  - Constant GFR is important as it allows kidneys to make filtrate and maintain extracellular homeostasis.
    - Goal of local **intrinsic controls** (**renal autoregulation)**: maintain GFR in kidney
  - GFR affects systemic blood pressure
    - Increased GFR causes increased urine output, which lowers blood pressure and vice versa.
    - Goal of **extrinsic controls**: maintain systemic blood pressure
      - Nervous system and endocrine mechanisms are main extrinsic controls.
      - Will override renal intrinsic controls if blood volume needs to be increase.
      - SNS: under normal conditions at rest:
        - Renal blood vessels dilated
        - Renal autoregulation mechanisms prevail.
  - 3 regulatory influences allow for an **optimal rate of flow:**
  - **Renal autoregulation (intrinsic)**
    - Kidney keeps GFR~ constant by determining own rate of flow and adjusting nephron blood flow when MAP is in range of 80-180 mmHg.
      - Autoregulation ceases if out of that range.
    - Regulates **diameter** of **afferent** (primarily) and **efferent** arterioles.
    - 2 types of controls:
      - **Myogenic mechanism**
        - Vascular smooth muscle contracts when stretched and relaxes when not.
        - Rising systemic BP stretches vascular smooth muscle in arteriolar walls, causing the afferent arterioles to constrict→ restrict blood flow and decrease BP.
          - Protects glomeruli from damaging high BP.
        - Declining systemic blood pressure causes dilation of afferent arterioles→ increase BP.
        - Both help to maintain normal GFR despite normal fluctuations in BP.
      - **Tubuloglomerular feedback mechanism.**
        - Directed by the macula densa cells of the juxtaglomerular complex. Cells located in the walls of the ascending limb of the nephron, respond to filtrate NaCl concentration.

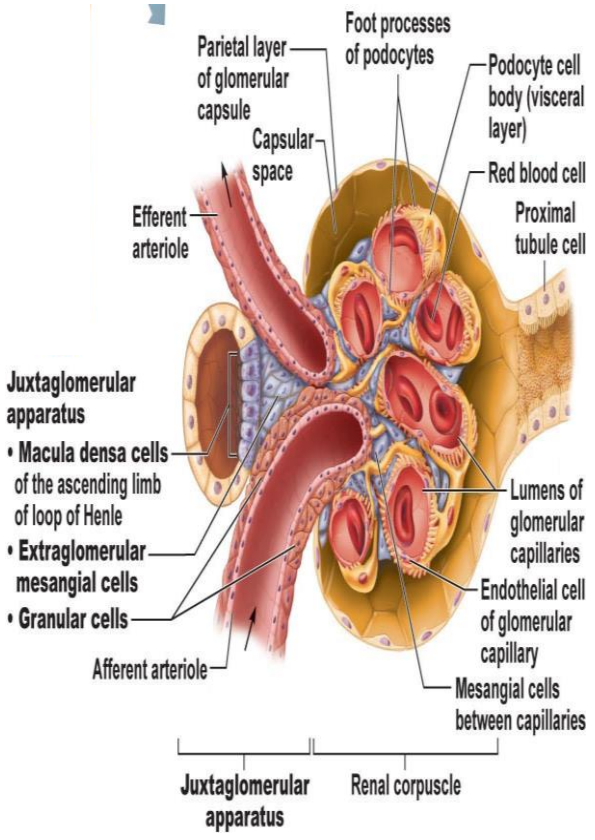


- High levels of NaCl in filtrate→ release vasoconstrictor chemicals from macula densa cells(ATP) → Adenosine constricts the afferent arteriole→ reduce blood flow→ decreased NFP and GFR, filtrate slows down and allows for NaCl reabsorption.
- Low NaCl levels in filtrate→ inhibit ATP release from macula densa cells→ vasodilation of afferent arterioles→ increased NFP and GFR.

- **Juxtaglomerular apparatus:** at junction of thick ascending limb and afferent/efferent arterioles; regulate renal function:
  - Arteriole walls: JG cells (granular cells): enlarged smooth muscle cells- mechanoreceptors; secrete renin for extrinsic mechanisms.
  - tubule wall: macula densa: chemo or osmoreceptors- monitor filtrate and adjust GFR for intrinsic mechanisms. In the macula densa, ATP→ adenosine. Adenosine constricts the afferent arteriole.
  - JGA regulates: filtrate formation + systemic BP
- **Neural controls**

angiotensinogen (from liver)
↓ (renin)
angiotensin I
↓ (ACE)
angiotensin II

  - **Sympathetic** NS comes into play during times of extreme stress. Overrides renal autoregulation and shunts blood to heart, brain, skeletal muscles at the expense of kidneys
    - Direct sympathetic induced vasoconstriction of afferent arterioles
    - Activation of renin-angiotensin system through
      - (JC) granular cells (smooth muscle cells in afferent arterioles- **mechanoreceptors)**.
      - Macula densa cells: tubule cells= **chemoreceptors- osmoreceptors.**
  - If extracellular fluid volume extremely low (BP low)
    - Norepinephrine released by SNS. Epinephrine released by adrenal medulla
      - Systemic vasoconstriction→ increased blood pressure
      - Constriction of afferent arterioles→ decreased FGR→ increased (restore) blood volume and blood pressure to normal.
- **Hormonal Renin-angiotensin system**
  - body's main mechanism for increasing BP. w/o BP→ no glomerular filtration.
  - Low BP causes granular cells of the juxtaglomerular complex to release **renin.**
  - Three pathways for renin release by granular cells
    - Direct stimulation of granular cells by SNS to release renin (baroreceptor reflex)→ b-adrenergic receptors by SNS.
    - Stimulation by activated macula densa cells when filtrate NaCl concentration is low, they activate the granular cells to release renin.
    - Reduced stretch of granular cells. These cells act as mechanoreceptors. Decrease blood pressure reduces the tension in the granular cells and stimulates the release of renin.



Intrinsic Mechanisms:

maintain glomerular filtration rate (GFR) relatively constant

Myogenic Mechanism:

↑ Bl.Pr → ↑ Stretch → ↓ arteriole diameter→ ↓ HPg → ↓ GFR
↓ Bl.Pr → ↓ Stretch → ↑ arteriole diameter → ↑ HPg → ↑ GFR

Tubuloglomerular Feedback Mechanism:

↑ GFR → ↑ NaCl → ↑ secretion of ATP → ↓ arteriole diameter → ↓ HPg → ↓ GFR
↓ GFR → ↓ NaCl → ↓ secretion of ATP → ↑arteriole diameter → ↑ HPg → ↑ GFR

Extrinsic Mechanisms:

maintain glomerular filtration rate (GFR) and blood pressure (Bl. Pr.) relatively constant

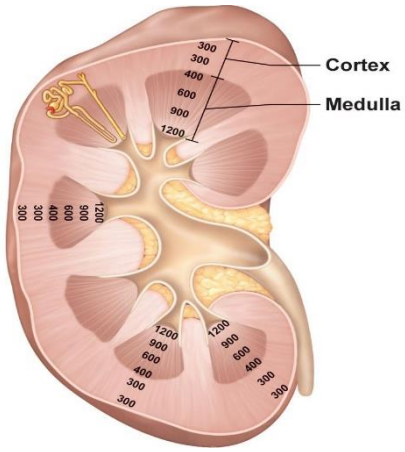
Sympathetic nervous system:

↑ Sympathetic stimulation → ↓ arteriole diameter→ ↓ HPg → ↓ GFR

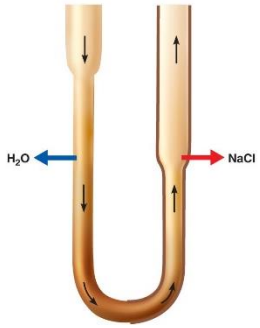
Renin-Angiotensin Mechanism:

↑ Angiotensin II → ↓ arteriole diameter → ↓ HPg → ↓ GFR

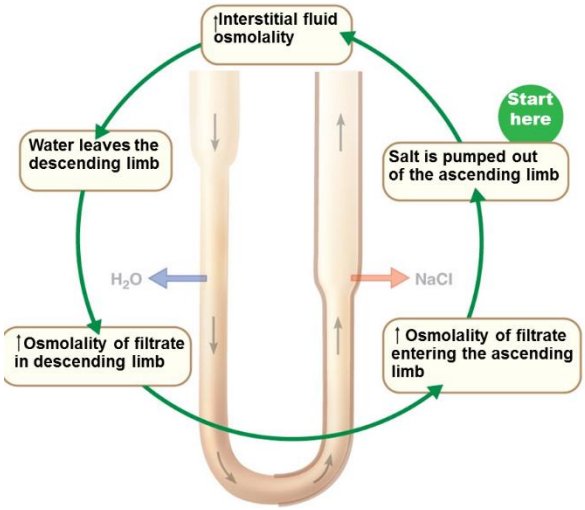
↑ Angiotensin II → ↑ Aldosterone release → ↑Blood volume → ↑ Blood pressure



Concentrating Mechanisms of the Kidney- Excretion of excess water and solutes

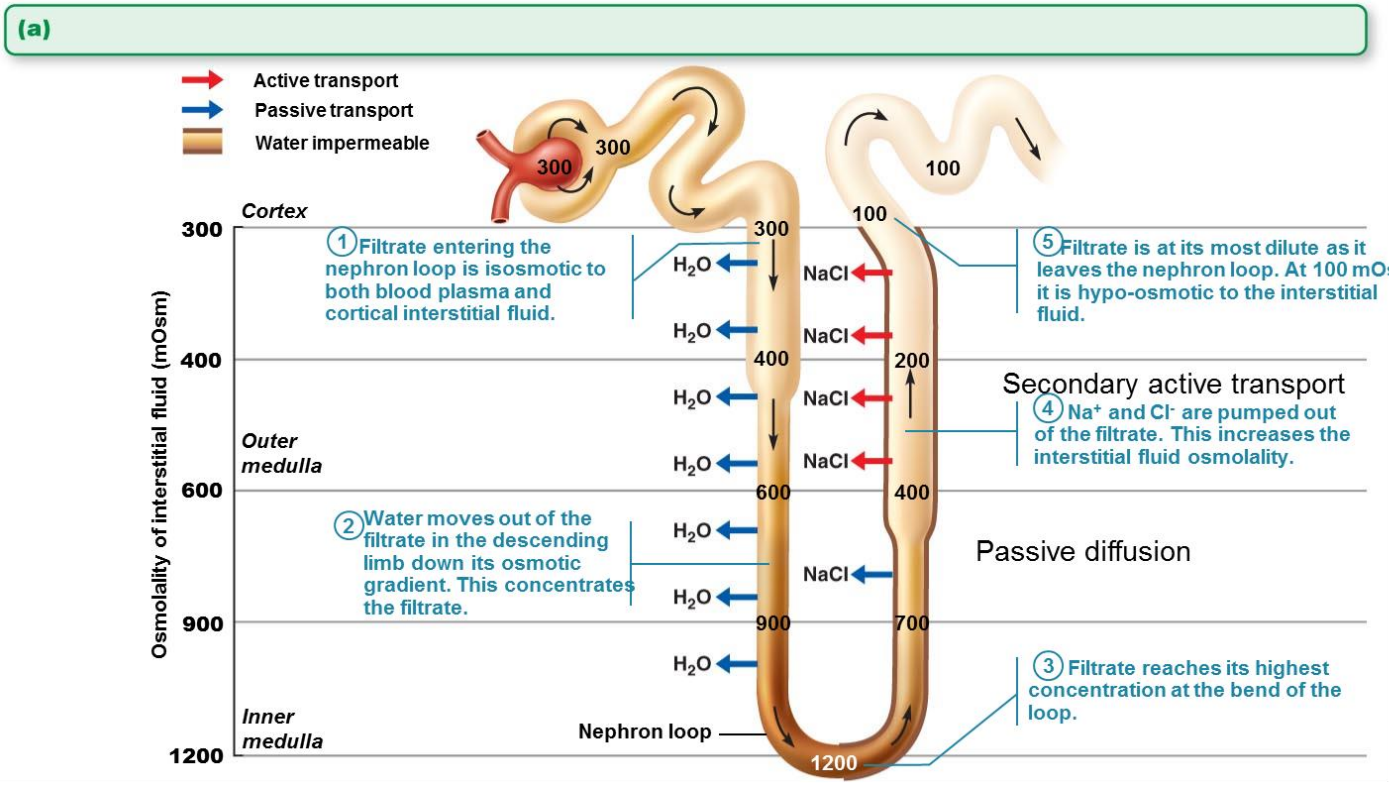


- **Composition of the urine of an adult**
  - In the urine, there is: Na+, K+, Cl-, Mg+, urea, creatinine
  - pH- 5.0-7.0 (acidic)
  - Osmolality 500-800 mOsm/kg H20
- **Loop of Henle**
  - Concentrating mechanism
  - If you live in the water you don't need to concentrate urine (no loop of Henle)
  - If you're a mammal, you have a loop of Henle to concentrate urine.
  - Start with osmolality off 300 and go down to 1200.
  - Higher osmolality= more concentrated
- **Juxtamedullary nephrons create an osmotic gradient within the renal medulla that allow the kidney to produce urine of varying concentrations.**
  - Long nephron loops of juxtamedullary nephrons create the gradient.
  - The countercurrent multiplier depends on three properties of the nephron loop to establish the osmotic gradient
    - Fluid flows in the opposite direction (countercurrent) through two adjacent parallel sections of the nephron loop (loop of Henle).
    - The descending limb is permeable to water, but not to salt.
    - The ascending limb is impermeable to water, and pumps out salt.
  - These properties establish a positive feedback cycle that uses the flow of fluid to multiply the power of the salt pumps.
  - As water and solutes are reabsorbed, the loop first concentrates the filtrate, then dilutes it.
    - Filtrate entering the nephron loop is isosmotic to both blood plasma and cortical interstitial fluid.
    - Water moves out of the filtrate in the descending limb down its osmotic gradient. This concentrates the filtrate.
    - Filtrate reaches its highest concentration at the bend of the loop.
    - Na+ and CL- are pumped out of the filtrate. This increases the interstitial fluid osmolality.
    - Filtrate is at its most dilute as it leaves the nephron loop. At 100mOsm, it is hypo-osmotic to the interstitial fluid osmolality.



- The three key players and their orientation in the osmotic gradient
  - The **long nephron loops** of juxtamedullary nephrons create the gradient. They act as **countercurrent multipliers.**
  - The **vasa recta** preserve the gradient. They act as **countercurrent exchangers.**
    - Descending vasa recta is permeable to salt and urea.
  - The **collecting ducts** of all nephrons use the gradient to adjust urine osmolality.
  - The osmolality of the medullary interstitial fluid progressively increases from the 300 mOsm of normal body fluid to 1200 mOsm at the deepest part of the medulla.

- **Urea-recycling**
  - Urine is a byproduct of the deamination of protein, you need urea to concentrate urine.
  - Without urea, you can't excrete concentrated urine.
  - Inner medulla region, vasa recta reabsorbs some urea because you need it to concentrate urine so you don't want to excrete ALL of it, you always want to have some in your body.
  - **Osmolarity (Osm/L) is the total concentration of all solutes in the solution.**
  - **Osmolality is the concentration of a solution expressed as the total number of solute particles per kilogram.**

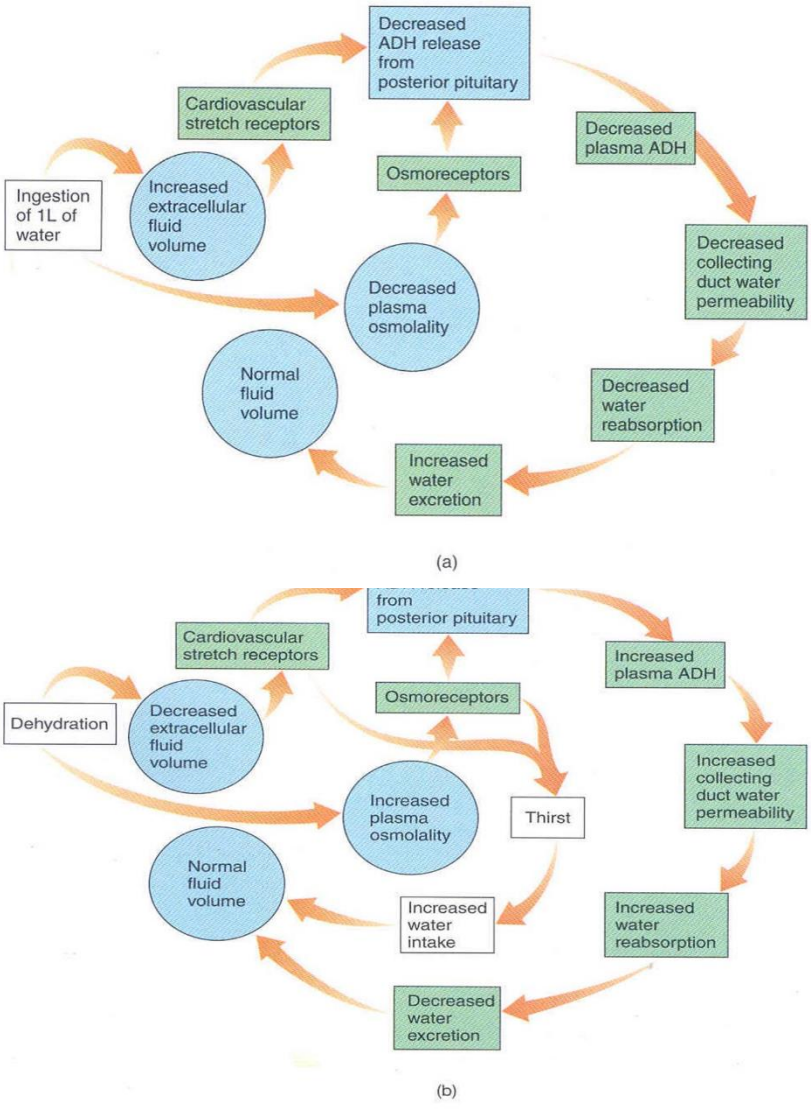


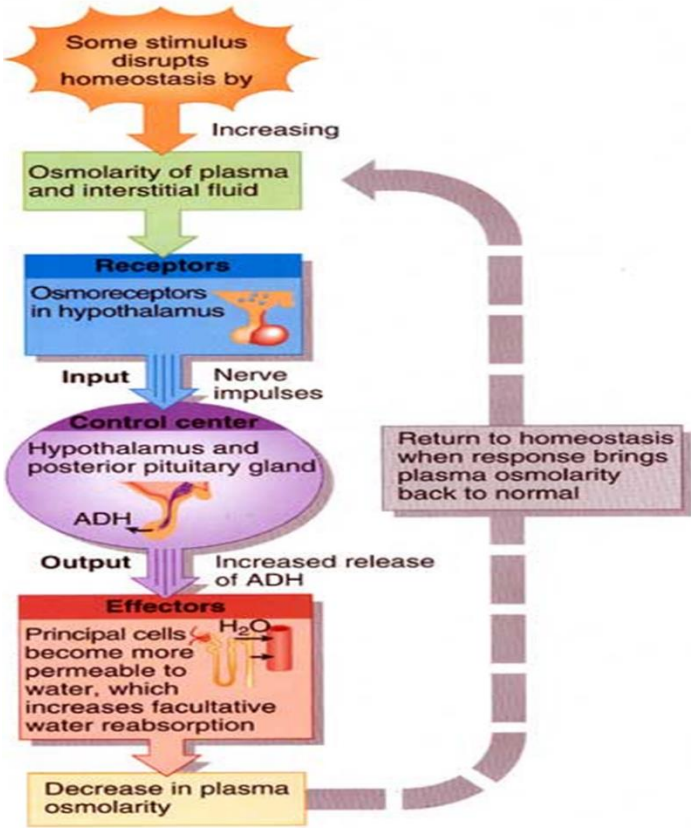
- **Functions of ADH**
  - blood rises→ posterior pituitary releases ADH→ collecting ducts become more permeable to water→ increased reabsorption of water into the peritubular capillaries and vasa recta→ osmolarity of blood returns to normal→ inhibits ADH release.
  - ADH makes principal cells of the collecting ducts more permeable to water by causing more aquaporins to be inserted into their apical membranes. Amount of ADH determines the number of aquaporins.
  - ADH binds to receptors on the basolateral membrane and activates a G-protein which activates adenylate cyclase and changes ATP → cAMP. cAMP activates kinases that cause more aquaporins to go the the membrane.
  - Osmoreceptors of the hypothalamus sense the ECF solute concentration and trigger or inhibit ADH release from the posterior pituitary.
  - Large changes in blood volume or blood pressure influence ADH secretion (detected by baroreceptors in the atria and various blood vessels and indirectly via the renin-angiotensin-aldosterone mechanism).

- Osmolality also influenced by reduced blood volume due to sweating, vomiting, diarrhea, severe blood loss, traumatic burns, and prolonged fever. High concentrations of ADH constrict arterioles (vasopressin)

- **Excretion of urine of varying concentrations:**
  - IF ADH (aka vasopressin) present→ water reabsorbed is conserved for body→ small volume of concentrated urine.
    - Filtrate has concentration 100mosm/l as it enters collecting tubule.
    - Collecting tubule permeable to water because of aquaporins
    - Concentration of urine may be up to 1200 mosm/l as it leaves collecting duct.
  - If Low ADH present (aka vasopressin)→ water not reabsorbed in the distal portion of nephron→ large volume of dilute urine; excess water eliminated.
    - Filtrate has concentration of 100mosm/l as it enters distal and collecting tubule
    - Collecting tubule- impermeable to water.
    - Concentration of urine may be as low as 100 mosm/l as it leaves collecting duct.

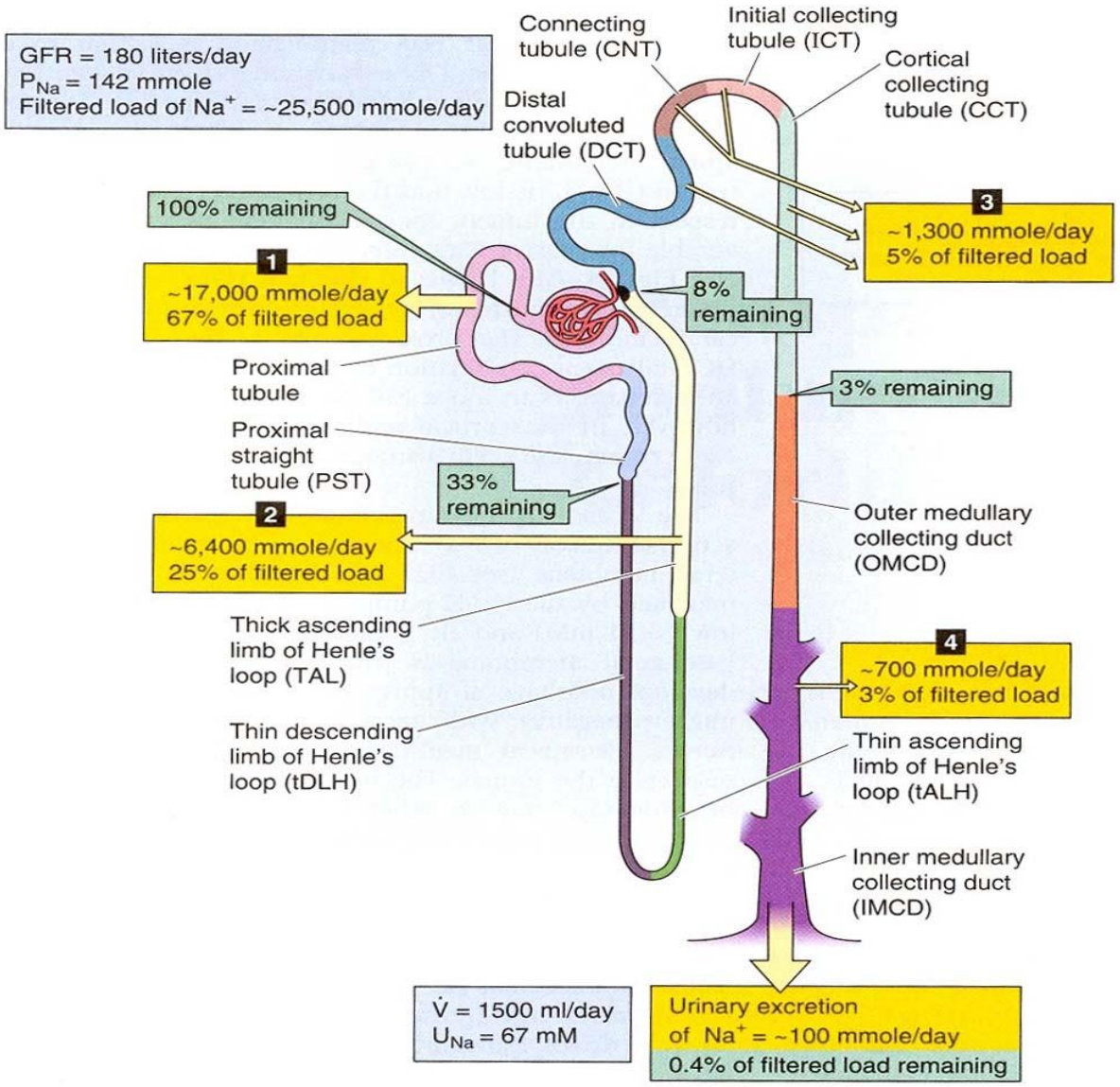
- **Negative feedback regulation of facultative water reabsorption by ADH**





Filtration

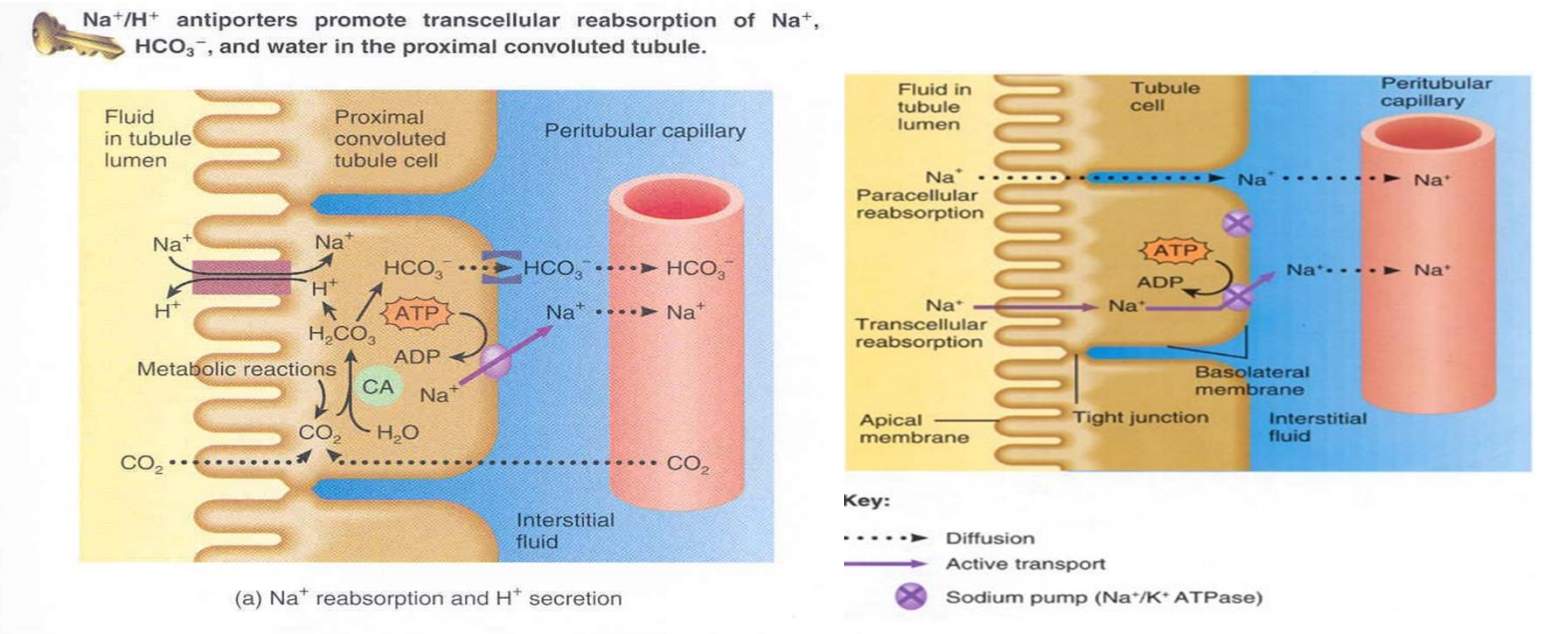
- For solutes to which glomerulus is readily permeable:
  - **Filtration rate** = [] in plasma x GFR (125ml/min)
    = [] in plasma x 180L/day
- Ex. [Na]= 140mmole/L
  - Filtration rate= 140 x 180L/day= 25,200 moles/day

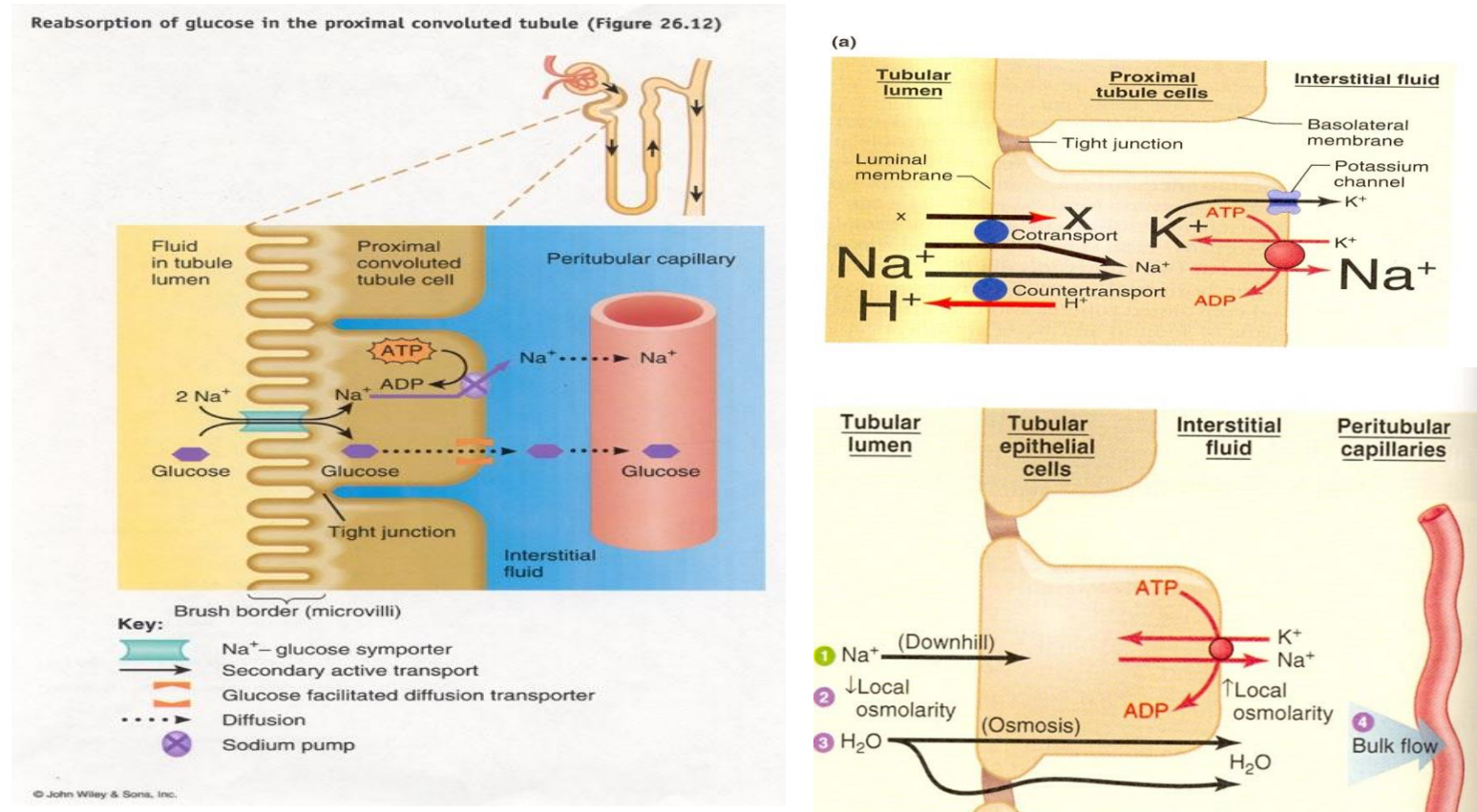


Tubular Transport Process: Renal Handlings of Sodium and Glucose

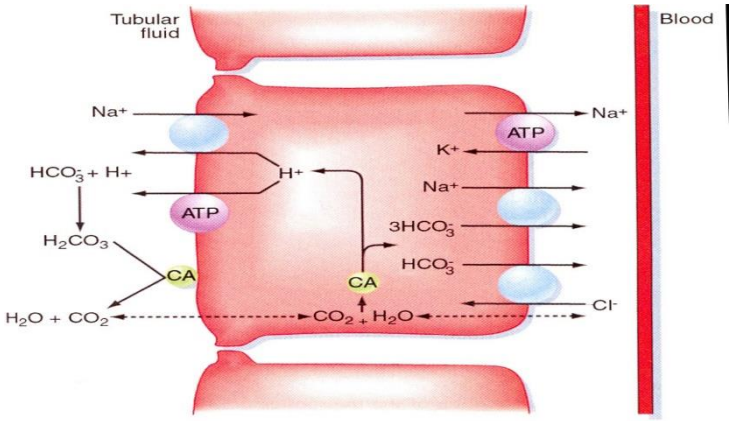
- **Reabsorbed substances route**
  - **Transcellular route:** move through the apical membrane, the cytosol, and the basolateral membrane of the tubule cell and then the endothelium of the peritubular capillaries.
  - **Paracellular route:** between cells- limited by tight junctions connecting these cells, in the proximal tubule, these tight junctions are leaky and allow water and some important ions through.
- **Transport properties of the Proximal tubule**
  - Reabsorbs all the glucose and amino acids in the filtrate and 65% of the sodium and water.
  - Nearly all the uric acid and about half of the urea are reabsorbed in the proximal tubule.
  - **Primary active transport of sodium ions via basolateral Na+-K+ pumps;** crosses apical membrane through channels, symporters, or **antiporters (**one goes in and 1 goes out**).**
  - Virtually all nutrients (glucose, a.a., vitamins, some ions) through secondary active transport with Na+.
  - Cl-, K+, Mg2+, Ca2+ and others through passive paracellular diffusion driven by electrochemical gradient.
  - **Bicarbonate through secondary active transport linked to H+ secretion and Na+ reabsorption.**
  - Water through osmosis; driven by solute reabsorption.
  - Liquid-soluble solutes through passive diffusion driven by the concentration gradient created by reabsorption of water.
  - Urea through primarily passive paracellular diffusion driven by chemical gradient.
  - 2/3 of filtrate is reabsorbed in the proximal tubule.

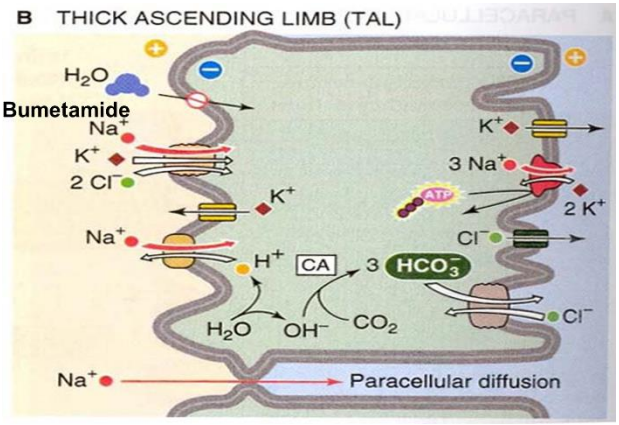
- **Proximal tubule transport of Sodium**
  - Na+/H+ antiporters promote transceullar reabsorption of Na+, HCO3-, and water in the proximal convoluted tubule.



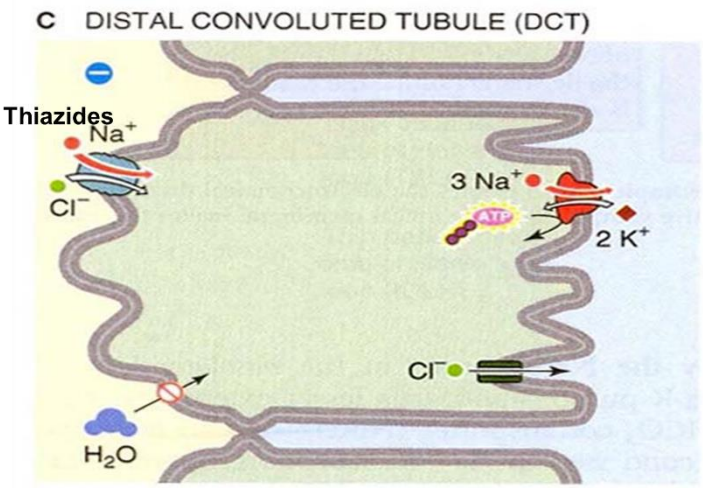


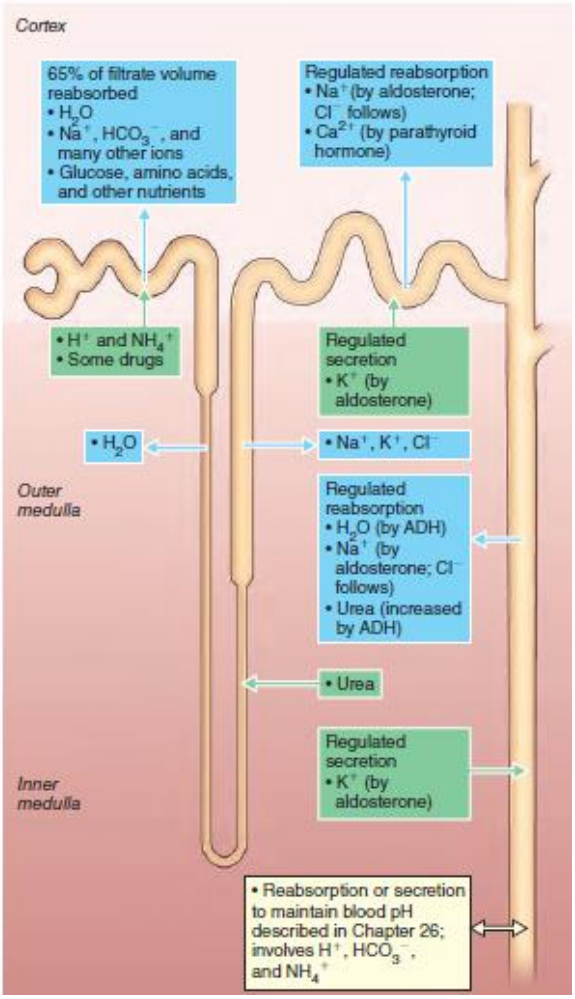
- **Nephron Loop reabsorption**
  - Descending limb: Water through osmosis
  - Ascending limb:
  - Na+, Cl-, K+ through secondary active transport of Cl-, Na+ and K+ via Na+-K-2Cl cotransporter.
  - Ca2+ and Mg2+ through passive paracellular diffusion driven by electrochemical gradient.

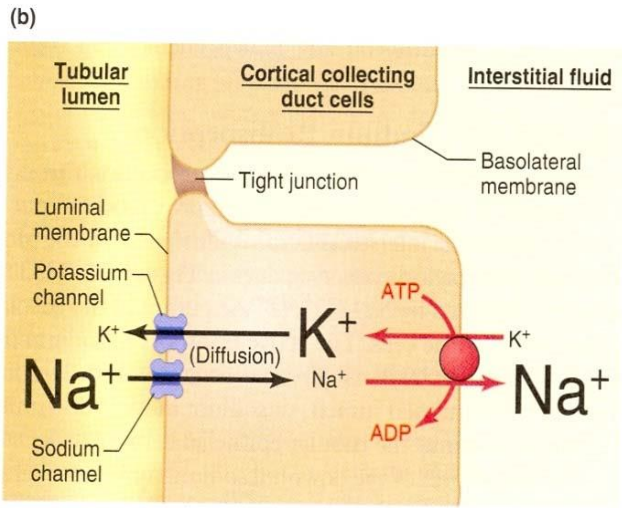




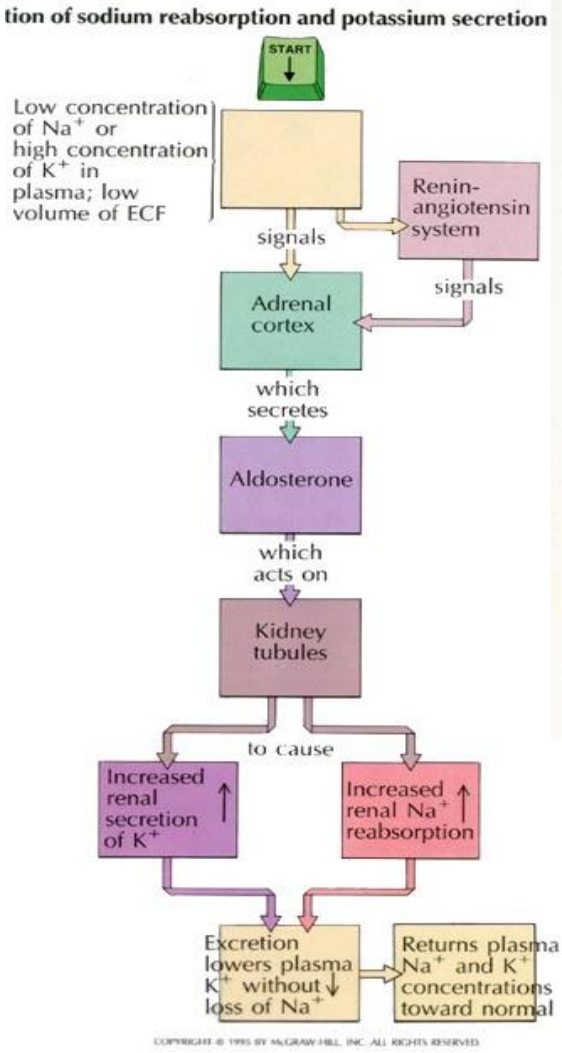
- **Distal convoluted tubule**
  - Na+, Cl- through primary active transport at basolateral membrane; secondary active transport at apical membrane through Na+-Cl- symporter and channels; aldosterone-regulated at distal portion.
  - Ca2+ passive uptake via PTH-modulated channels in apical membrane; primary and secondary active transport (antiport with Na+) in basolateral membrane.
- **Collecting duct**
  - Na+, K+, HCO2, CL- → primary active transport of Na+ (requires aldosterone); passive paracellular diffusion of some Cl-; cotransport of Cl- and HCO2; K+ is both reabsorbed and secreted (aldosterone dependent), usually resulting in net K+ secretion.
  - Water through osmosis; controlled (facultative) water reabsorption; ADH required to insert aquaporin.
  - Urea through facilitated diffusion in response to concentration gradient in the deep medulla region; recycles and contributes to medullary osmotic gradient.







- **Renin-Angiotensin-Aldosterone Mechanism**



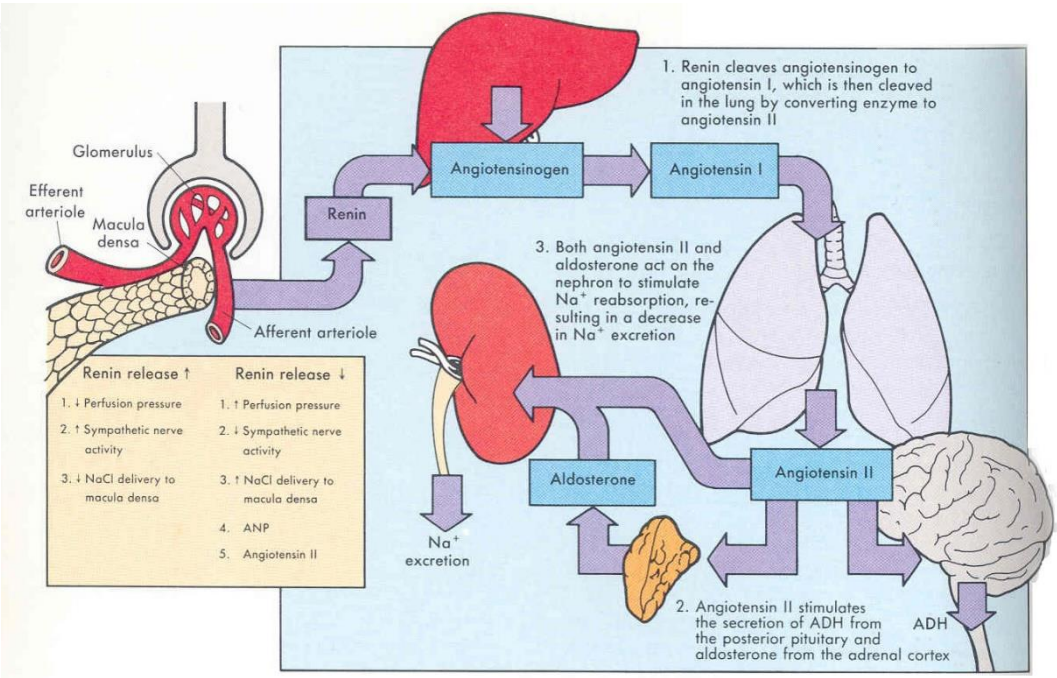


FIGURE 33-10 The renin-angiotensin-aldosterone system, and the factors that control the secretion of renin.

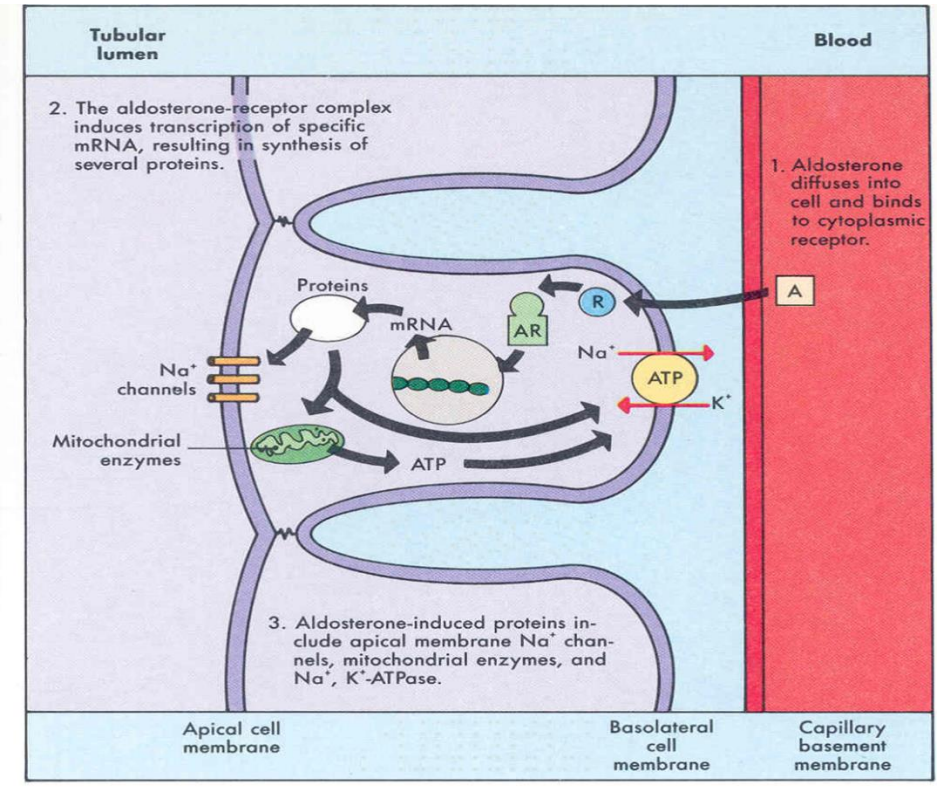
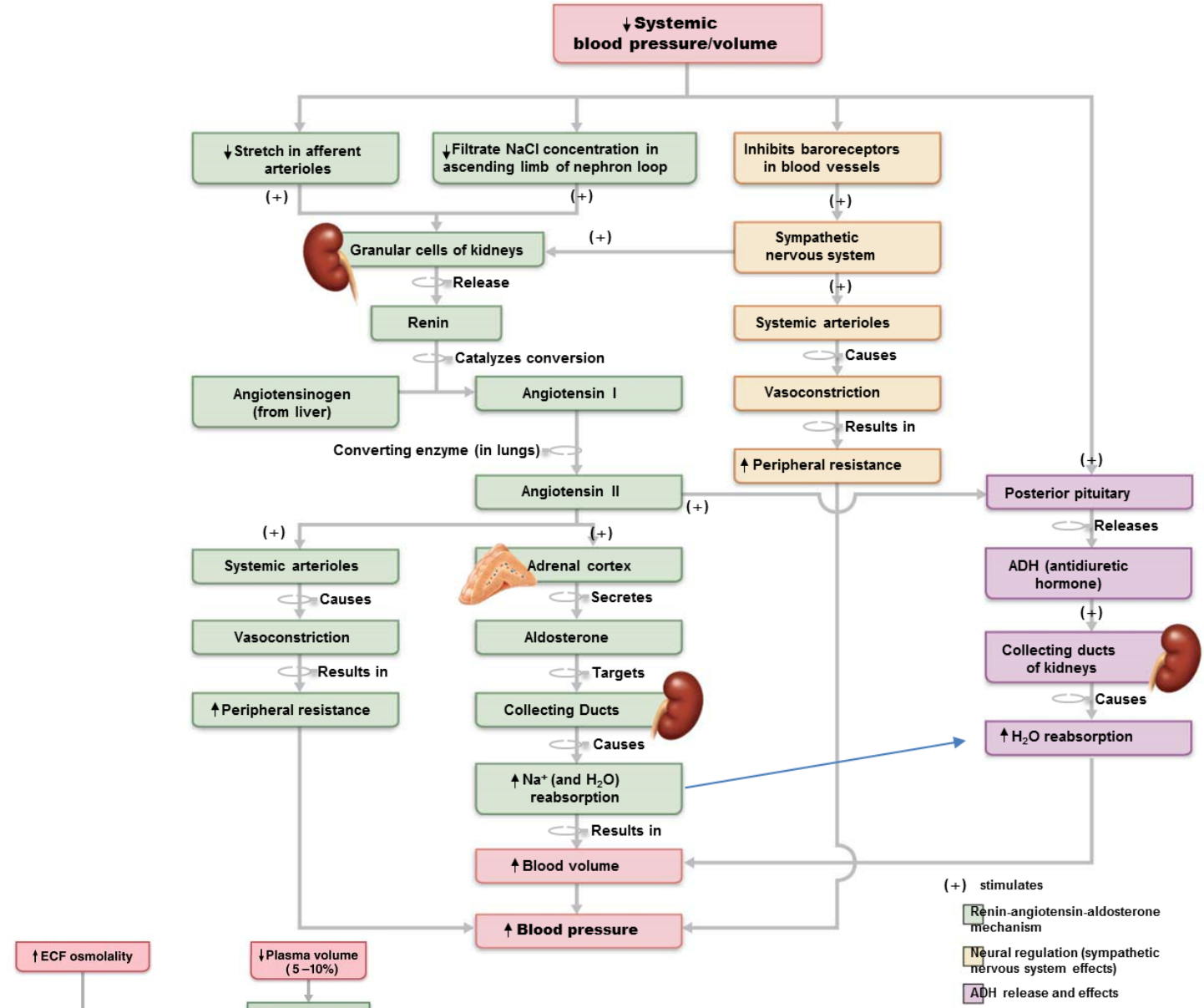
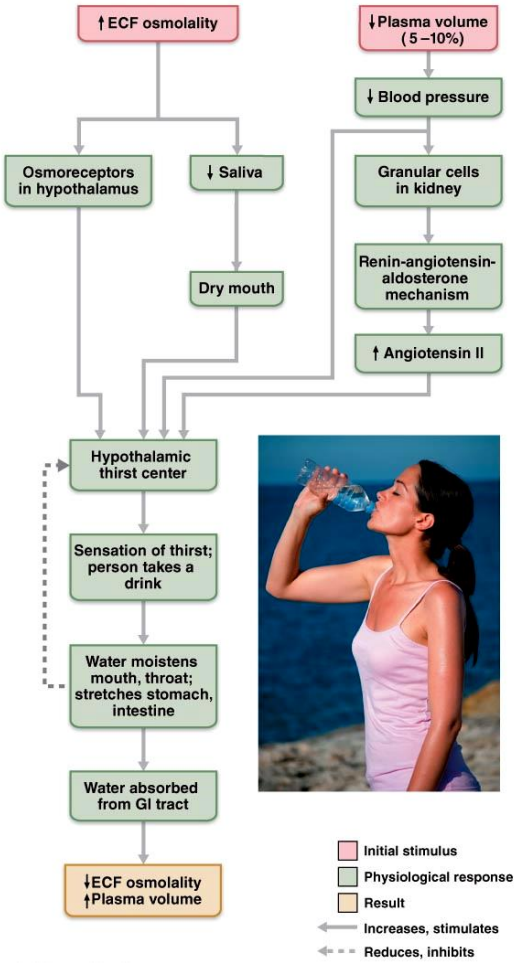
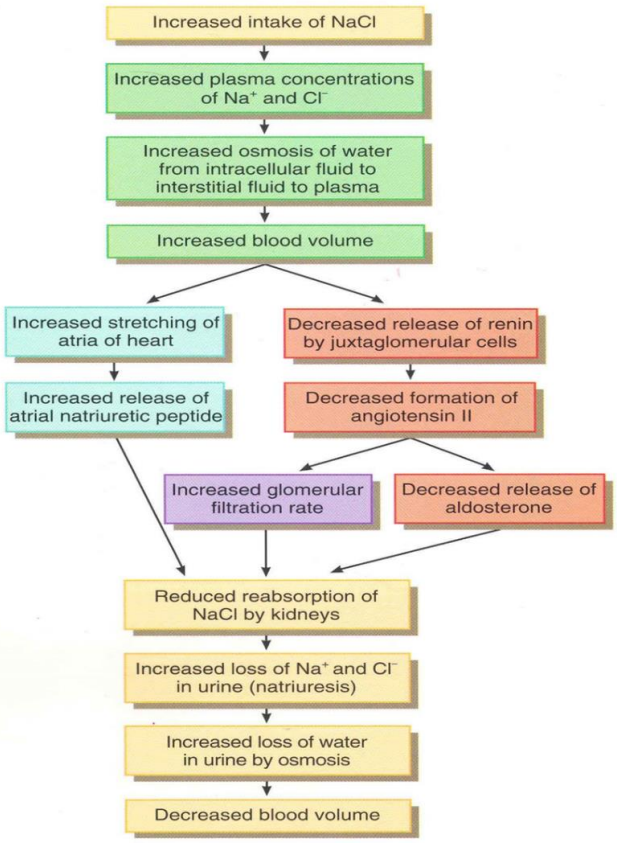


FIGURE 33-11 Cellular actions of aldosterone on principal cells of the collecting duct. See text for abbreviations and details.

- **Tubular Transport Maximum (T_m)**
  - This is the maximal amount of glucose that can be reabsorbed by the proximal tubule per minute.
  - The T_m glucose is 375mg.min--!
- **Plasma Threshold**
  - The plasma glucose concentration at which glucose first appears in the urine. The plasma threshold for glucose is 300mg/100mL or 3mg.ml-.
- **Bilirubin excretion**
  - In hepatocytes bilirubin is converted to bile and stored in the gall bladder.
  - Bile is metabolized into urobilinogen which is converted to urobilin and excreted in urine.



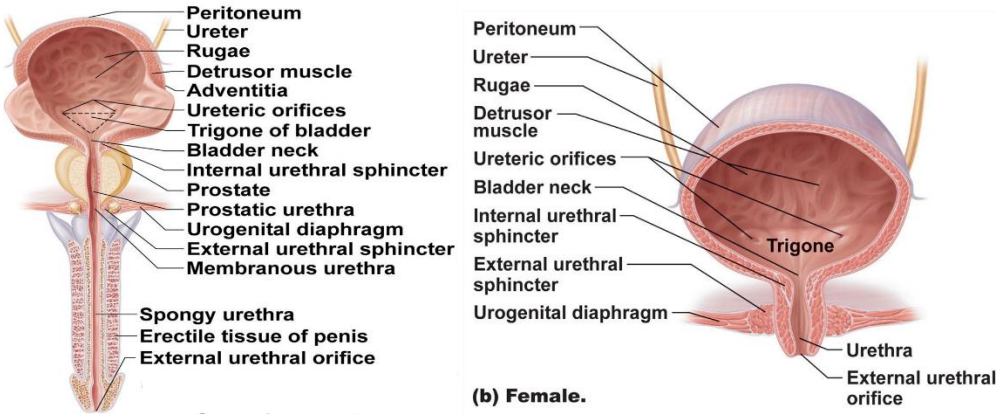




- ↓ renin secretion
- ↓ aldosterone secretion by adrenal glands
- ↓ Na^+ reabsorption in medullary collecting duct

Regulation of micturition and the micturition reflex

Micturition pathway in males versus females

- Moderately full bladder (500mL) ~12.5 cm long can hold up to about double that volume.
- 

- **Incontinence:** inability to control micturition voluntarily→ emotional problems, pressure of pregnancy, nervous system problems.
- **Urinary retention:** bladder unable to expel urine; eg. after general anesthetic; can also result from prostate hypertrophy.

Micturition

- **Urination or voiding**
  - Distention of bladder activates stretch receptors
  - Excitation of PNS neurons in reflex center in sacral region of spinal cord
  - Contraction of detrusor muscles
  - Contraction (opening) of internal sphincter
  - Inhibition of somatic pathways to external sphincter, allowing its relaxation (opening of external sphincter by somatic nervous system)

Role of Kidney in fluid and electrolyte balance

Body water content

- Infants are 73% or more water (low body fat, low bone mass)
- Adult males: ~60% water
- Adult females: ~50% water (higher fat content, less skeletal muscle mass)
  - Adipose tissue is less hydrated of all
  - Total body water in adult averages ~40L
- Water content declines to ~45% of 40L in old age

Fluid compartments of the body

- Total body water: 0.6 x body weight
  - ECF: 0.2 x body weight
    - Interstitial fluid (3/4 of ECF)
  - ICF: 0.4 x body weight

Ionic composition of a typical cell

- Na+ mostly in ECF (most abundant)
- K+ mostly in ICF
- Cl-, HCO3-, Pi mostly ECF

Fluid movement among compartments

- Osmotic and hydrostatic pressures regulate continuous exchange and mixing of fluids
  - Water moves freely along osmotic gradients

- All body fluid osmolality is almost always equal
- Change in solute concentration of any compartment leads to net water flow
  - Increase in ECF osmolality→ water leaves cell
  - Decrease in ECF osmolality→ water enters cells

Differences between electrolytes and non-electrolytes and the key electrolytes in ICF and EFC

- Electrolytes have greater osmotic power than non-electrolytes, coz they are charged
- **In ECF:** chief cation is sodium and chief anion is chloride
- **In ICF:** chief cation is potassium and chief anion is HPO42-
- Na+ and K+ are **opposite**, when comparing ECF and ICF→ ATP-dependtdent Na/K pumps keep intracellular [Na+] low and maintain high intracellular [k+].
- **Renal mechanisms can reinforce these ion distributions by secreting K+ as Na+ is reabsorbed from filtrate.**

Water balance and ECF osmolality

- Water intake must = water output ~2500ml/ day
- **Intake:** liquids, foods, cellular metabolism
  - Most water is taken in via ingested foods and beverages, but small amount from metabolism.
  - Metabolic water (oxidation of the water): water produced by cellular metabolism
- **Output:** ~60% via kidney; also lungs, skin, sweat, feces
  - urine (60%), **insensible water loss** (lost through skin and lungs), perspiration, and feces.
- Osmolality is maintained around 300mOsm/L.
- Increased plasma osmolality above 300 mOsm/L:
  - **Thirsty:** Increase water intake
  - **ADH:** stimulate renal water absorption
- Decreased plasma osmolality
  - Thirst not stimulated
  - ADH secretion not stimulated.

Regulation of water intake

- Thirst mechanism is driving force for water intake
- Governed by the hypothalamic thirst center
  - Hypothalamic osmoreceptors detect ECF osmolality and are activated by:
    - Increased plasma osmolality of 1-2%
    - Dry mouth
    - Decreased blood volume or pressure
- Drinking of water inhibits the thirst center
- Inhibitory feedback signals include:
  - Relief of dry mouth
  - Activation of stomach and intestinal stretch receptors.

Disorders of Water Balance

- Three principal abnormalities of water balanc**e:**
- **Dehydration:**
  - ECF water loss due to hemorrhage, severe burns, prolonged vomiting or diarrhea, profuse sweating, water deprivation, diuretic abuse, endocrine disturbances.
  - Signs and symptoms: oral mucosa, thirst, dry flushed skin, oliguria or hypouresis: production of a small amount of urine.
  - May lead to weight loss, fever, mental confusion, hypovolemic shock, and loss of electrolytes.
  - Excessive loss of water from EXF→ ECF osmotic pressure rises→ cells lose water to ECF→ cells shrink.
- **Hypotonic hydration:**
  - cellular overhydration, or water intoxication

    - occurs with renal insufficiency or rapid excess water ingestion
    - ECF osmolality decreases, causing **hyponatremia**
        - Results in net osmosis of water into tissue cells and swelling of cells
        - Symptoms: severe metabolic disturbances, nausea, vomiting, muscular cramping, cerebral edema, and possible death.
        - Insufficient sodium in the blood is hyponatremia→ either too much water or not enough sodium.
    - Treated with hypertonic saline.
    - Excessive water enters the ECF→ ECF osmotic pressure falls→ water moves into cells→ cells swell.
    - Excessive blood loss, sweating, vomiting, or diarrhea coupled with intake of plain water→ decreased sodium concentration of ECF (hyponatremia)→ decreased osmolarity of ECF→ osmosis of water from ECF to ICF→ water intoxication (cells swell)→ convulsions, coma and possible death.
- **Edema**
    - Atypical accumulation of interstitial fluid, resulting in tissue swelling (not cell swelling) (usually tissue beneath the skin and in the cavities of the body which cause severe pain)
        - Only volume of IF is increased, not of other compartments.
    - Clinically, edema manifests as swelling; the amount of IF is determined by the balance of fluid homeostasis, and the increased secretion of fluid into the interstitium.
    - Can impair tissue function by increasing distance for diffusion of oxygen and nutrients from blood into cells.
    - General response of the body to injury or inflammation. Can be isolate to a small area or affect the entire body.
    - Could be caused by increased fluid flow out of blood or decreased return of fluid to blood.
    - **Pitting edema:** results whenever small blood vessels become "leaky" and release fluid into nearby tissues. The ECF accumulates, causing the tissue to swell.

Factors necessary for the kidneys to be able to excrete maximally water (H_2O)

- ADH must be low. This prevents water reabsorption by the collecting duct.
- The thick ascending limb is qualitatively the most important segment involved in the separation of solute and water.
- Factors that reduce delivery (eg. Decreased GFR or enhanced proximal tubule reabsorption) impair the ability of the kidneys to maximally excrete H_2O.
- An individual could ingest 18L of water over a 24 hours period, and the kidneys would be able to excrete water. In doing so, the osmolality of the body fluids would be maintained at a normal level (Posm= 300 mOsm/kg).
- However, if water intake exceeded 18L/ 24 hours period, body fluid osmolality would fall.
- **ADH**
    - Water reabsorption in collecting ducts relies on ADH secretion
    - **Osmoreceptors in the hypothalamus:**
        - **Low [Na+]=** excess fluid→ reduced ADH secretion and dilute urine
        - **High [Na+]=** decreased blood volume→ ADH and reduced urine volume.
- **Hypernatermia:** usually water deficit not sodium excess.
- **Hyponatremia:** usually water overload not sodium deficit.
- **Pseudohyponatermia:** presence of large amounts of an osmotically active solute, not normally present in the E.C.F will attract extra water into the E.C.F and dilute the sodium. Ex. Diabetic→ glucose remains in plasma and increases plasma osmolality.

Electrolyte Balance

- Usually refers only to salt balance even though electrolytes also include acids, bases and some proteins.
- Salts control fluid movements, provide minerals for excitability, secretory activity, and membrane permability.

- Salt enter body by ingestion and metabolism and are lost via perspiration, feces, urine, vomit.

Center Role of sodium in fluid and electrolyte balance

- Sodium is most abundant cation in ECF
  - Sodium salts in ECF contribute 280 mOsm of total 300 mOsm ECF solute cconcentration
- This is the only cation exerting significant osmotic pressure.
  - Controls ECF volume and water distribution because water follows salt
  - Changes in sodium levels affect plasma volume, blood pressure, and ECF and IF volumes.
- **Sodium concentration vs. sodium content**
  - Concentration of Na+
    - Determines osmolality of ECF and influences excitability of neurons and muscles
    - Remains stable because of water shifts out of or into ICF
  - Content of Na+
    - Total body content determines ECF volume and therefore blood pressure.

Regulation of sodium Balance

- There are no known receptors that monitor Na+ levels in body fluids
- Na+-water balance is linked to blood pressure and blood volume control mechanisms
- Changes in blood pressure or volume trigger neural and hormonal controls to regulate Na+ content
- **Influence of aldosterone and angiotensin ll:**
  - Aldosterone plays biggest role in the fine regulation of Na+ by kidneys (mainly the cortical collecting duct).
  - <u>Regardless of aldosterone presence</u>
    - 67% of Na+ is reabsorbed in proximal tubules, and 25% is reclaimed in nephron loops (thick ascending limb); Na+ is never secreted into filtrate.
    - Urinary excretion of Na= ~100 mmole/day (0.4% of filtered load).
  - <u>When Aldosterone concentrations are high:</u>
    - Na+ is reabsorbed by aldosterone in the collecting duct.
  - <u>When aldosterone concentrations are low:</u>
    - Sodium is not reabsorbed and is lost to urine. (if ADH present→ more concentrated urine).
  - Renin catalyzes production of **angiotensin ll**
    - Prompts aldosterone release from adrenal cortex
    - Results in increased Na+ reabsorption by kidney tubules mainly the cortical collecting duct.
  - Aldosterone release is also triggered by elevated K+ levels in ECF
  - Aldosterone brings about its effects slowly (hours to days).
- Renin-angiotensin-aldosterone mechanism is main trigger for aldosterone release
  - Granular cells of juxtaglomerular complex secrete renin in response to:
    - SNS stimulation
    - Decreased filtrate NaCl concentration
    - Decreased stretch of granular cells, due to decreased blood pressure
    - JG cells: mechanoreceptors, macula densa cells: chemoreceptors
- Aldosterone mechanism:
  - Diffuses into cells and binds to cytoplasmic receptors
  - Aldosterone-receptor complex induces transcription of specific mRNA, resulting in synthesis of several proteins.
  - Aldosterone-induced proteins include apical membrane sodium channels, mitochondrial enzymes, and Na+-K+ ATPase.
  - Increase Na+ reabsorption and K+ secretion.

Acid-Base Balance

Acid-Base balance

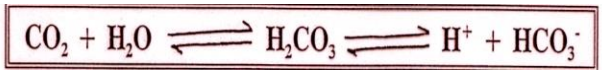
- pH affects all functional proteins and biochemical reactions, so it is closely regulated by the body.
- Normal pH of body fluids
  - Arterial blood: pH 7.4
  - Venous blood and interstitial fluid: pH 7.35
  - ICF: pH 7.0
- **Alkalosis** or **alkalemia:** arterial pH > 7.45
- **Acidosis** or **acidemia:** arterial pH <7.35

Renal Regulation

- Chemical buffers cannot eliminate excess acids or bases from body.
  - Lungs eliminate **volatile** carbonic acid by eliminating CO2
  - Kidneys eliminate **nonvolatile** (fixed) acids produced by cellular metabolism (phosphoric, uric, and lactic acids and ketones) to prevent metabolic acidosis.
  - Kidneys also regulate blood levels of alkaline substances; renew chemical buffers.
- Kidneys regulate acid-base balance by adjusting amount of bicarbonate in blood by either:
  - Conserving (reabsorbing) or generating new HCO3-
  - Excreting HCO3-
- Generating or reabsorbing one HCO3- is same as losing one H+ by secretion.
- Excreting one HCO3- is same as gaining one H+
- Renal regulation of acid-base balance depends on kidney's ability to secrete or retain H+
  - To reabsorb bicarbonate, kidney must secrete H+
  - To excrete bicarbonate, kidney must retain H+

Generating New Bicarbonate ions

- Metabolism of food generates a new H+, which must be balanced by generating a new HCO3-
- Secreted H+ used to reclaim filtered HCO3- is not really excreted from body; it is incorporated into a H2O molecule, which can be reabsorbed.
  - So body has same number of HCO3- and H+ as it started out with, no net gains
- Two mechanisms in PCT and type A intercalated cells generate a new HCO3- by getting rid of body H+
  - **via excretion of buffered H+**



    - Most important urine buffer is phosphate buffer system
    - Intercalated cells actively secrete H+ into urine, which is buffered by phosphates and excreted in urine.
    - New HCO3- is generated in process and moves into interstitial space via cotransport system, then moves passively into peritubular capillary blood.
  - **via NH4+ excretion**
    - more important mechanism for excreting acid
    - involves metabolism of glutamine in PCT cells
    - each glutamine produces 2 NH4+ and 2 "new" HCO3-
    - HCO3- moves to blood, and NH4+ is excreted in urine
    - Replenishes alkaline reserve of blood.

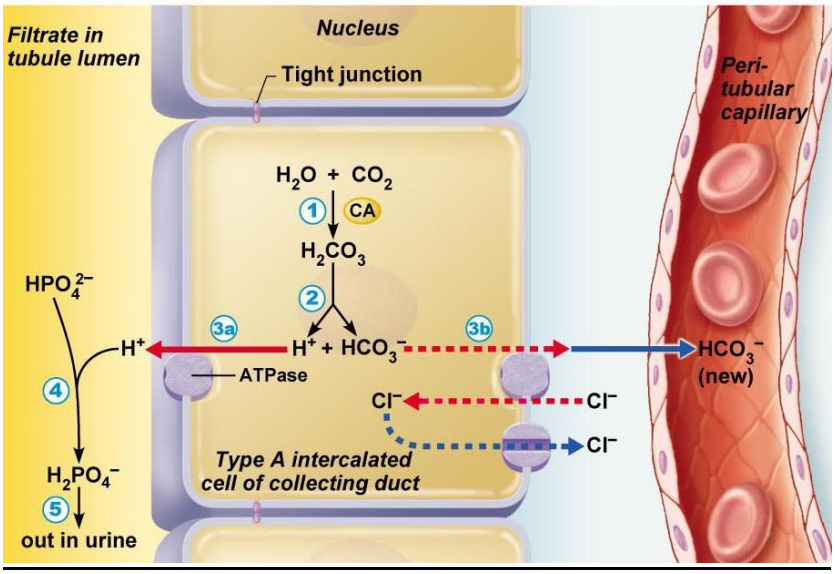
Bicarbonate Ion Secretion

- When body is in alkalosis, type B intercalated cells can:
  - Secrete HCO3-
  - Reclaim H+ to acidify blood
- Mechanism is opposite of bicarbonate ion reabsorption process by type A intercalated cells
- Even durinig alkalosis, nephrons and collecting ducts conserve more HCO3- than they excrete.

Conserving filtered bicarbonate ions: Bicarbonate reabsorption

- To maintain **alkaline reserve,** kidneys must replenish (reabsorb) bicarbonate
- Tubule cells are impermeable to bicarbonate but are permeable to CO2
    - Bicarbonate can gain entry back into body in a roundabout way- by being converted to CO2
    - Once back in cell, CO2 can be converted back into bicarb or leave cell as CO2
- Mechanism is coupled to H+ secretion- for every H+ secreted, a bicarbonate is reabsorbed.

Blood [H+] is regulated by:

- **Chemical buffer systems:**
    - H2CO3 ←→ HCO3-
    - NA2HPO4 ←→ NaH2PO4
    - Protein buffers
    - **Bicarbonate buffer system**
        - Secretion: rarer occurrence, type B intercalated cells; reverse of reabsorption.
    - **Phosphate buffer system**
        - Weak base is HPO4
        - Components freely filter into tubules; usually ~75% reabsorbed, **<u>except during acidosis</u>**
        - <u>Type A</u> intercalated cells actively secrete H+ (new HCO3- generated as byproduct; HCO3-/Cl- antiport)
        - 

- **Renal mechanisms**
    - Excreting bicarbonate (= gaining H+)
    - Reabsorbing or generating new bicarbonate (=getting rid of H+)

Metabolic Acidosis and Alkalosis

- **Metabolic acidosis**
    - Low blood pH and HCO3-
        - Ingestion of too much alcohol (converts to acetic acid)
        - Excessive loss of HCO3 (example: persistent diarrhea)
        - Accumulation of lactic acid (exercise or shock), ketosis in diabetic crisis, starvation, and kidney failure.
- **Metabolic alkalosis:**
    - High blood pH and HCO3-
        - Much less common than metabolic acidosis
        - Causes include vomiting of acid contents of stomach or intake of excess base (eat antacids)