How the body works PHR1031 - Book 2

STOP

How The Body Works 2

HOW THE BODY WORKS 2

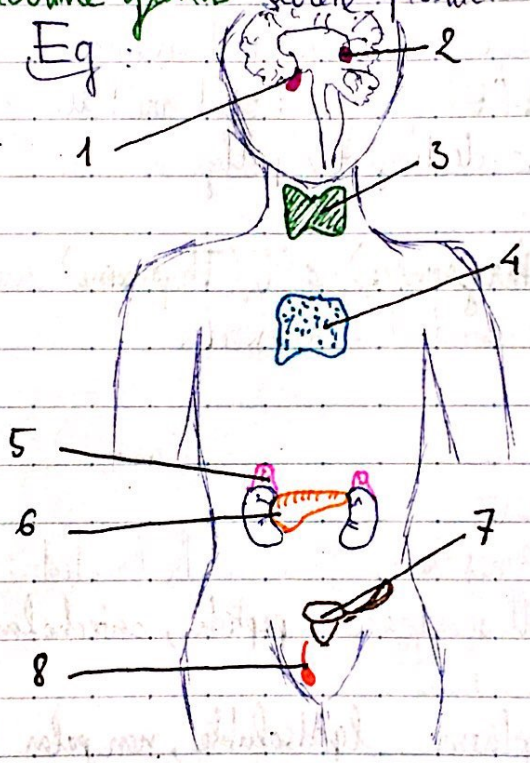
Week 7 10/4/2017

I) Endocrinology

Exocrine & Endocrine glands

- **Exocrine glands** secrete products onto a surface or duct
  They are controlled by autonomic nerves
  Eg: sweat, sebaceous, mucus, digestive

- **Endocrine glands** secrete product into the bloodstream
  Eg: Controlled by feedback controls or other hormone



1. Pituitary gland
2. Pineal gland
3. Thyroid gland
4. Thymus
5. Adrenal gland
6. Pancreas
7. Ovary (♀)
8. Testis (♂)

Hormones

- 3 types: amine, steroid, peptide

  - **Amine**: simplest, derived from tyrosine
    Eg: T_3 & T_4 from thyroid gland
  - **Steroid**: derived from cholesterol
  - **Peptide**, Eg: oxytocin & insulin

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Hormone interaction

- **Direct**: Hormone + receptor → minute change
- **Permissive**: Need 2nd hormone to permit the primary hormone to exert full effect.

Storage & secretion

→ Diverse in storage & secrete mechanisms

- NA(NE) & A(E) from adrenal medulla are released quickly, and are destroyed rapidly
- T_3(tri-iodothyronine) & T_4(Thyroxine) are release slowly, effects can last for weeks

Hormone receptor

- Receptors for hormones are specific, can be located:
  - In or on cell membrane: peptide, catecholamine
  - In the cytoplasm: lipidsoluble, non polar hormones
  - In the nucleus:

- Hormones that binds to plasma membrane use 2nd messenger since they cannot enter the cell. Including { catecholamine; thyroid-stimulating hormone (TSH); Oxytocin

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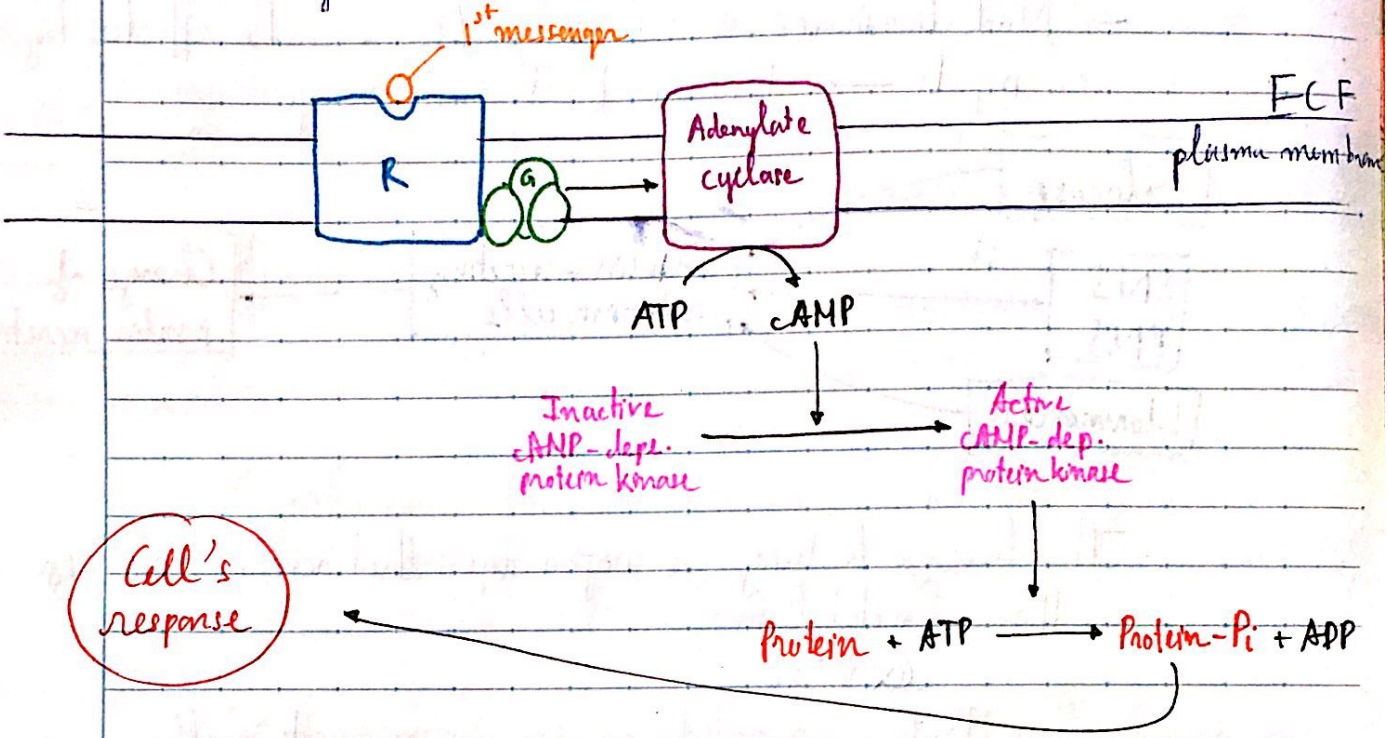
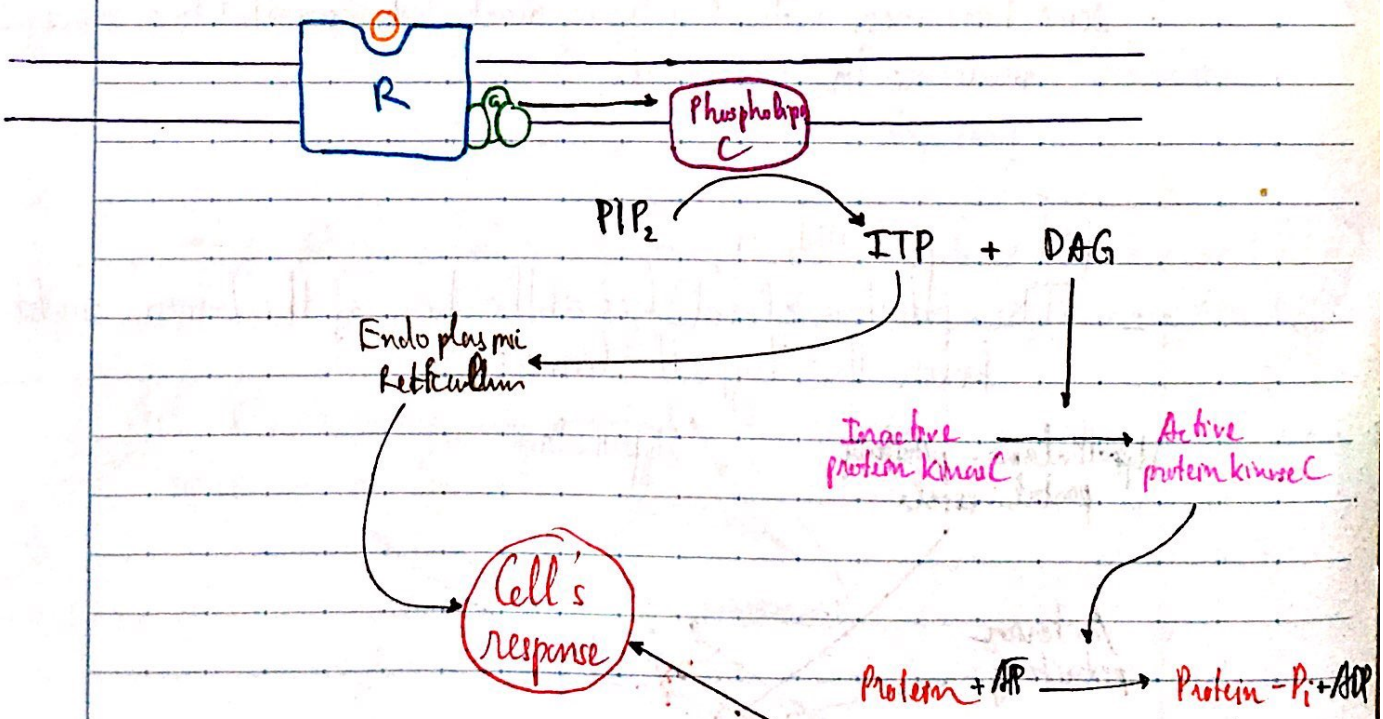
Eg : • cAMP messenger :



• Phospholipase C, DAG, inositol triphosphate (ITP)



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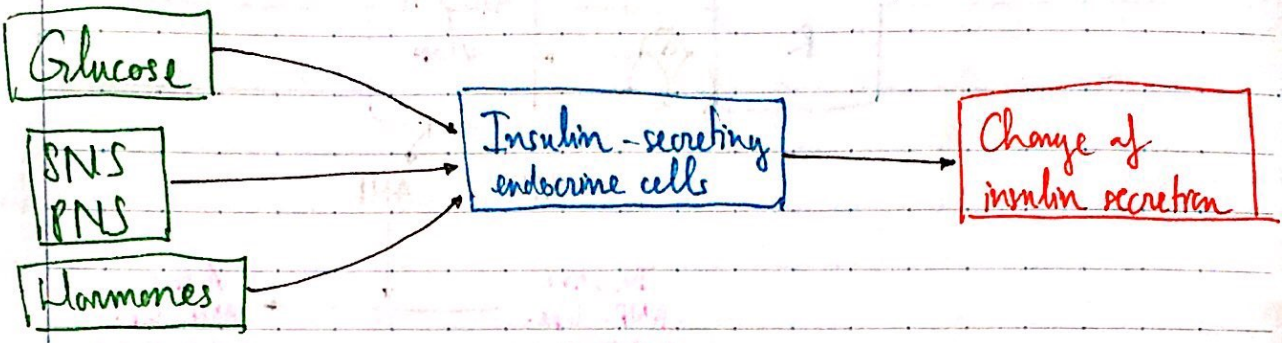
Hormone metabolism

- Most hormones are release quickly & combe affected by many inputs → Plasma [ ] can change

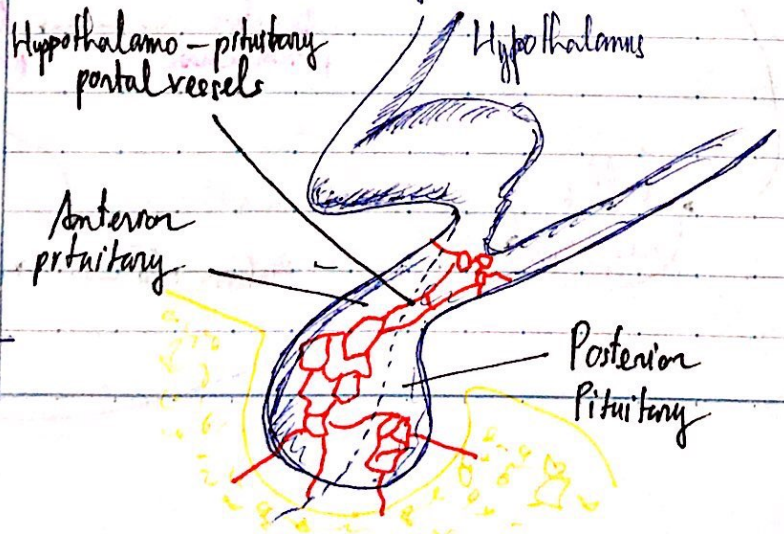


- The liver & kidney are major organs that remove hormones thru { metabolism / excretion
  - Peptides & catecholamines are removed quickly
  - Steroid & TSH " slowly

- Some hormones, instead of being inactivated, converted to a more active molecule in target cells

The pituitary

- The pituitary gland lies at the base of the brain, right below the hypothalamus



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Anterior pituitary gland

- Synthesise & release hormone
All releasing hormone (= RH) can be referred as releasing factor (= RF)

- **Somatotrophins**: Human growth hormone (HGH) ①
  + Released by hypothalamic Growth hormon - releasing hormon (GHRH)
  + Inhibited by hypothalamic somatostatin

- **Thyrotrophins**: Thyroid - stimulating hormone (TSH) ②
  + Released by hypothalamic Thyrotropin - releasing hormone (TRH)
  + Inhibited by somatostatin

- **Corticotrophins**: Adrenocorticotropic hormone (ACTH) ③; β-endorphine
  + Released by hypothalamic Corticotropin - releasing hormone (CRH)

- **Lactotrophins**: Prolactin (PRL) ④
  + Released inconsistently by TRH, oxytocin, vasopressin ...
  + Inhibited by hypothalamic dopamine

- **Gonadotrophins**: Luteinizing hormone (LH) ⑤; follicle - stimulating hormone (FSH) ⑥
  + Released by Gonadotropin - releasing hormone (GnRH)

All these hormones are secreted to the anterior lobe via special capillary system ⟶ Hypothalamo - pituitary portal system

Anterior Pit,

- GH: growth via protein, CH, lipid meta
- TSH: TH release, Thyroid growth
- ACTH: Adrenal cortex activity & growth
  → cortisol
- PRL: milk production
- FSH: ♂ gamete prodn.
  ♀ ovarian follicle growth
- LH: ♂ testosterone
  ♀ ovulation

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Posterior pituitary gland

- Release 2 store hormone (no synthesis)
  - Antidiuretic hormone (ADH)
  - Oxytocin: 1 in few hormone that can create positive feedback loop
    Milk ejection

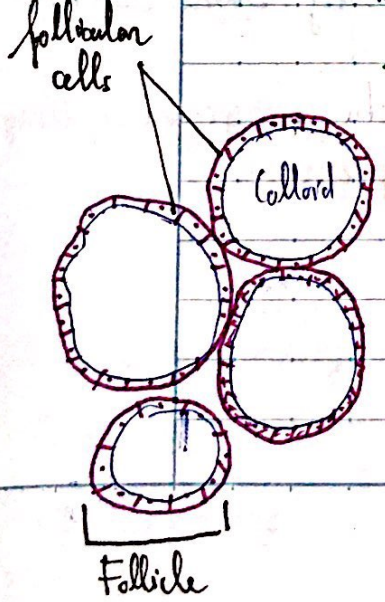
Thyroid gland

- The thyroid gland is bow-shaped, lids inside the neck

Controlled by anterior pituitary hormones & secretes { T_3 (triiodothyronine)
T_4 (thyroxine)
calcitonin

Thyroid hormones (T_3; T_4)

- Thyroid hormones are stored in the **Colloid**, a gel-like substance in the center of **follicles** (a spherical structure with the walls are single layer of epithelial cell called follicular cells) in a form of a larger molecule: Thyroglobulin



- Thyroid hormones are derived from Tyrosin, and is unique because it is the only use for Iodine in the body.

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- Although more T_4 is synthesised by the thyroid gland, at the target tissue, it is converted to T_3, which is the active form by removing 1 Iodine

- Thyroid hormones are lipophillic → transported by binding protein
  - Thyroxine-binding globulin (75%)
  - Albumin (25%)

  About 99.96% of Thyroid hormone is protein bound, but the 0.04% free hormone is the one that binds to receptor.

- **Function**

  - Growth & maturation
    - lung
    - skeletal
  - Neurological
    - brain growth
    - neuronal proliferation & diff
    - CNS function
  - Cardiovascular
    - vasodilation
    - ↗ heart rate
    - ↗ cardiac output
  - Metabolism
    - ↗ mito. activity → ↗ ATP formation
    - ↗ basal metabolic rate
    - ↗ CO_2 uptake
    - ↗ glycolysis & gluconeogenesis
    - ↗ lypolysis & fatty acid mobilisation
    - ↗ breathing
    - ↗ heat production

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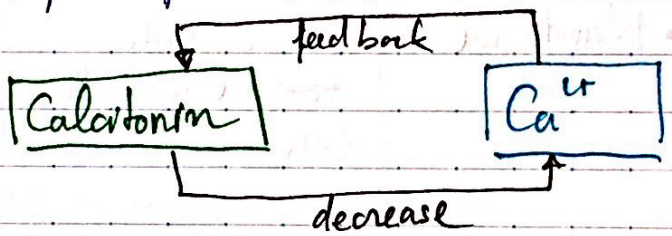
Calcitonin

- Synthesised by the parafollicular cell (C cells) located between the follicles

- Function
  - ↓ Ca^{2+} & PO_4^{3-} in blood

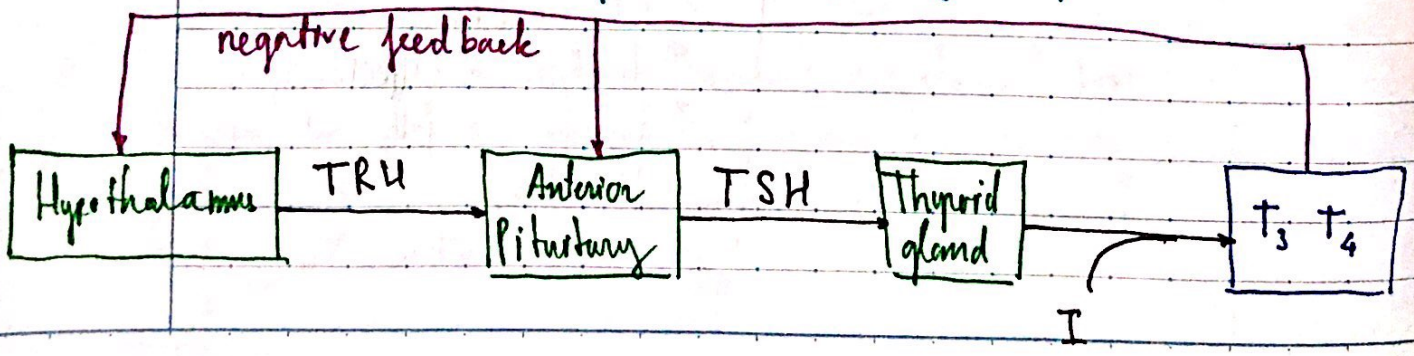
- The mechanism involves the inhibition of osteoclast activity → ↓ bone breakdown (demineralisation)
  Calcitonin has no direct effect on bone formation

- The release of calcitonin is regulated by plasma Ca^{2+} level thru negative feedback:



Regulation of the thyroid by anterior pituitary

- The thyroid hormones are regulated by negative feedback loop in the hypothalamic – pituitary – thyroid axis



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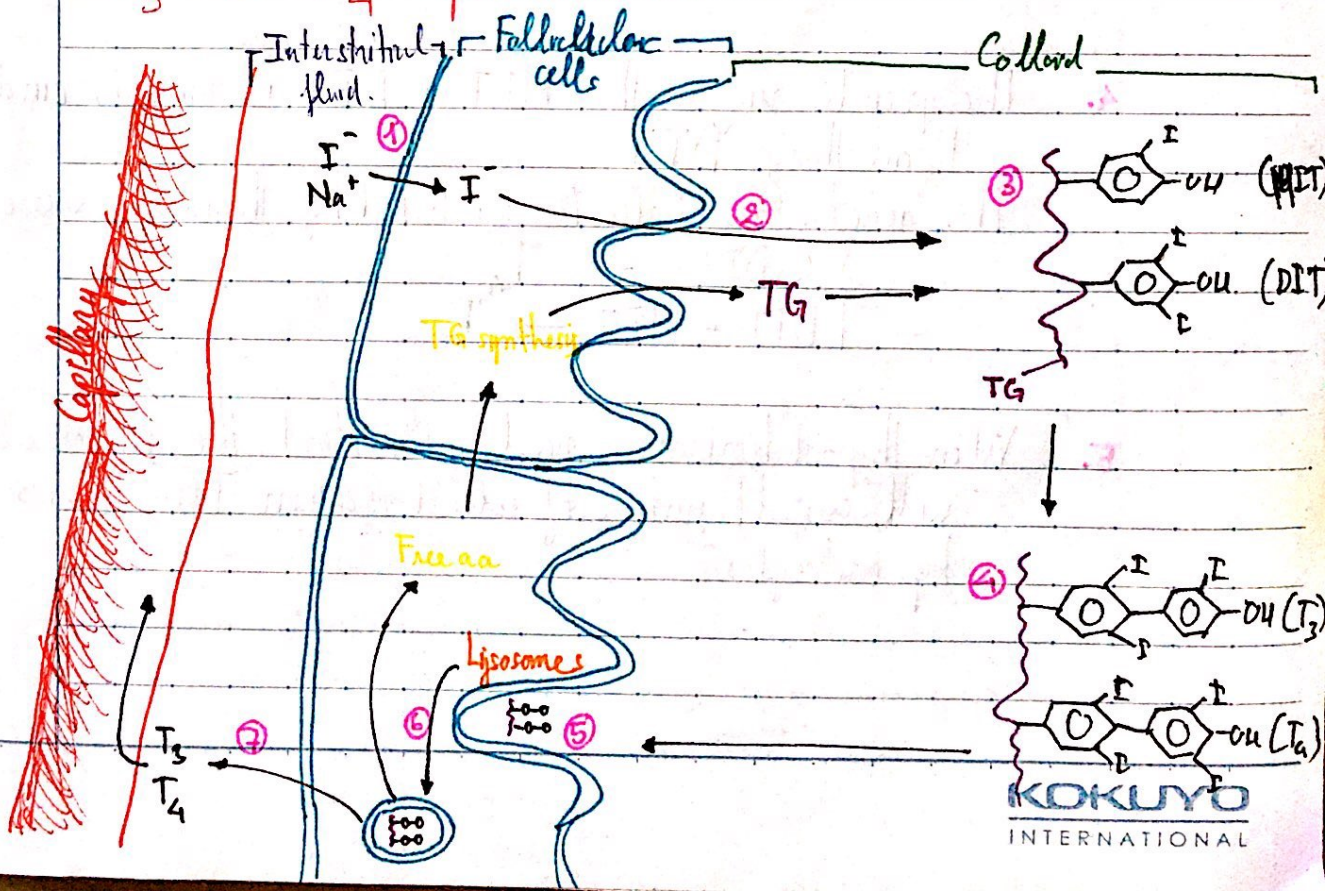
- The hypothalamus secretes thyrotropin-releasing hormone (TRH), which in turn stimulate the pituitary to release TSH to promote T_3 & T_4 secretion.

As the concentration of T_3 ↗, there will be a decrease in the TRH secretion, therefore less T_3 is released.

The excess T_3 { 80% deiodine T_4
20% serum T_3

- The negative feedback also has effect on the Anterior Pituitary gland as it decrease the responsiveness of the TSH-producing cells, which involves the down regulation, or a decrease in number, of TRH receptors. ⟶ ↓ TSH

T_3 & T_4 formation



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Steps in T_3 & T_4 pathway / synthesis

1. I^- is cotransported w/ Na^+ across the follicular membrane.
   Once inside the cell, the I^- cannot diffuse back because of its size → Iodide trapping
   The Na^+ is pumped back out by Na^+/K^+ - ATPase

2. The trapped I^- diffuse into the colloid, where is full of a protein called Thyroglobulin (TG).
   At the luminal surface of the follicular cell (in contact w/ the colloid) the I^- is rapidly oxidised to become $I^\bullet$ by thyroid peroxidase.

3. The radical $I^\bullet$ is attached to a phenol ring of Tyrosine residues in the TG molecule, also by thyroid peroxidase
   Iodine can bind to either 1 or 2 position on a given Tyrosin within the TG: {1I → Monoiodotyrosine (MIT); 2I → Diiodotyrosine (DIT)}

4. The phenolic ring in the MIT or DIT is removed, and coupled to another DIT
   This reaction may also be mediated by thyroid peroxidase
   {2 DIT → T_4; DIT + MIT → T_3}

5. When thyroid hormone is need by the blood, the follicular cells will engulf portion of colloid (contain TG - T_3 ; TG - T_4) by endocytosis

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6. The lysosomes in the cytoplasm will release the T_3 & T_4 from the TG by breaking down the molecule (Proteolysis)
Free aa can be reused to synthesised TG in follicle cells and then secreted to the colloid

7. T_3 & T_4 diffuse out into the blood stream

Thyroid diseases

Hypothyroidism

- Causes:
  - Auto-immune (Hashimoto's disease)
  - Drug-induce
  - Synthetic enzyme deficiency
  - Sloppy X-ray
  - Congenital
  - Disease states < cretinism (congenital)
    myxoedema (adult)

- Symptoms
  - Impaired growth
  - ↗ sleep
  - Intolerance to cold
  - Dry skin
  - ↓ Perspiration
  - Slow pulse
  - Constipation, ↓ appetite, ↑ weight
  - Depression, apathy
  - ↗ blood Cholesterol

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- Treatments:
  - Long duration T_4
  - Rapid T_3 (for severe hypothyroidism)
  - Surgery

- Hypothyroidism could lead to goiter:
  - The lack of Thyroid hormone leads to the negative feedback on the thalamus, which will secrete more TRH, thus more TSH. The overstimulation on the thyroid can produce goiter.
  - The anterior pituitary gland can be unresponsive to TH.
- Hashimoto's disease: the T-cells attack & destroy thyroid tissue, leads to the decrease in thyroid hormone → goiter

Hyperthyroidism

- Cause: mostly due to auto immune (Grave's disease)
  The plasma contain the antibodies that can recognize TSH receptors. Unlike typical auto-immune, where the cells are being attacked, these antibodies can bind to and activate TSH receptor → ↑ Thyroid hormones
  ↳ Goiter

- Symptoms: (almost opposite to hypothyroidism)
  - ↓ sleep, ↗ activity
  - Intolerance to heat
  - Rapid pulse
  - ↗ growth
  - Frequent bowel mvt
  - ↗ appetite, ↓ weight
  - Nervous

Note that:

- The goiter due to { hypothyroidism / hyperthyroidism } is indistinguishable since both conditions result in the hypertrophic environment to the thyroid:
  - Hypo: ↗ TSH
  - Hyper: ↗ antibodies (antiTSH receptor antibodies)

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- Treatments :
  - Thyroid peroxidase inhibitor (carbimazole ; propylthiouracil)
  - Surgery
  - Radioactive Iodine → thyroid tissue destroyed.

- Special considerations !!
  - Pregnancy { lowest effect dose
    propylthiouracil has lowest placental transfer
    Could induce fetal hypothyroidism
  - Lactation { lowest effect dose
    propylthiouracil has lower secretion in breast milk

Parathyroid gland

- 4 glands, 2 on each side of the thyroid.

Even though the parathyroid & thyroid are next to each other, the function & structure is distinct

- Parathyroid produces parathyroid hormone (PTH)
  → Calcium metabolism
  (Calcitonin & PTH have opposite effect):
  - ↓ Ca^{2+} excretion in urine
  - ↗ PO_4^{3-} excretion in urine
  - ↗ bone resorption
  - Activation of vitamin D_3

- The release of PTH is regulated by plasma Ca^{2+} thru negative

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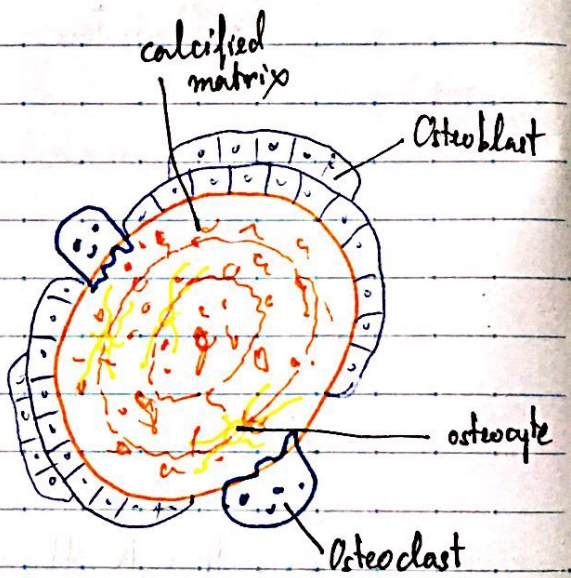
feedback: ↓ Ca ⟶ inhibition

- The role of Ca^{2+} in body:
  - Stabilise excitable cell membrane
  - Release of neurotransmitter
  - Involved in 2nd messenger function
  - Muscle contractility
  - Exocytosis of hormones & other regulators
  - Blood coagulation & platelet aggregation

Parathyroid diseases

Hypoparathyroidism

- Cause:
  - Throat surgery
  - Auto immune
  - Familial
  - Idiopathic



- Symptoms (similar to Hypocalcaemia & tetany)
  - Muscle spasms
  - Convulsions
  - Paralysis
  - Dyspnoea
  - Gastrointestinal (GI) haemorrhage & haematosis
  - Death

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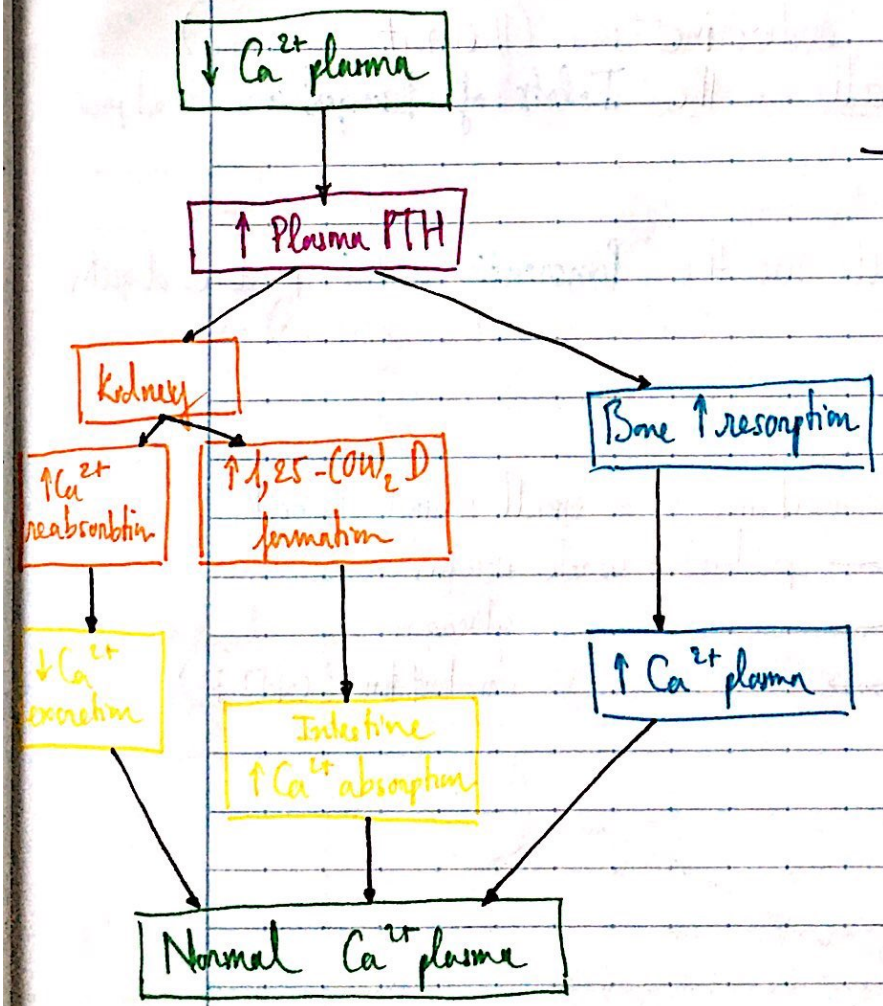
Hyperparathyroidism

- Cause :
  - Parathyroid adenoma
  - Spontaneous hyperplasia

- Symptoms :
  - Renal stones
  - Bone pain
  - Pathological fractures



- Overactivity of parathyroid results in the increased amount of plasma PTH which will
  - Bone resorption (demineralisation)
  - & ↗ Ca^{2+} absorption by kidney & GI system

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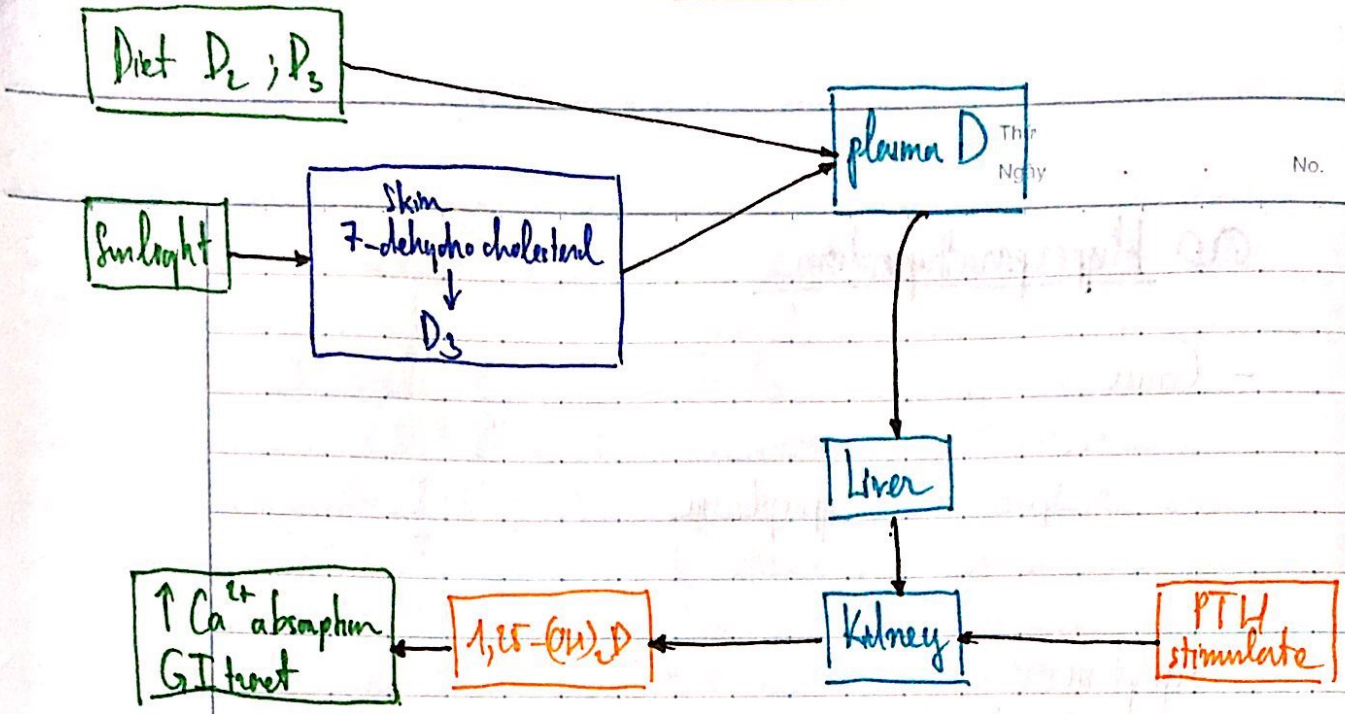

Pancreas

- Made up of 2% endocrine tissue (the rest is exocrine)
- The endocrine cells are the **Islets of Langerhans** that produce hormones.

- The exocrine cells are the **pancreatic acini**, produce digestive enzymes.

- The Islets of Langerhans is a small island of cells:
  - β cells → produce & secrete insulin
  - α cells → glucagon
  - δ cells → somatostatin (GHIF)

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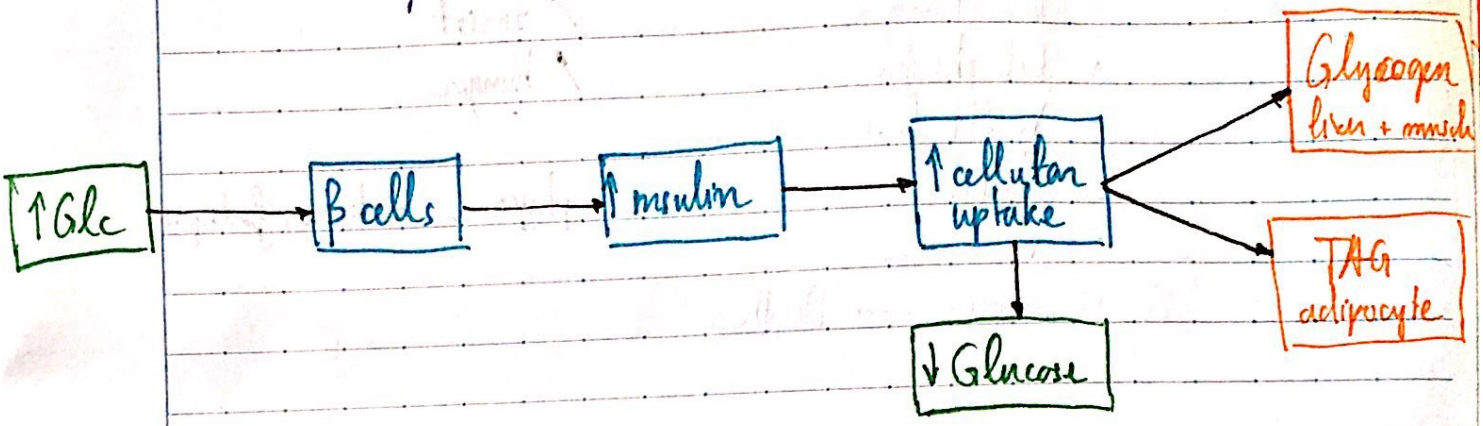
Glucose homeostasis

- Review glucose metabolism (week 4)

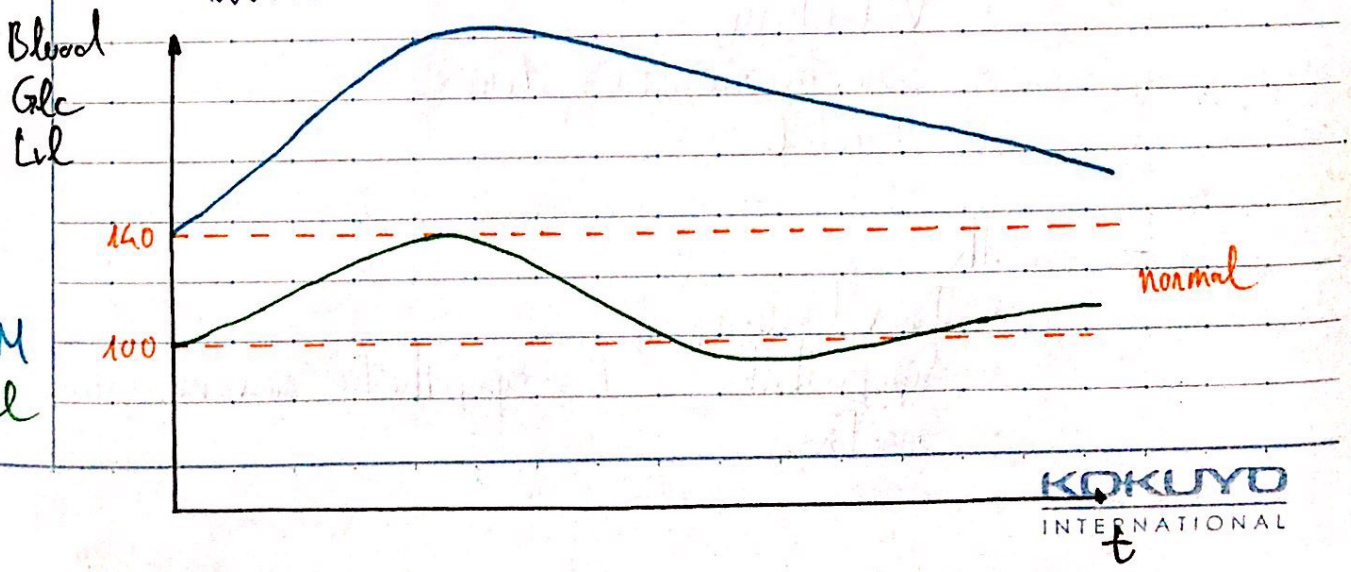


Diabetes mellitus (DM)

Insulin-dependent diabetes (IDDM) ①

- Least common, happens when β cells are destroyed by viral infection

- Glucose tolerance test
  - Normal: after glucose intake, insulin is secreted → decrease
  - IDDM: cannot produce insulin → decrease by excretion



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- Symptoms:
  - Polyuria (Glycosuria)
  - Polydipsia ↗ thrist
  - Polyphagia ↗ hunger
  - Weight loss
  - Asthenia : physical weakness, fatigue
  - Vision loss
  - Coma → Death

~ Non-insulin-dependent diabetes (NIDDM) ②

- Most common, mature onset
- Due to decrease in responsiveness of tissue to insulin

II) Control of skeletal muscle

Types of muscles

- Skeletal:
  - Voluntary
  - Somatic nervous system
  - Striatal

- Smoth:
  - Involuntary
  - Sympathetic / Parasympathetic nervous system
  - Smooth

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- Cardiac : in between smooth & skeletal

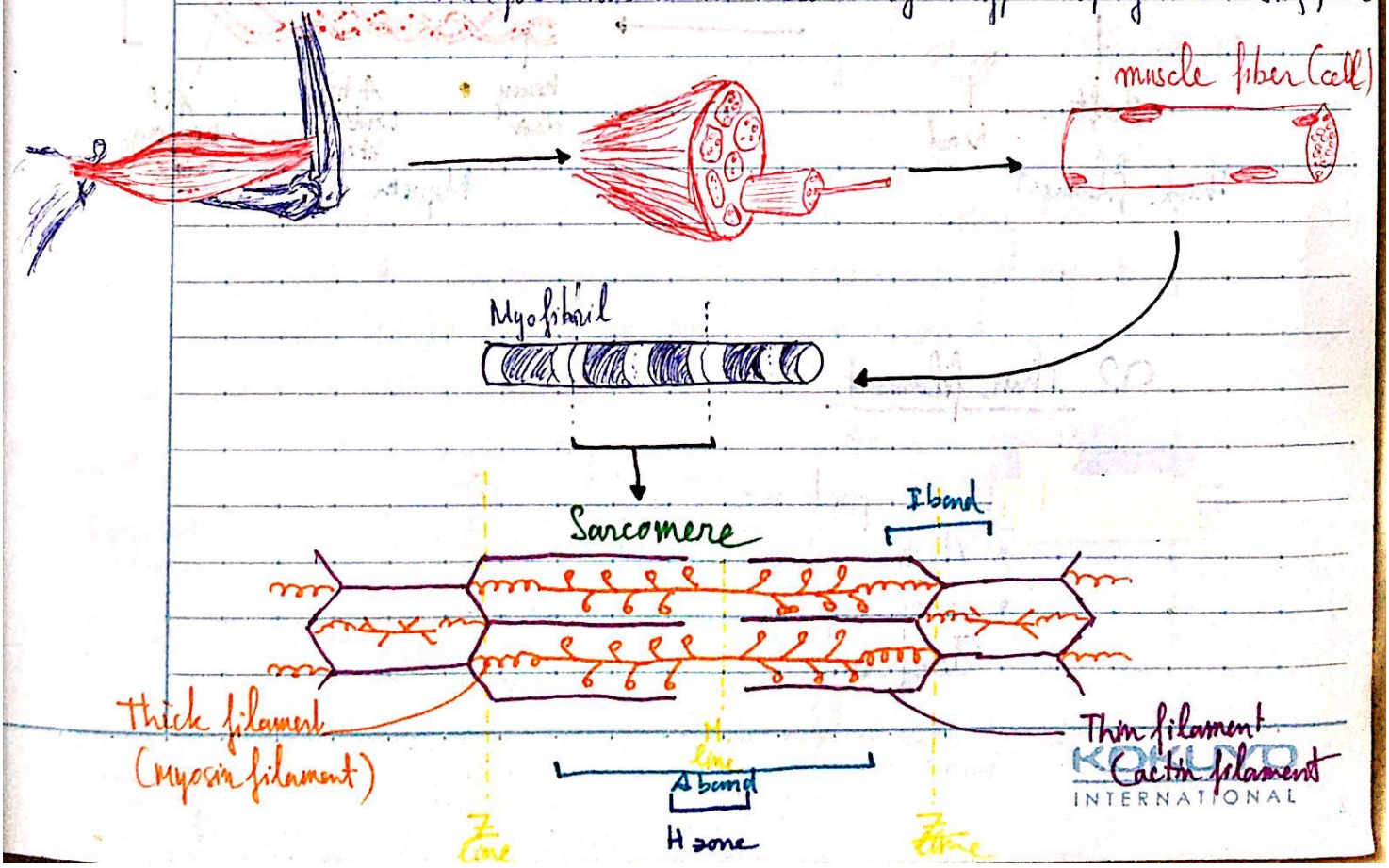
Somatic neuromuscular junction

- There are no gap junctions between muscle fibers
  → electrical activity cannot pass from 1 cell to another
  → α - motor neuron
- For the step of initiating contraction → Week 5

Structure of muscle fiber

- A whole muscle is made out of muscle cells, or muscle fibers
  A muscle fiber is actually a fusion of many smaller fibers during embryo

- Muscle fiber cannot undergo mitosis
  → Larger muscle is because of hypertrophy in existing fiber



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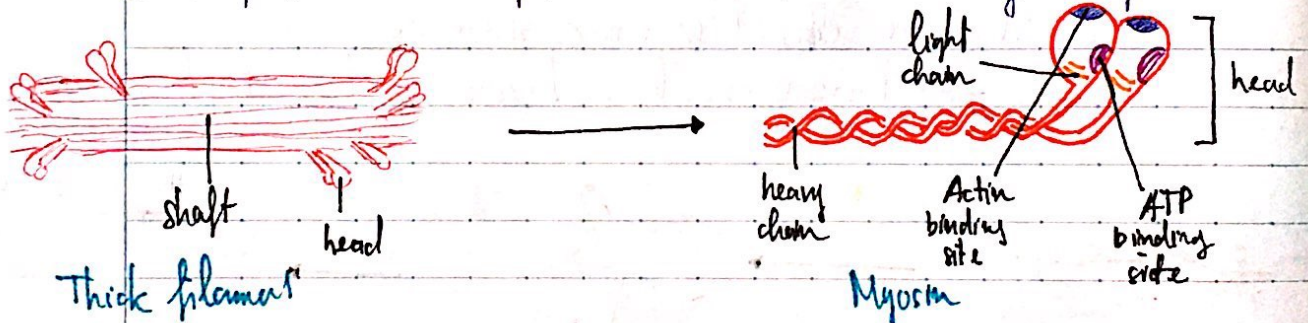
Sarcomere

- An organised structure in muscle fiber, and is the functional unit in the muscle
- Composed of { thick filament / thin filament }
- The Z lines anchor the thin filament in place.

Thick filament

- Each contain 200 - 300 Myosin molecules
  Myosin is made up of 2 identicle subunit with a "head", or cross-bridge. These heads point outward at either end of the filament.



Thin filament

- 3 types of proteins:
  - Actin
  - Tropomyosin
  - Troponin

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- **Actin** is a globular protein, arrange themselves in to 2 chains twist around each other

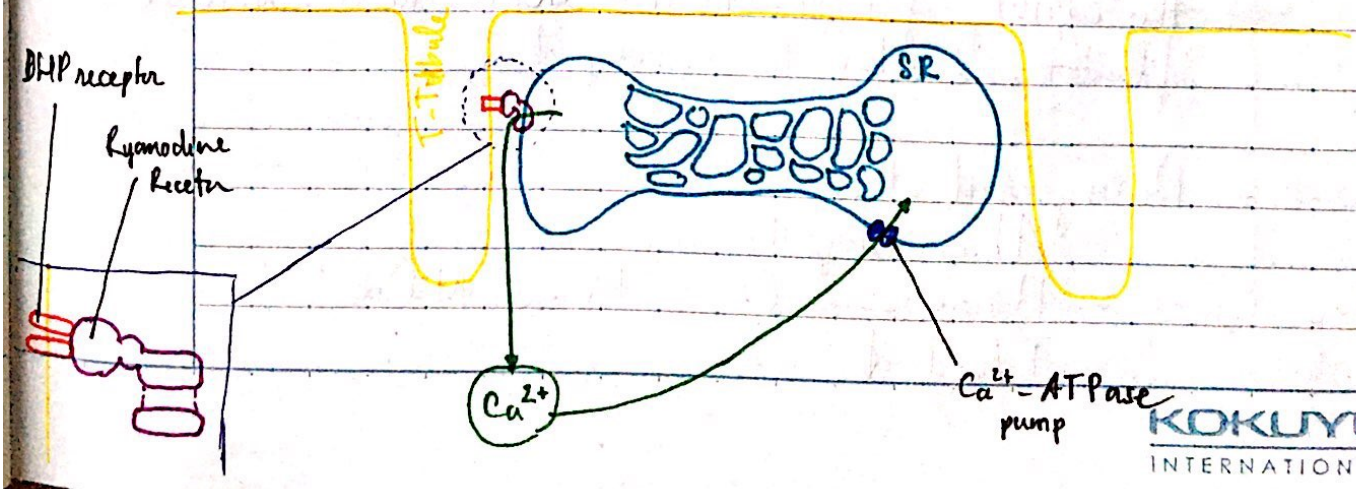
- **Tropomyosin** is a thread-like protein, cover the actin binding site to the myosin when muscle is at rest

- **Troponin** is a small protein, bind with 3 places by 3 subunit: actin, tropomyosin & Ca^{2+}. When in rest state, the troponin hold the tropomyosin in its blocking position

Action potential & muscle contraction
— Sliding filament theory

- An AP introduced at the neuromuscular junction is propagated along the **sarcolemma** (membrane). Since muscle fiber is a very big cell → need away for action potential to reach the center myofibrils → **Transverse tubules**

- All muscle contraction requires Ca^{2+}. Ca^{2+} is store in a network called **sarcoplasmic reticulum**, sit right next to the T-tubule, connected by a structure called "Junctional feet":
  - Dihydropyridine (DHP) receptor: voltage receptor
  - Ryanodine receptor: Ca^{2+} channel



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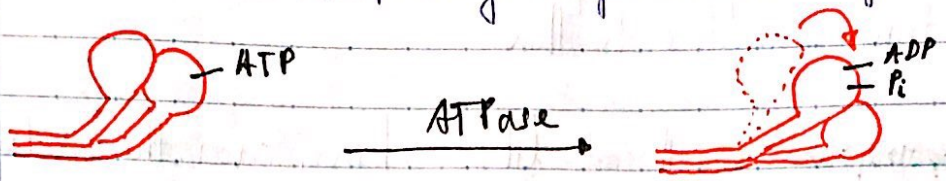
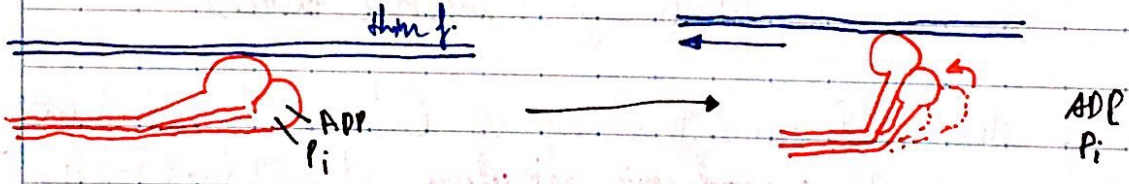
- Start with "priming" myosin cross-bridge by ATP



On the head contain myosin ATPase for this process. The energy of ATP is use to bend the cross bridge onward
→ High-energy state myosin + capable of binding to actin

- Ca^{2+} is release upon the activation of AP from the sarcoplasmic reticulum binds to troponin → change the conformation of tropomyosin → reveal the actin binding site for myosin.

- Myosin then bind to actin, and ADP & Pi are removed from myosin, which pull the thin filament inward.



- To disassociate the myosin from actin, ATP is used to bind w/ myosin crossbridge at ATP-binding site, reduce the affinity of myosin head to actin, which release the thin filament and return to original position.

- During contraction:
  - A band stays the same
  - H zone → 0 (toward M line)
  - I band ↓

simplify

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- The steps of muscle cont be simplified as this: (crossbridge cycle)

1) $A + M-ATP \xrightarrow[ATPase]{} A + M-ADP-P_i$

2) $A + M-ADP-P_i \longrightarrow A-M-ADP-P_i$ (A ↑ Ca^{2+})

3) $A-M-ADP-P_i \xrightarrow{mvt} A-M + ADP + P_i$

4) $A-M + ATP \longrightarrow A + M-ATP$

- Not all caoss bridges cycle at the same time, some may remain attached w/ actin, some may bind w/ ATP...
  → main tain the shortening of sarcomere
  & prevent the thin filament from retain its original position

- After death, Ca^{2+} ↗, ATP ↘ → muscle rigid (rigor mortis)

III) Co-ordination of skeletal & smooth muscle

Skeletal muscle contral:

- Various muscles are orientated differently so body can move in many directions

Multiple muscles are attached to each bone via tendon (collagen fiber)

- The portion of muscle fibers controlled by a single nerve is called a motor unit. Single muscle may have multiple motor units

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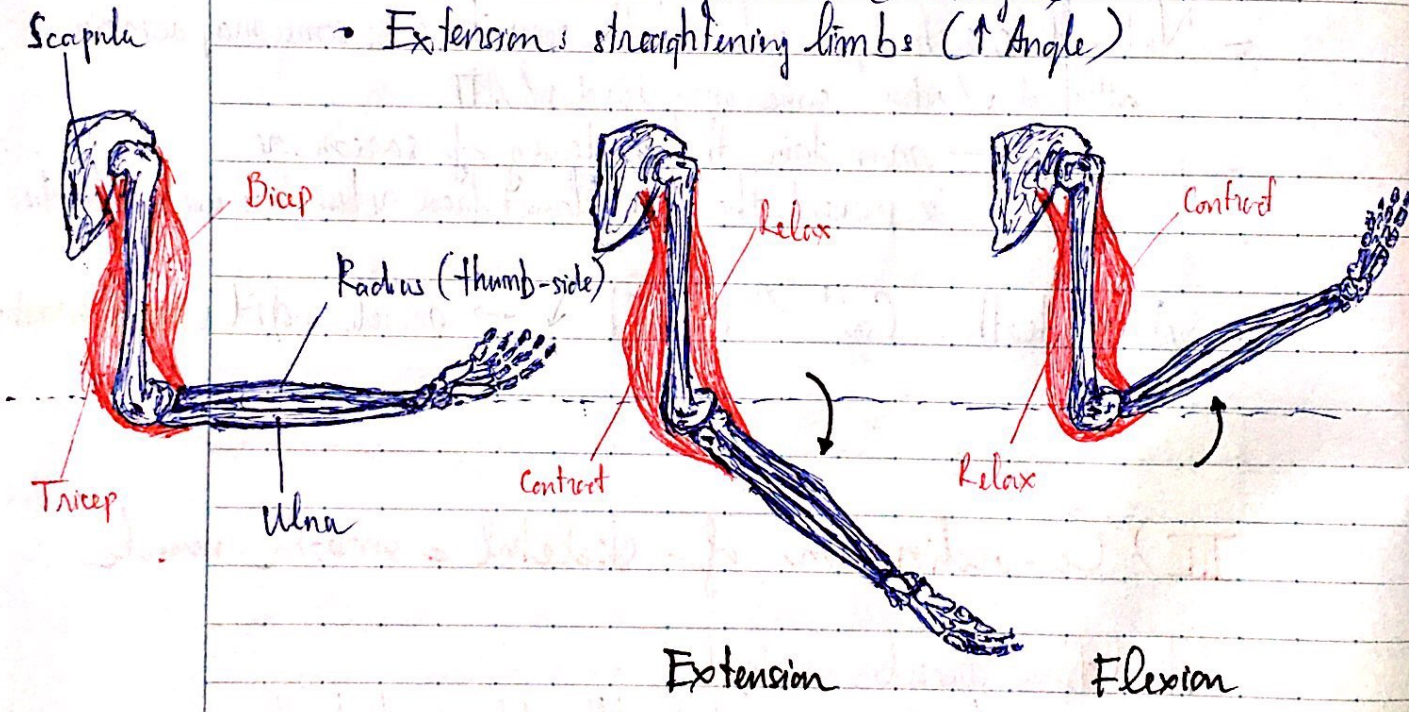
- The muscle movement is controlled by contraction & relaxation of antagonistic muscles

The muscles can only shorten or pull bones. The tendons don't change in length

- Muscle contraction is done upon the release of ACh in contact w/ nicotinic receptor. If long & sustained contraction → more ACh is released

- Flexion : bending limbs (↓ Angle)
- Extension : straightening limbs (↑ Angle)



- The force & speed is amplified as distance increases.
  - The muscles only need to move a bit for the whole limb to move very far
  - The muscles need to exert greater force for the limb to lift an object

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Smooth muscle control

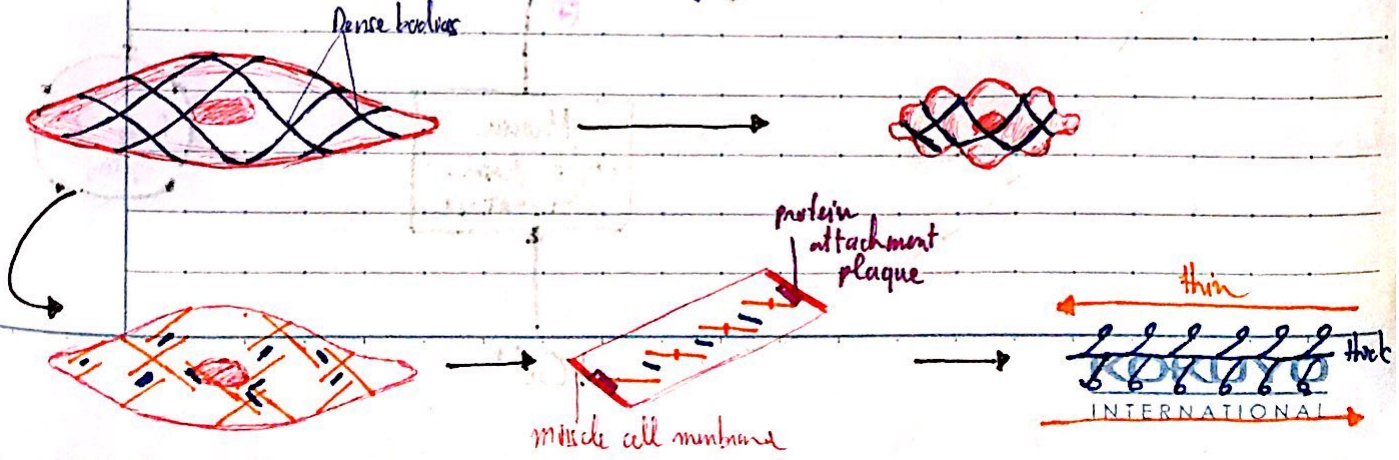
- Smooth muscle lacks cross striated banding found in skeletal musch and under control of autonomic nervous system.

- Similar to skeletal muscle:
  - Contain actin & myosin
  - Use cross-bridge mvt
  - Use Ca^{2+} to control cross-bridge activity

- Different from skeletal muscle:
  - Not attached to skeleton
  - Organisation of filament:
  - Excitation – contraction coupling
  - Single nucleus

- Smooth muscles are much smaller than skeletal muscle, and can divide throughout life (stimulated by paracrine agents in response to injury)

- The loose arrangement of diagonal chain of actin & myosin in smooth muscle (not sarcomere)
  → lower proportion of myosin & higher of actin
  → broader range of muscle lenghts



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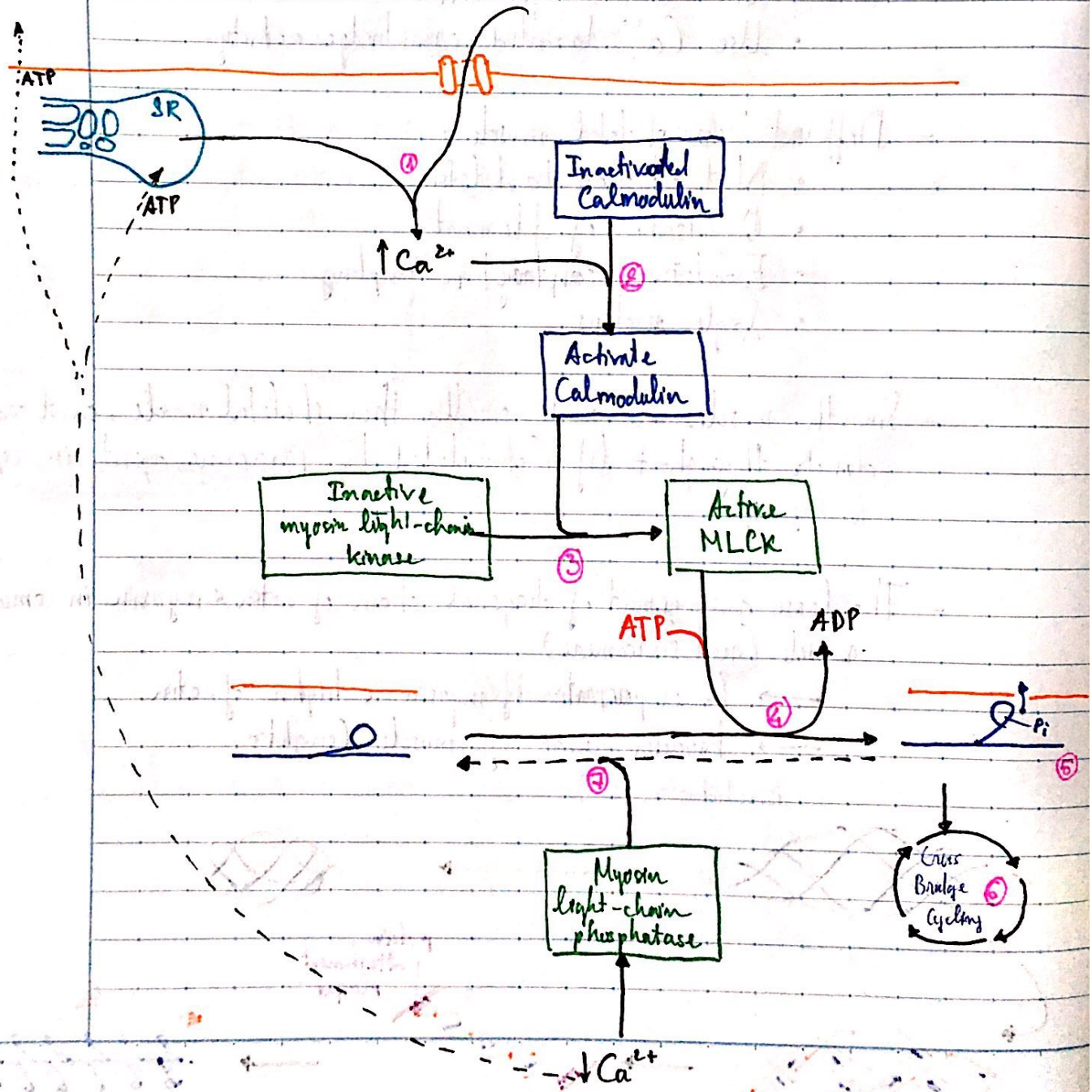
- The myosin of smooth muscle has a slow rate of ATPase
  → { muscle shortening is much slower
  { not go fatigue as quickly as skeletal muscle

- The Ca^{2+} source in smooth skeletal from { Sarcoplasmic reticulum
  { Extracellular fluid

No troponin molecules → Ca^{2+} in different pathway ?



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1. Ca^{2+} from ECF & sarcoplasmic reticulum influx
2. ↑Ca^{2+} in cytosol, bind to Calmodulin and activate it
3. Activated Calmodulin activates Myosin light-chain kinase (MLCK)
4. Active MLCK uses ATP to phosphorylate the light chain in the head
5. Phosphorylation bend the cross bridge away from back bone → bind w/ actin
6. Cross bridge undergo cycle, repeatedly as long as the light chains are phosphorylated → tension
7. When ↓Ca^{2+}, the rate of phosphorylation by MLCK falls below the rate of dephosphorylation by Myosin light-chain phosphatase (which is tonically active during resting & contraction)
   → Remove P_i → relax

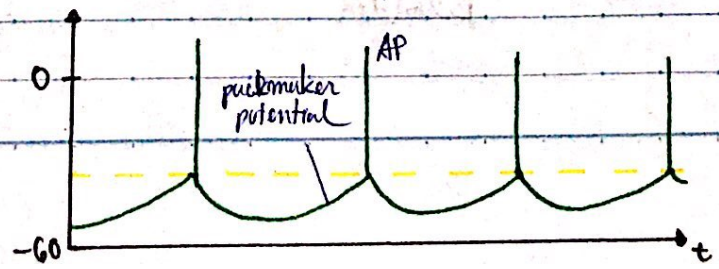
Factors determine / influence smooth muscle contractility

- 5 factors:
  - Spontaneous electrical activity
  - Neurotransmitter (by autonomic neuron)
  - Hormones
  - Local factors
  - Stretch

∿ Spontaneous electrical activity

- Some smooth muscles can contract under the absence of any input
  → under control of pacemaker cells

Pacemakers can cause gradually depolarisation → AP when reach threshold



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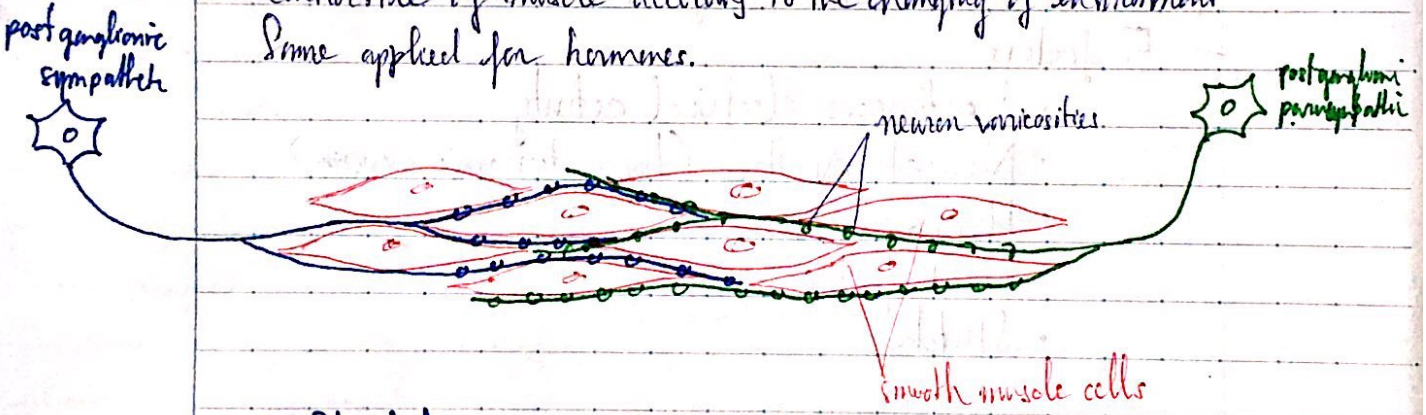
∿ Local factor

- Paracrine agent, pH, O_2 concentration, osmolarity, ion composition are all factor that can alter smooth muscle contractility.

∿ Nerve & Hormones

- Neurotransmitters & hormones can be excitatory or inhibitory depending on the receptor on muscle

- Most smooth muscle cells are innervated by both sympathetic & parasympathetic neuron/nerves.
  Generally, these 2 types have opposite effects & act to influence the contractile of muscle according to the changing of environment
  Same applied for hormones.



∿ Stretch

- Some smooth muscle cells respond by contracting when being stretch
  The opening of mechanosensitive ion channels leads to depolarisation

Eg: Uterus
Stomach
Bladder

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Types of smooth muscles

Simple-unit:
- cells are connected to each other by gap junction for communication
- contract at the same time
- Eg: GI tract, uterus, blood vessels, bladder, vas deferens

Multi-unit:
- no gap junction
- contract upon idividual signal, must be stimulate independantly
- Eg: Ciliary muscle

Characteristics of Muscle:

	Skeletal	Simple-unit	Multi-unit	Cardiac
Thick & thin filament	✓	✓	✓	✓
Sarcomere	✓	✗	✗	✓
T- tubule	✓	✗	✗	✓
Sarcoplasmic reticulum	✓✓ ✓✓	✓	✓	✓✓
Gap junction	✗	Yes	Few	Yes
Ca^{2+} source	SR	SR + ECF	SR + ECF	SR + ECF
Site for Ca^{2+}	Troponin	Myosin	Myosin	Troponin
Speed of contraction	fast + slow	very slow	very slow	slow
Pace-maker cells	✗	✓	✗	✓ ✗
Resting tone	✗	✓	✗	✗
Effect of nerve stimulation	Excitatory	Excitatory + Inhibitory	Excitatory + Inhibitory	Excitatory + Inhibitory
Affected by hormones?	✗	✓	✓	✓
Affected by stretch?	✗	✓	✗	✗

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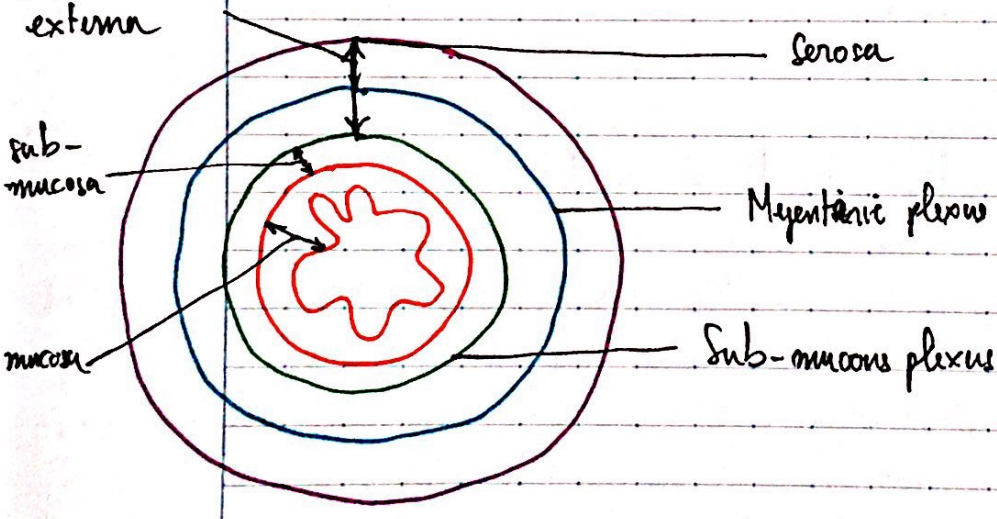
I) Digestive system 1

Structure of the digestive tract

- Same wall structure for most parts., some region of the digestive tract have variations for specific function

- 4 main tissue layers:
  - Mucosa
  - Submucosa
  - Muscularis externa
  - Serosa

- 2 nerve layers:
  - Myenteric plexus (Auerbach's)
  - Submucous plexus (Meissner's)



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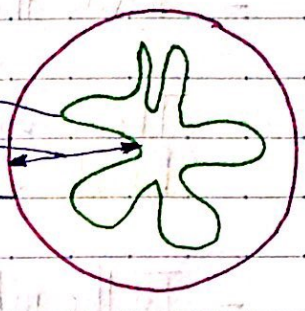
Mucosa

- Highly folded, the degree of folding is different in different areas, and the surface folding can be modified by muscle contraction

- The muscosa has 3 layers:
  - Mucous membrane
  - Lamina propria
  - Muscularis mucosa



~ Muscous membrane

- Inner epithelial cell layer of the GI wall
- Protective surface, involved in secretion & absorption

~ Lamina propria

- Thin middle layer of connective tissue, containing small blood vessels, lymph vessels & nerve fibers
- Mast cell, leukocytes & macrophage can also be found

~ Muscularis mucosa

- The outer layer of smooth muscle that lies adjacent to sub-mucosa.

Interstitial cells of Cajal: can be found in the lamina propria, are the pacemakers for the GI tract

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Submucosa, smooth muscle layer & serosa

~ Submucosa

- Thick layer of connective tissue
- Provide the GI tract distensibility & elasticity

- The submucous plexus lines outside the submucosa
  Blood & lymph vessel can be found in this layer (submucosa)

- In the intestine, mucous secreting glands are also found in submucosa

~ Muscularis externa

- The smooth muscle layer, 2 parts:
  - Inner layer w/ circular smooth muscle
  - Outer layer w/ longitudinal smooth muscle
- Responsible for peristaltic mvt of GI tract (mvt & mixing)

~ Serosa

- The outermost layer of the GI tract wall
  Secretes watery, serous fluid
- Mostly continuous w/ the mesentery

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Nerve layers

- 2 layers
  - The submucous plexus locates on the outer of the submucosa
  - The myenteric plexus lies between the longitudinal & circular smooth muscle layers.

- Both regulate local gut activity, & receive inputs from hormones:
  - ACh
  - Serotonin (5-HT)
  - Histamine (H)
  - Calcitonin gene-related peptide (CGRP)
  - Neurokinin (NK)
  - Nitric Oxide (NO)
  - Substance P (SP)
  - Prostaglandins (PG)

- The nerve layers also get input from mechanical stretch

Neural aspects

~ Enteric nervous system

- The GI tract is endowed w/ its own division of the ANS
  → the Enteric nervous system, made up of the submucosal plexus & myenteric plexus

- The ENS receives input from both the SNS & the PNS, and respo to local stimuli & control all aspects of GI function:
  - Initiating peristaltic activity in response to gastric distension
  - Controlling secretory & absorptive functions
  - Triggering biliary contractions.

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- The 2 layers of plexus are connected through a dense network of nerve fiber:
  - Myenteric plexus: motility
  - Submucosal plexus: ion control & fluid transport.

~ Central nervous system

- The CNS receives sensory info from the GI tract & modifies the GI function
- Emotions can influence the function of the digestive function, eg: butterfly in the stomach, traveller's constipation

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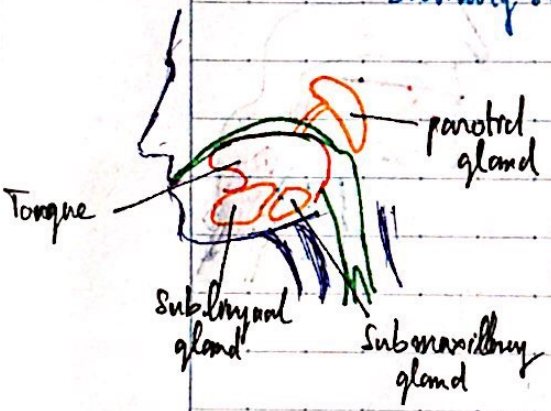
II) Digestive system 2

Upper digestive tract:

- Mouth
- Pharynx & oesophagus
- Stomach

The mouth

- Has 2 main functions
  - Chewing:
    - Begin mechanical digestion
    - Mastication of food
    - Produce bolus
  - Salivary secretion:
    - Begin digestion process
    - Under autonomic control
    - Triggered by multiple stimuly
    - Soften & lubricate food
    - Dissolve → taste
    - Protection



- Sjögren's syndrome: autoimmune disease → affect the moisture-producing glands → dry mouth & eyes

- The mouth also secretes amylase → breaks down polysaccharides

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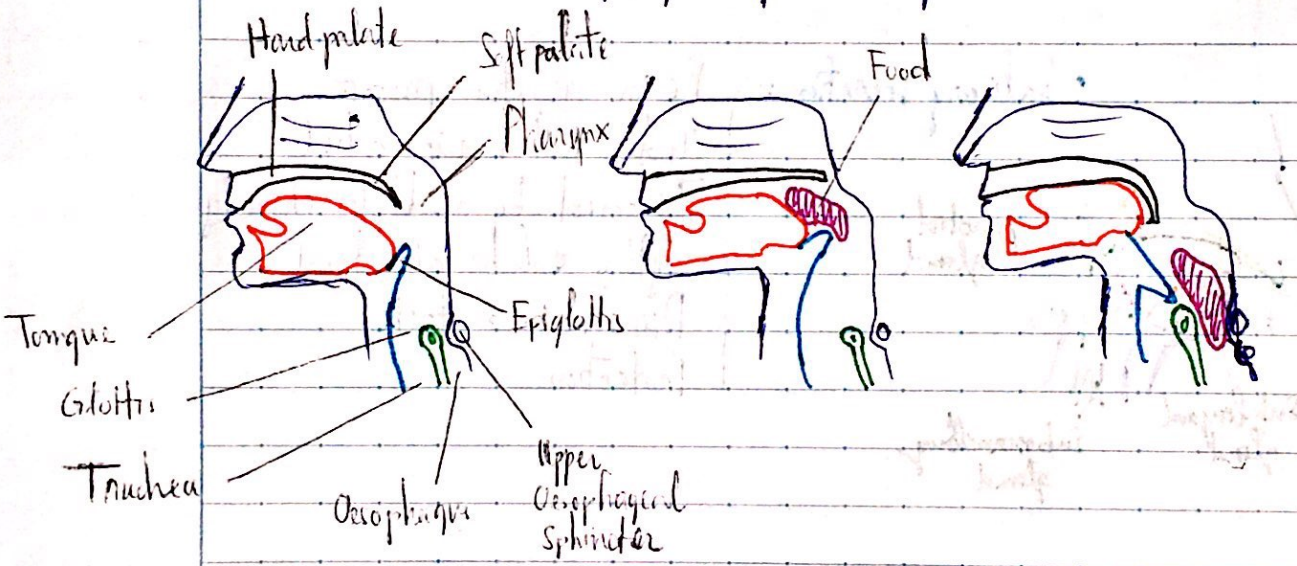
Pharynx & Oesophagus

- Swallowing = reflex action by pushing the bolus of food or liquid into the oesophagus
  - Pressure is created when the tongue pushes the bolus against soft palate and back of the mouth
  - Epiglottis folds down over larynx to prevent food from entering the air way.
  - Respiration is inhibited, upper oesophageal sphincter relaxes as the bolus enters the oesophagus
  - Waves of peristaltic contraction push the bolus toward the stomach aided by gravity
  - Lower Oesophageal sphincter opens



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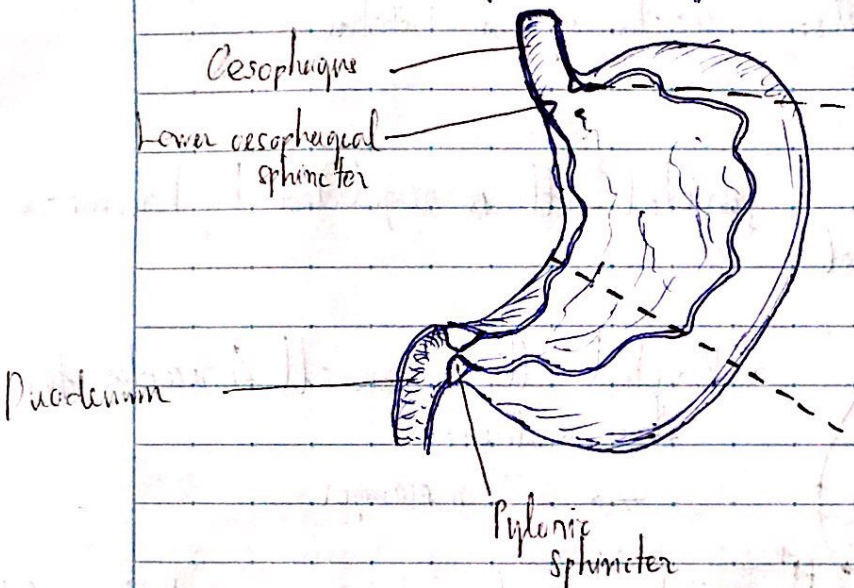
Stomach

- Main functions:
  - Receiving & providing temporary storage
  - Mixing food w/ H_2O & gastric secretory products
  - Grinding → ↓ particle size
  - Regulating the exit of chyme into the duodenum



Fundus : extra space

Body : Mucus, pepsinogen HCl

Antrum Mucus, pepsinogen gastrin

- The stomach has gastric glands that secrete:
  - Acid
  - Pepsinogen
  - Mucus
  - Bicarbonate
  - Intrinsic factor → glycoprotein that aids metabolism
  - H_2O

- Each cell type will secrete different product:
  - **Parietal cells:** – secretion of acid, pepsinogen, mucus, bicarbon intrinsic factor & H_2O
  - **Chief cells:** – secretion of pepsinogen

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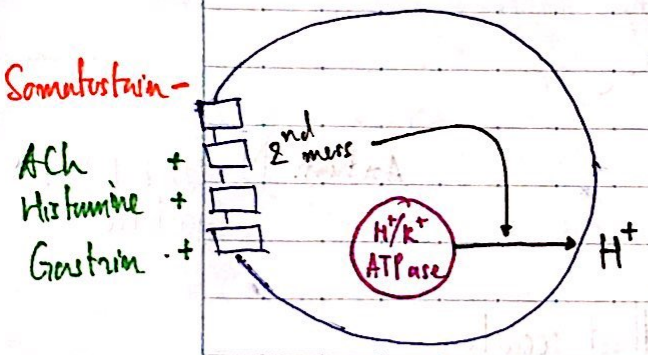
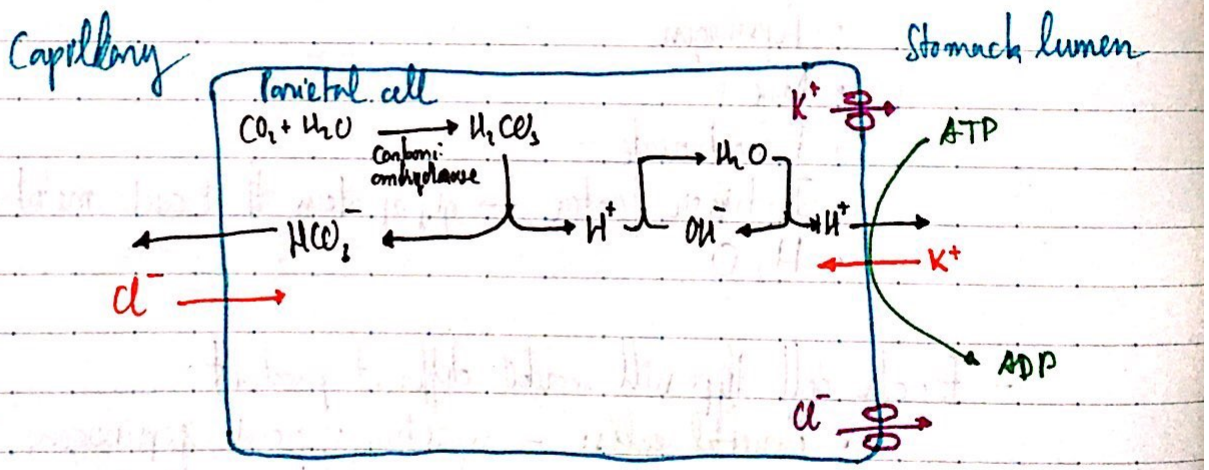
- Mucoid cells: - secretion of gastric mucus
- Gastrin cells: - secretion of acid-stimulating hormone gastrin
- Enterochromaffin-like cells: - secretion of serotonin
- Delta cells: - secretion of somatostatin

- Gastric secretion of parietal cells is regulated by hormones & neuronal control:



- Parietal cells contain all 4 receptors for these molecules.
  → 2nd messenger

- These 4 chemical messengers not only act directly on the parietal cells, but also other's secretion



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Lower digestive tract

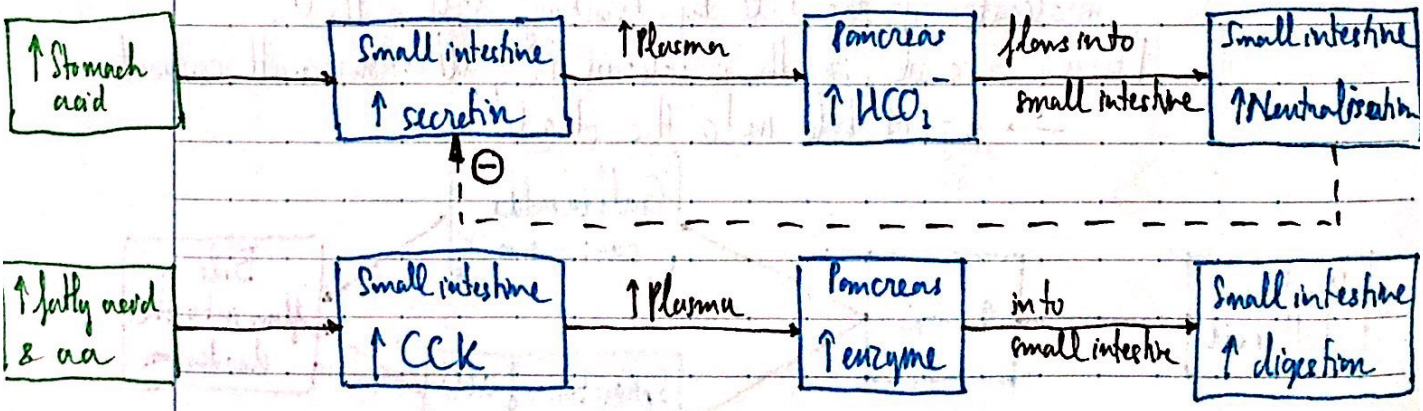
- Pancreas
- Liver
- Small & large intestine

Pancreatic & biliary secretion

- The main functions of the lower GI tract:
  - Gastric motility
  - Gastric secretion
  - Digestion
  - Absorption
- The role of the pancreas & the liver is to produce secretions.

The pancreas

- Secretes digestive enzymes (trypsin/chymotrypsin, lipase, amylase) and bicarbonate-rich fluid.
- High acidity of the chyme will inactivate the pancreatic enzymes if the acid is not neutralised by the HCO_3^-.
- During a meal, pancreatic secretion is stimulated by hormone secretin & cholecystokinin (CCK).



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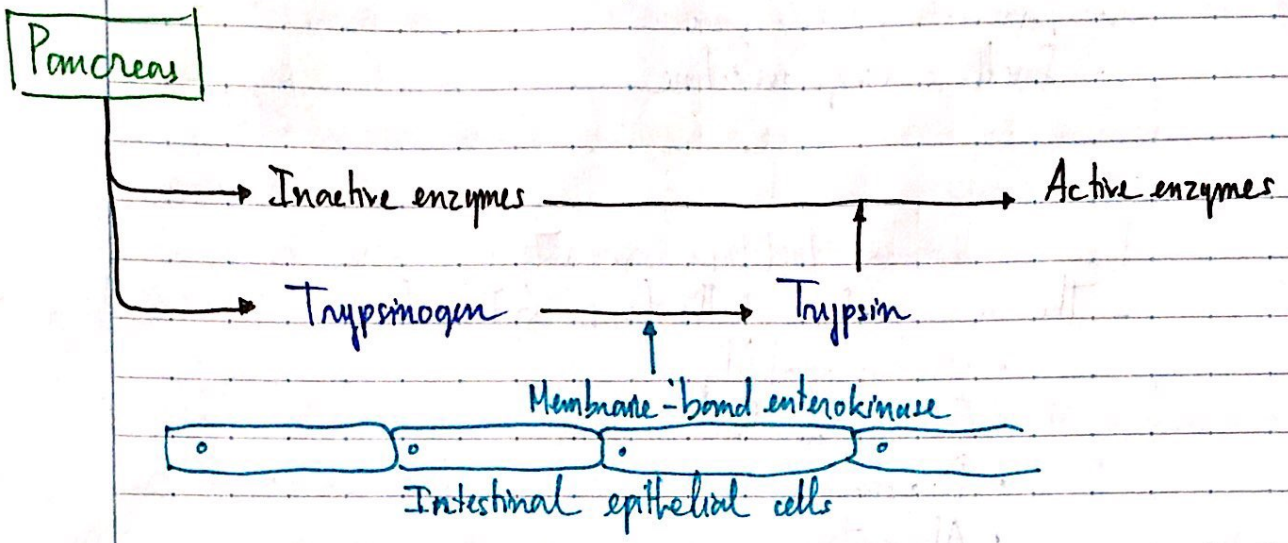
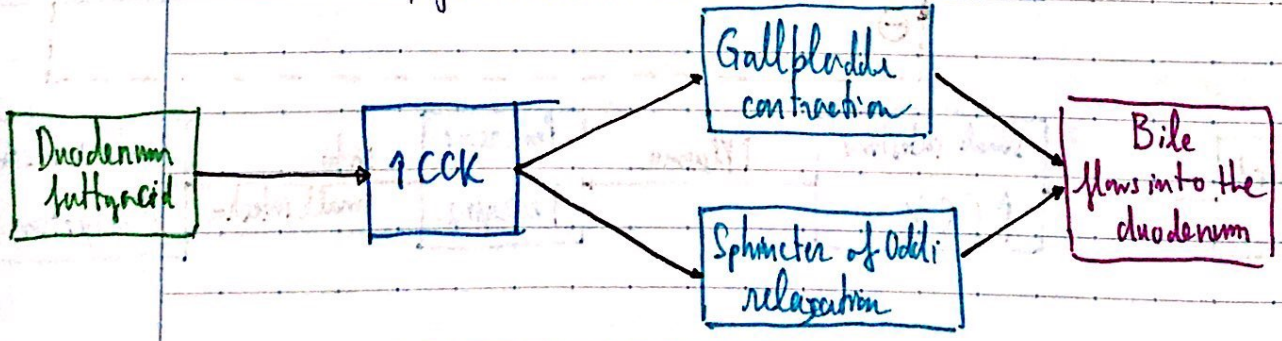
- Pancreatic enzymes are secreted under inactive form (zymogen), then are activated by other enzymes in the duodenum



~ Liver

- Secretes bile, contains:
  - HCO_3^-
  - Cholesterol
  - Phospholipids
  - Bile pigment → heme portion of dead erythrocytes
  - Organic waste
  - Bile salts
- The bile salts help solubilise dietary fat
- Bile is stored in the Gallbladder, which concentrates the organic molecules in the bile by absorbing salts & H_2O
- During a meal, smooth muscles in the gallbladder will contract → inject bile into the duodenum



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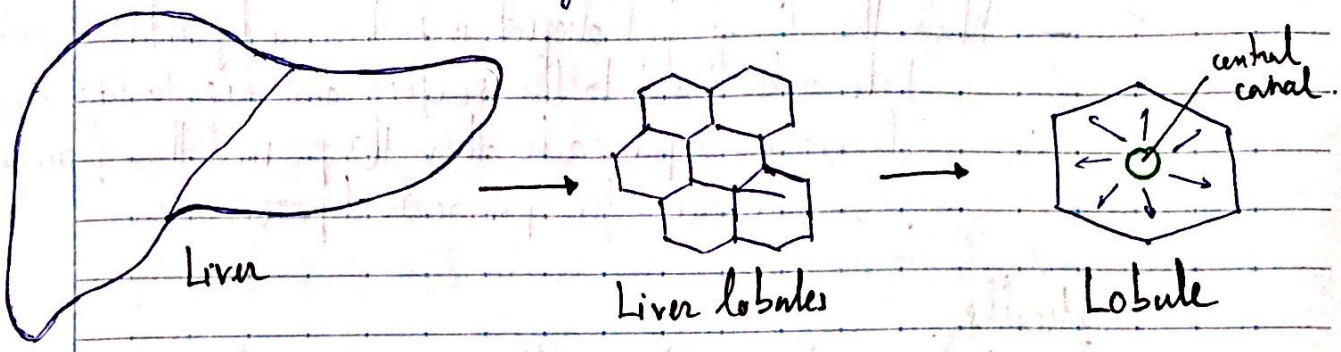
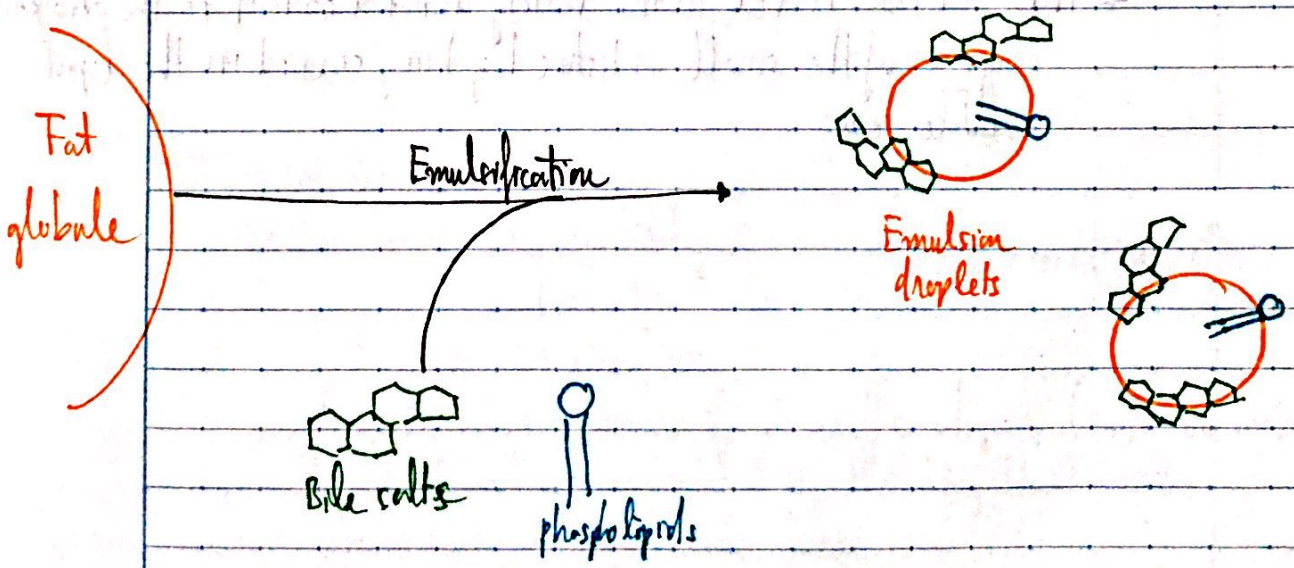
- One main function of the liver is to filter & process the nutrient rich blood delivered to it
  → Liver anatomy



The liver is made of a structure called lobule (hexagonal), contain hepatocytes. These liver cells radiated outward from a central vein running within the longitudinal axis of the lobule.

~ Bile:

- Bile salts aid fat digestion through emulsification & micellar formation
- Bile pigment (bilirubin) is produced in the spleen, liver & bone marrow



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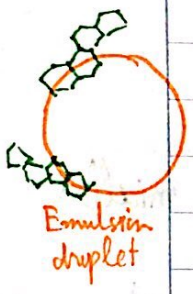
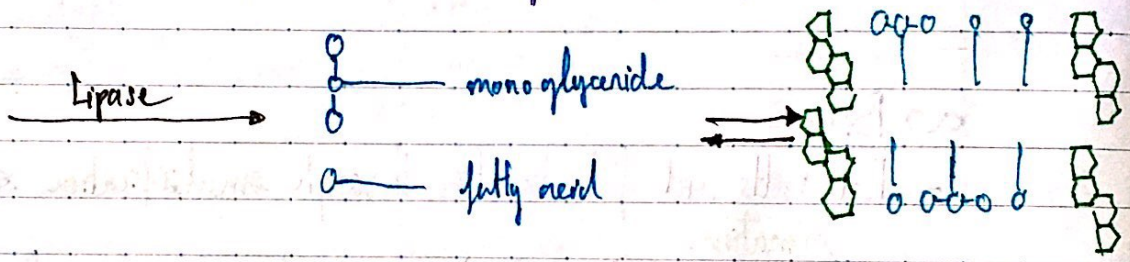
Emulsification

- Formation of lipid emulsion via bile salt.
- When the large fat droplet is broken up by intestinal contraction, bile salts bind to the surface and due to the negative charges → repel each other to prevent them from recoalesc
  ↗ surface area for pancreatic lipase

Micelle

- Second action of bile salts to speed up absorption
- Micelle has a similar structure to emulsion droplet, but much smaller.
  Consists of bile salts, fatty acids, monoglycerides & phospholipids





Micelle

- The fat can travel in the watery luminal content to the absorptive surface of the small intestine by being carried in the lipid soluble core.

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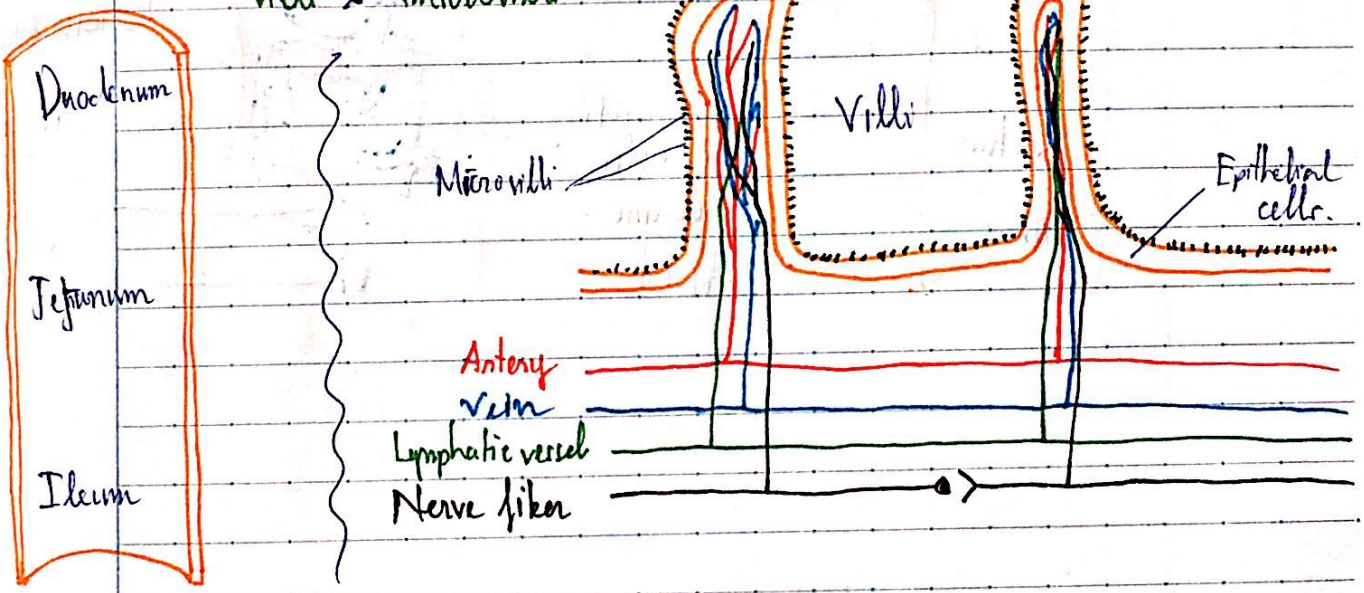
Small & large intestine

∿ Small intestine

- Main functions: motility, secretion, digestion, absorption

- Most substances are absorbed in the small intestine. Only a small volume of H_2O, salts & chyme pass onto the large intestine

- The surface of the small intestine is enhance by the presence of villi & microvilli



∿ Large intestine

- Main functions: motility, secretion, absorption — w/ minimal digestion

- The large intestine temporarily stores the chyme (some are metabolized by bacteria) & concentrates it by absorbing H_2O & salt
  → Convert chyme into faece

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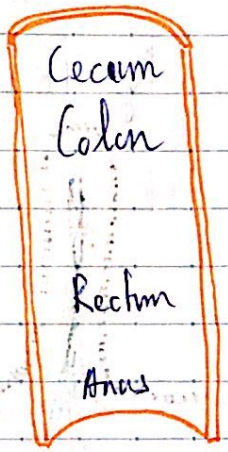
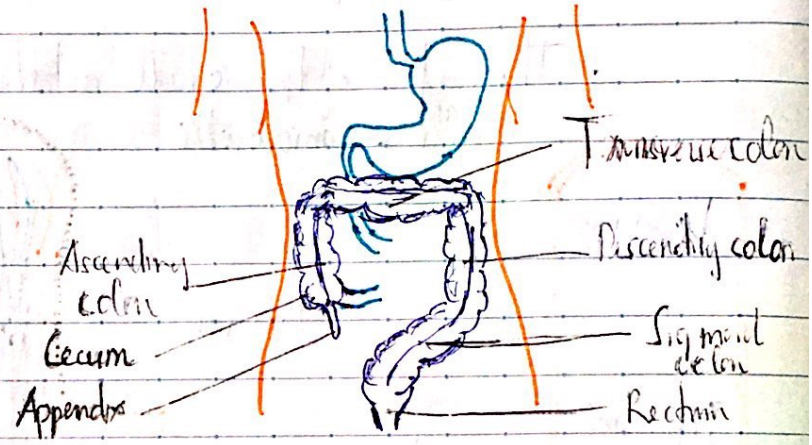
- Contraction of the rectum + relaxation of associated sphincter muscle
  → expel the faeces
  → Defecation

- When faeces move to the rectum → the urge to go defecate
  If not, the faeces will move back to the sigmoid colon until the next urge
  In this period → ↗ H_2O reabsorption → may constipation



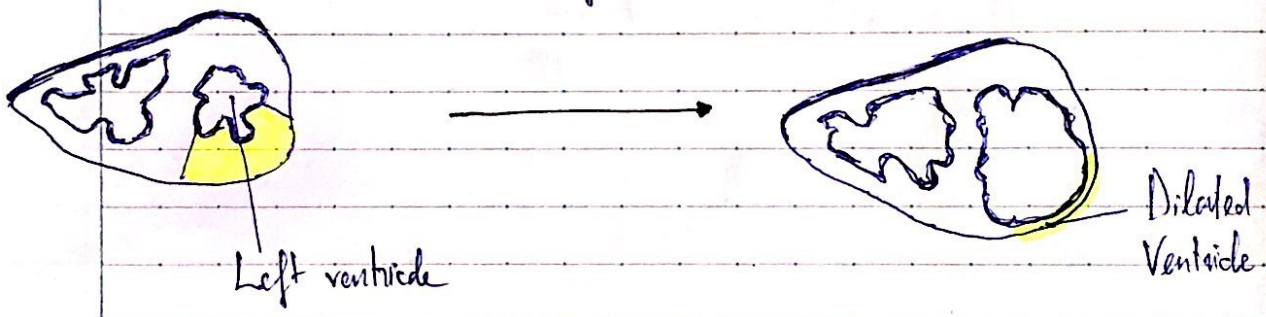


Week 9 1/5/2017 Thứ Ngày No.

I) Cardiovascular system Introduction

Why we need a heart?

- 1st organ to develop during embryo
- 1 key function of the Cardiovascular system is to provide nutrients
  → Eg: O_2
- Another function is to remove waste products
  → Eg: Urea
- The blood is crucial for t° control & delivering messengers
- Myocardial infarction: when 1 of the arteries that takes the blood back into the heart muscle is blocked
  → this region starts dying
  eventually leads to a thinner muscle wall



Heart structure

- The heart consists of 2 pumps: left & right.
  Each has 2 chambers: an atrium & a ventricle

- **Atria**: small chambers that get blood from the large vein; contract & pump blood to the ventricles.

- **Ventricle**: big chambers that get blood from the atria; contract & pump blood into the arteries

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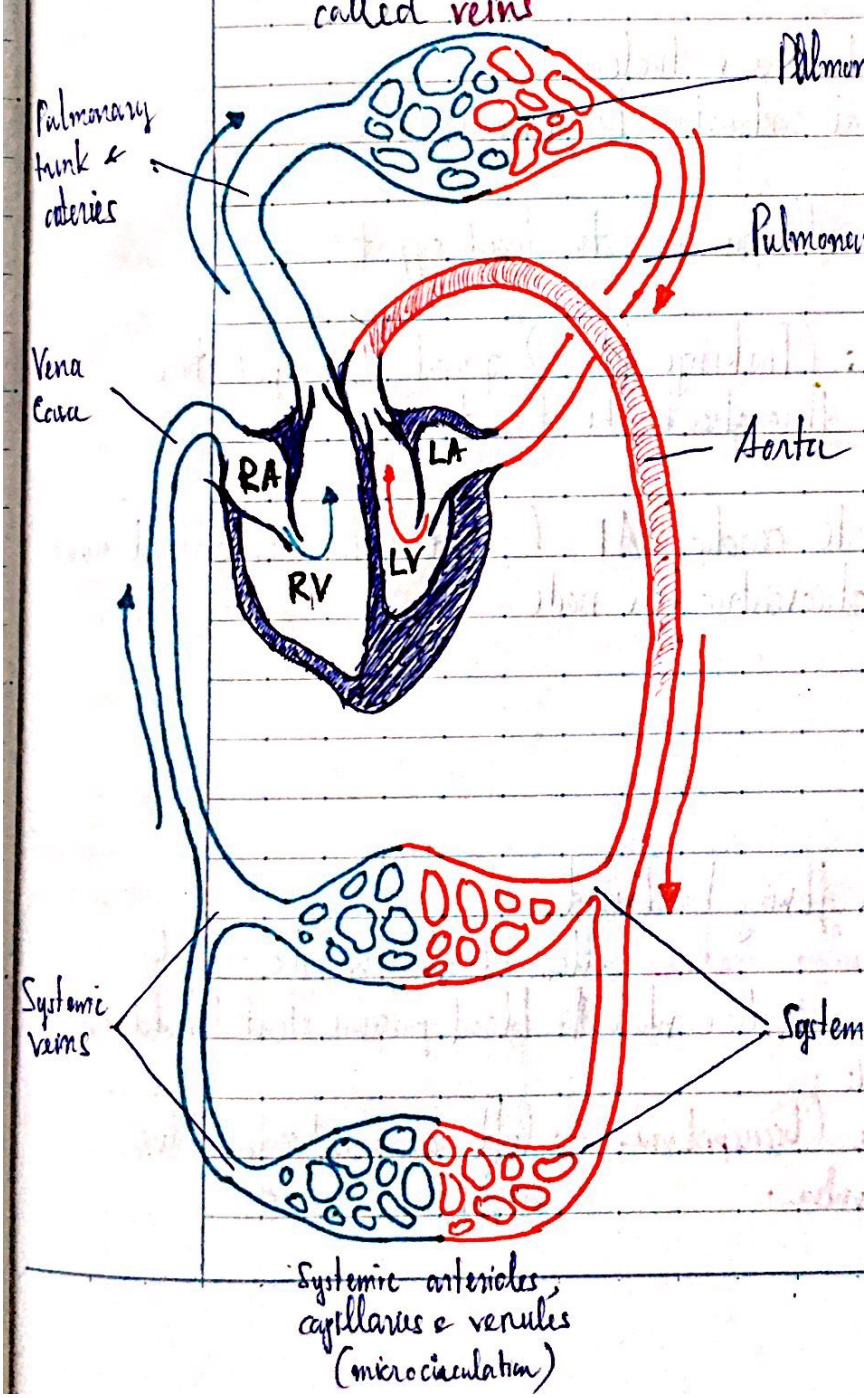
- 2 circles:
  - **Pulmonary circulation**: blood from the right ventricle to the lung then to the left atrium
  - **Systemic circulation**: blood from the left ventricle to every where in the body (except the lung) then to right atrium

In both circuits, the vessels that carry the blood away from the heart are called **arteries**, and those carry the blood to the heart are called **veins**



Lungs Pulmonary Circulation

There are 2 large veins:
- Inferior vena cava: collect blood from below the ♡
- Superior vena cava: collect blood from above the ♡

Systemic Circulation

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- The heart is located within a fluid-filled sac: pericardium
- The heart consists of:
  - Epicardium: outer lining – connective tissue & fat
  - Myocardium: cardiac muscle
  - Endocardium: inner lining – endothelial cells

Cell types

- Cardiomyocytes: [in atria & ventricles
  typical contracting heart muscle cells
- Fibroblasts: make collagen for structural support
- Fast conduction fibers: (Purkinje fibers) spread action potential throughout the heart.
- Pacemaker cells: initiate cardiac AP, located in the sinoatrial node & atrioventricular node

Valves & Vessels

Valves

- Prevent blood from flowing backward.
- The Atrioventricular valves allow blood from the atria to the ventricles, and close when the blood pressure start to build up in the ventricle:
  - Mitral valve (bicuspid valve): left atrioventricular valve
  - Tricuspid valve: right "

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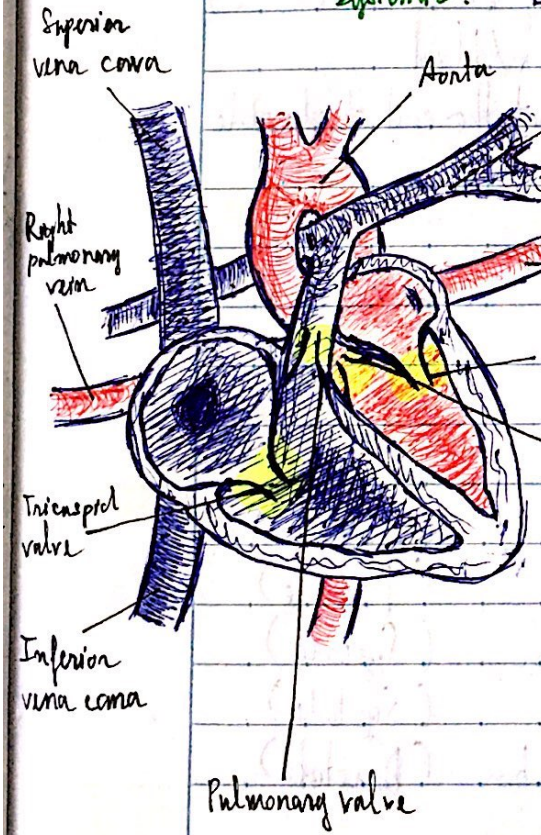
- The semilunar valves allow blood from the ventricles to the arteries:
  - Aortic valve: left semilunar valve
  - Pulmonary valve: right "
- The sound of the heart is the change of states of valves (open ⇌ closed)

~ Blood vessels

- The blood leaves the heart continues to the body or lung:
  - Pulmonary: RV → Pulmonary arteries → Lung capillaries → Pulmonary vein → LA
  - Systemic: LV → Aorta → Arteries → Arterioles → Capillaries → Venules → veins → Vena cava → RA



Arteries	Carry blood under high pressure to arterioles.
Arterioles	Determine blood flow to organ by changing diameter of resistance
Capillaries	Site of exchange between blood & tissue
Venules Vein	Low pressure, high capacity. vessels carry blood to the ♡

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II) The cardiac cycle, electrical & mechanical events

Cardiac cycle

- Each time the heart beats, many individual processes have to work in a coordinated way to result in ejection of blood:
  - Filling the heart w/ blood
  - Contraction of cardiomyocytes
  - Ejection of blood
  - Relaxation of cardiomyocytes.

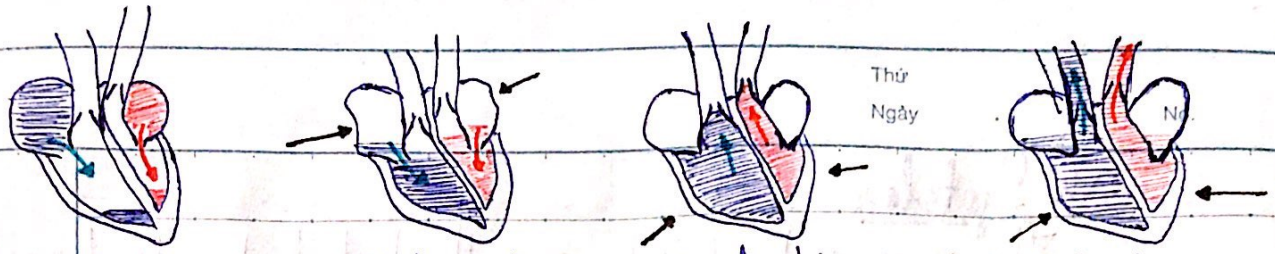
- 2 main phases of the cardiac cycle:
  - Systole: Ventricles contract & pump blood out (0.3s)
  - Diastole: Ventricles relax & fill w/ blood
    Atrial contraction occurs at the end of diastole

Mechanical events

- The mechanical events include:
  1. Ventricular filling (Diastole)
  2. Atrial contraction (Diastole)
  3. Isovolumetric ventricular contraction (Systole)
  4. Ventricular ejection (Systole)
  5. Isovolumetric ventricular relaxation (Diastole)

- During the 1st part of Systole, the ventricle is contracting but all the valves are closed → the volume is not change → isovolumetric
  Same applied for the 1st part of Diastole

- Some sounds, known as **heart murmurs**, can be a sign of heart disease
- The murmurs are caused by turbulence, when the valves are defected:
  - Abnormally narrow valves: stenosis
  - Damage, leaky valve: insufficiency
  - Flow between 2 | atria / ventricles: septal defe



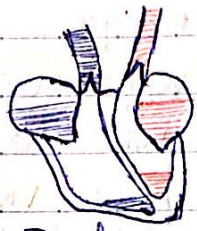
① Ventricular filling
AV valves open
Aortic & pulmonary closed

② Atrial contraction
open
closed

③ Isovolumetric contraction
closed
closed

④ Ventricular ejection
closed
open

Mid-to-late diastole → Ventricular systole



⑤ Isovolumetric relaxation

AV valves: closed
Aortic & pulmonary valves: closed.

Early diastole

~ Mid to late Diastole

- The atrium & the ventricle are both relax, but atrial pressure is slightly huge than ventricular pressure
- The AV valve is forced open by the pressure difference → blood entering the ventricle
- The aortic valve is closed throughout diastole
- The pressure in the ventricle slightly ↗ due to the blood
- Near the end of diastole, the atrium contracts, forces a small amount of blood into the ventricle (atrial kick)
- The amount of blood in the ventricle at this time is called end-diastolic volume (EDV)

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~ Systole

- The wave of depolarisation cause the Ventricles to contract right after atrial contraction.
- As the ventricles contract, ventricular pressure ↗ rapidly (120 mmHg)
- This change in pressure forces the AV valves to close → prevent from flowing back
- For a brief moment, the aortic pressure still exceed the ventricular pressure
  → aortic valve is not open
  → Isovolumetric ventricular contraction
- Shortly, the pressure in ventricle exceeds the aortic pressure, open the aortic valve, begins ventricular ejection.
- Ventricular ejection rapid at first, then tapper off
- The amount of blood remain in the ventricle after ejection is called end-systolic volume (ESV)

- The amount of blood that exits the heart is:

  Stroke volume = EDV − ESV

~ Early diastole

- As the ventricles relax, ventricular pressure ↓ → close the aortic valve
- For a brief moment, the pressure in the atria is still greater than in the ventricle
  → Isovolumetric ventricular relaxation
- Blood from the atria flows into the ventricles, aided by the reduction of pressure

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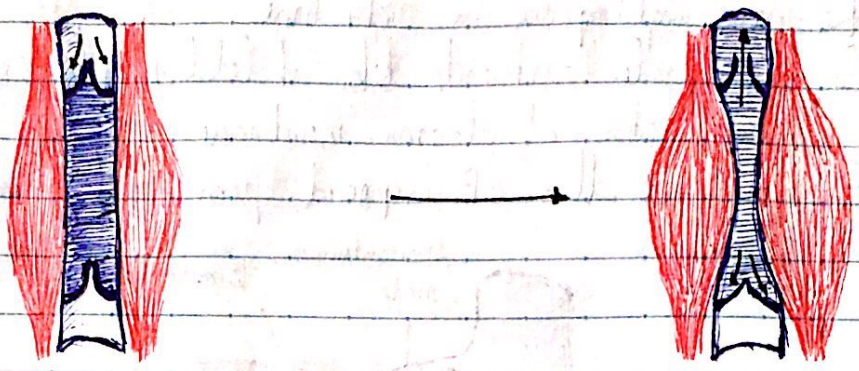
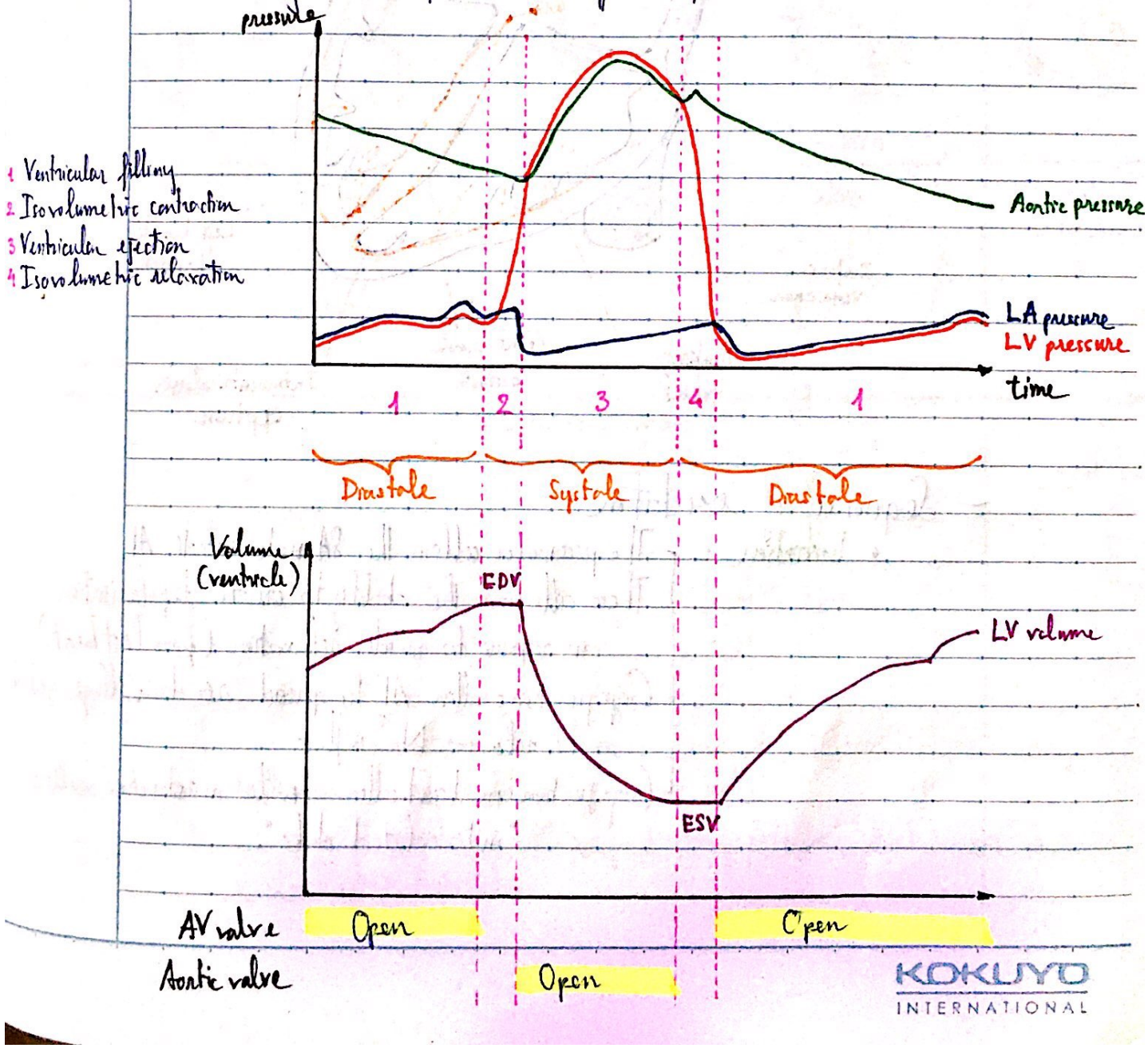
- The muscles also help to carry the blood back to the heart:



Relaxed muscle

Contracted muscle

- Breathing also helps to change the pressure in the veins → and



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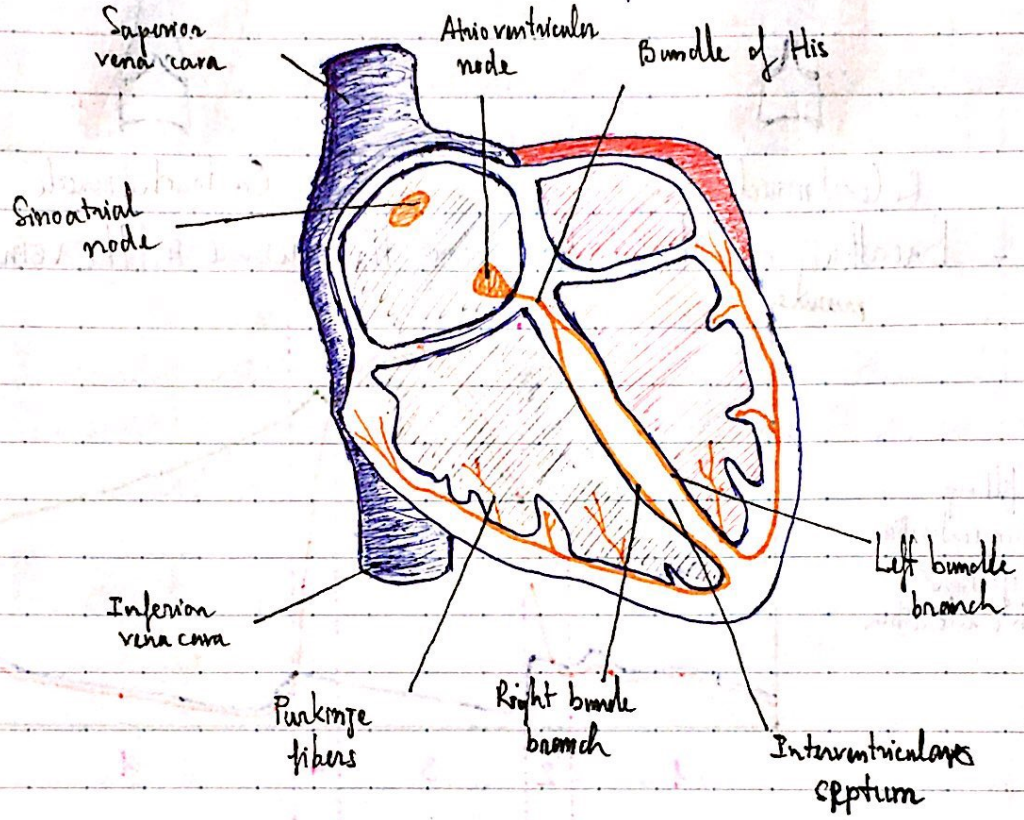
Electrical events:

- Requires right place & right time
- Cardiac muscle contracts like skeletal muscle, is triggered by depolarisation of plasma membrane.

Gap junctions allow AP to spread from 1 cell to another



- Sequence of excitation:
  - Initiation:
    - The pacemaker cells in the SA node initiate AP
    - These cells have the ability to create depolarisation in response to muscle relaxation (from last beat)
    - Gap junctions allow AP to spread, reach voltage-gated channels → Na^+ influx
    - Gap junctions in heart cells are ~~folded~~ in a structure called "intercalated disks"

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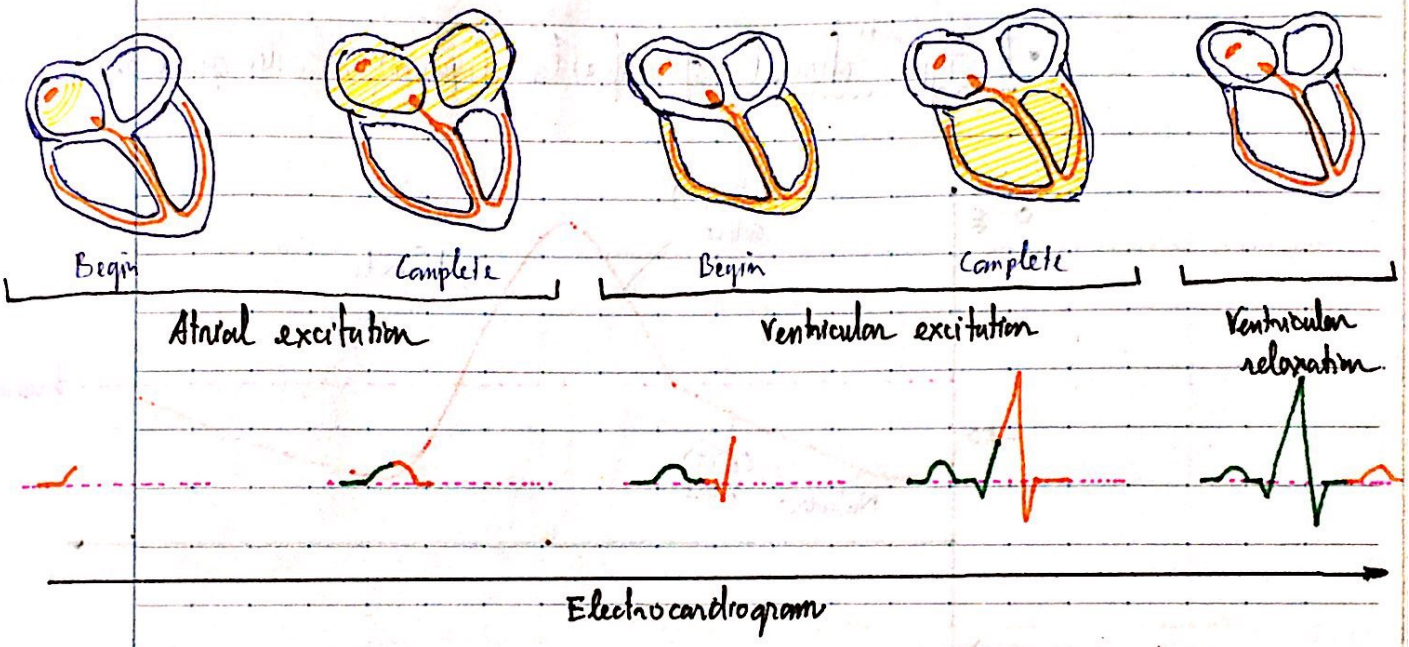
- Spreading: The AV node is located at right bottom of the Right atrium, and is the only gateway to spread AP to ventricles
  Delay the AP from the atrium ← AV nodal cells have slightly more (−) membrane potential

- Ventricle activation: – The AP moves to the bundle of His, then to the bundle branches → Purkinje fibers to activate cardiomyocytes



Electrical events – cellular mechanisms

~ Initiation = pacemaker cells

- The pacemaker cells in the SA node have very different depolarising mechanisms compared to the nerve cells
  These cells don't have steady resting potential, but rather undergo a slow depolarisation

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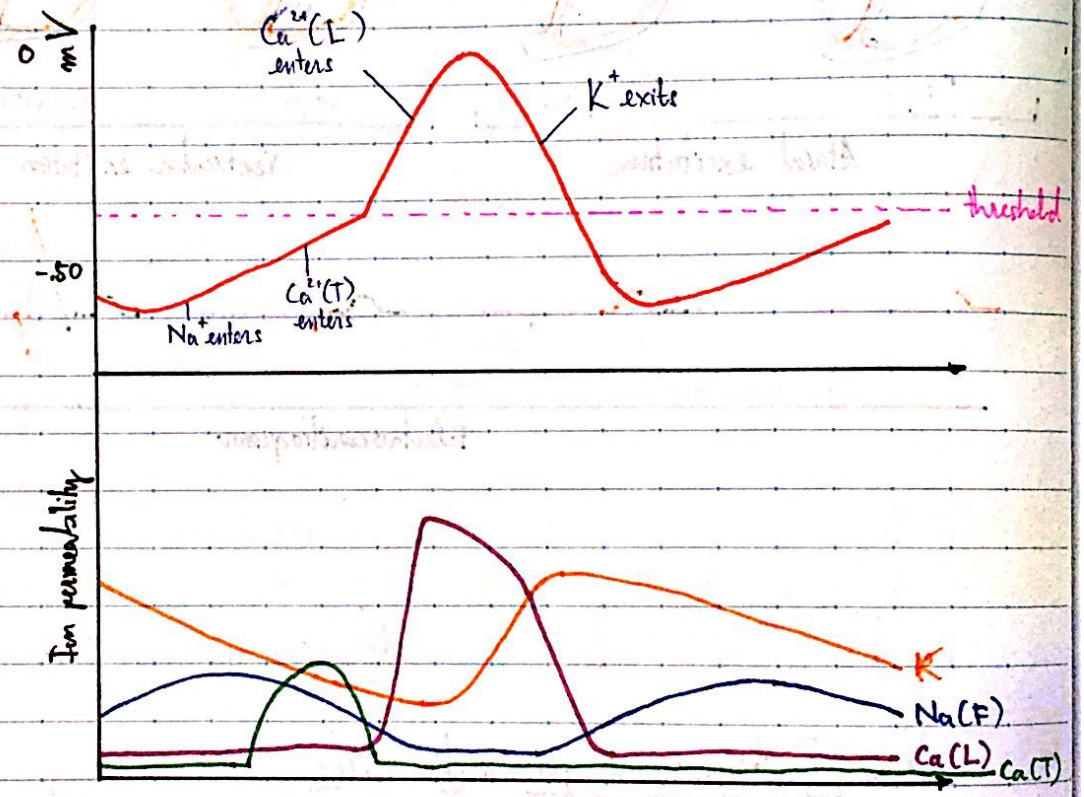
- Pacemaker potential → Ion channel mechanism:
  - K^+ channels: gradually close from the last repolarisation period (open) → return to (-) potential
  - F-type Na^+ channel: open while the potential is at (-) value, even at repolarisation → slowly depolarise
  - T-type Ca^{2+} channel: open briefly to boost the pace maker potential
  - L-type Ca^{2+} channel: open for longer period, cause quick depolarisation



- The funny ion channel (F-type) is non-specific, mainly conduct an inward, depolarising Na^+ current

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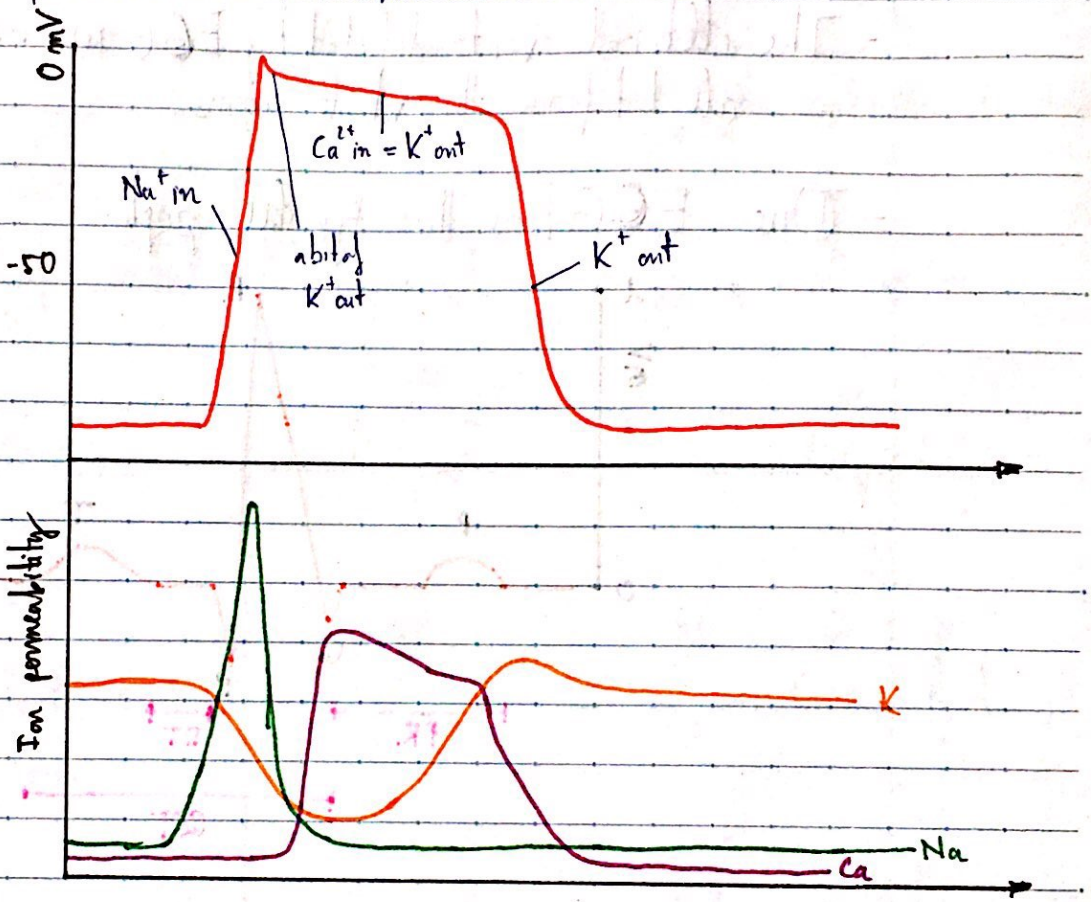
~ Spreading – Cardiomyocytes

- Once the AP is spreaded through the branches → reach the heart cells at the ventricle wall, and then to other cells via gap junction
- Membrane potential in the cardiomyocytes is quite like the neuron, except that there is another channel.



typical

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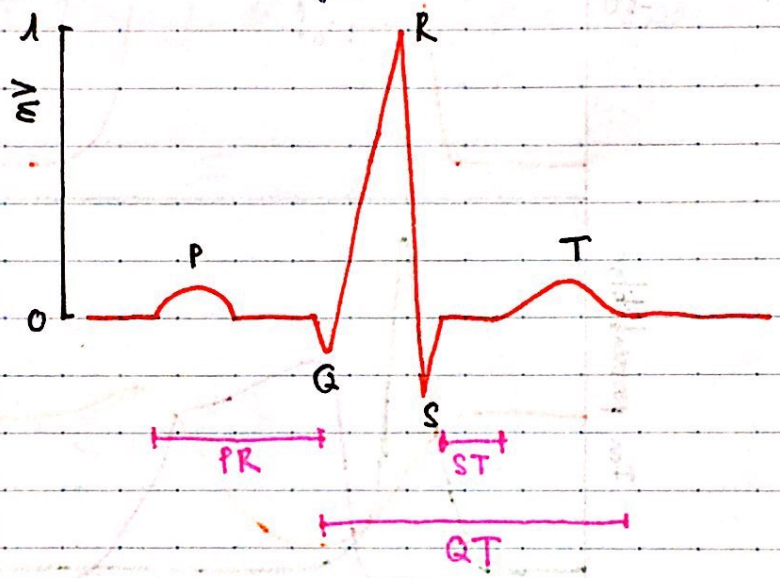
Electrocardiogram (ECG)

- A tool to evaluate the electrical events in the heart. The AP of the heart can be view as a battery that cause the charge to move throughout the body fluid

- The electrical events detected by ECG are not from a single cell but from the whole organ

- One ECG has this typical graph:



- P wave : atrial depolarisation
- QRS complex : ventricular depolarisation + atrial repolarisation
- T wave : ventricular repolarisation

- Sometime, there will be an U wave right after the T wave.

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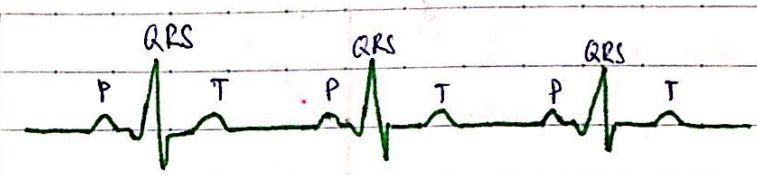
- There are intervals between deflections:
  - PR interval: time from start of P wave to start of QRS
    → depolarisation of atria
  - QT interval: start of Q wave to end of T wave
    → depolarisation & repolarisation of ventricles
  - ST interval: end of S wave to the start of T wave
    → period immediately after contraction of ventricles

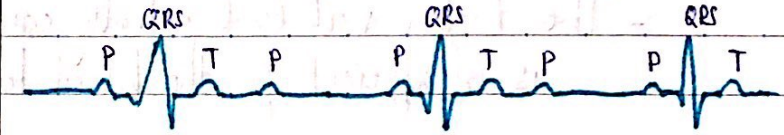
- The shapes & intervals is crucial in diagnosing heart condition:

Normal ECG



Partial block (AV)

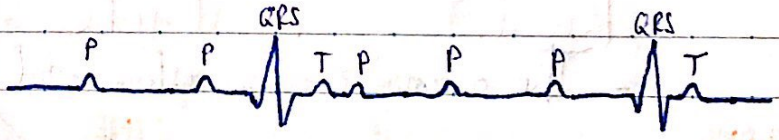
Damage to AV node → more P



Complete block

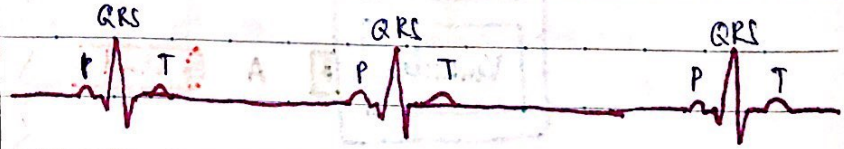
No sync between atrial & ventricular activity

→ Depends on the slow pace maker in the bundle of His

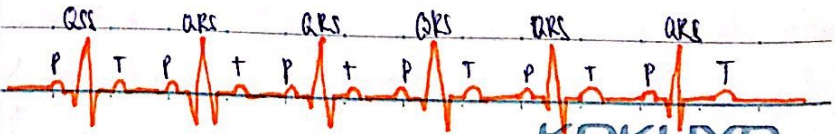


Cardiac arrhythmia

Sinus bradycardia (slow beat)



Sinus tachycardia (fast beat)



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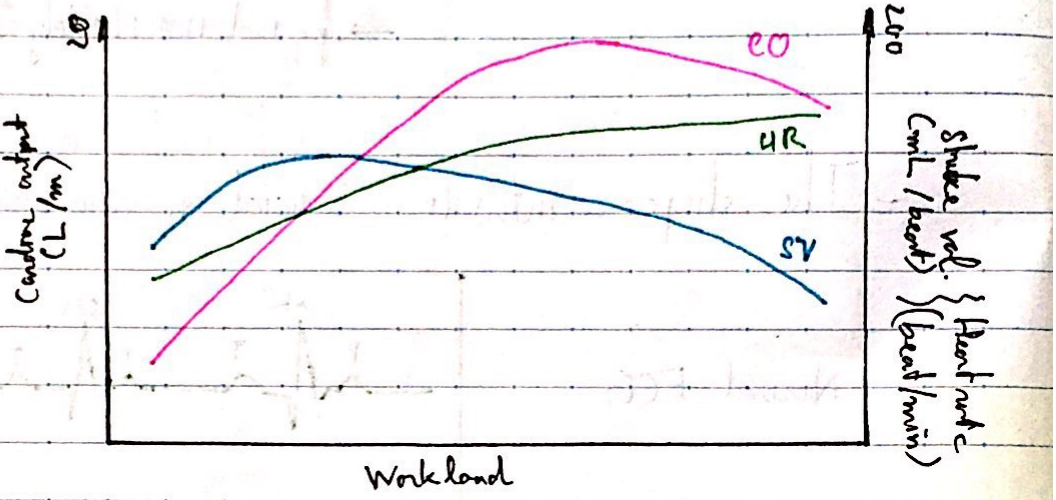
Regulation of cardiac output

- Cardiac output is the amount of blood ejected by each ventricle per minute

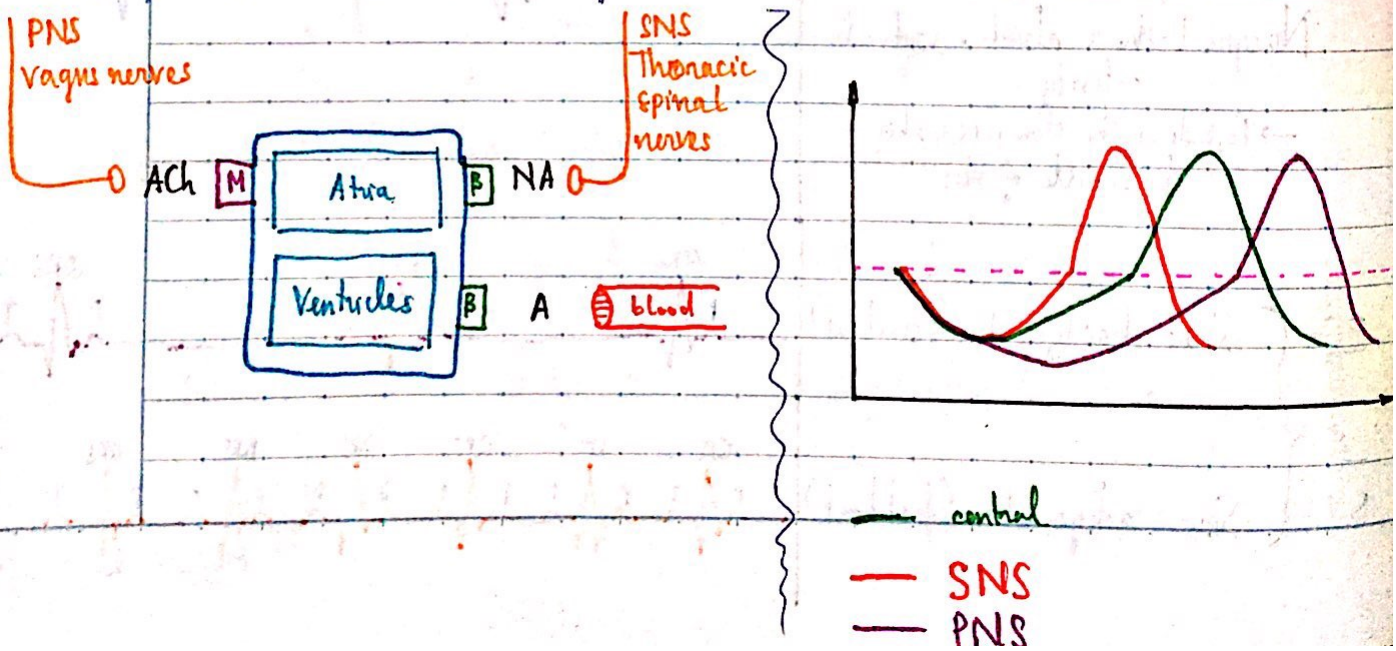
Cardiac output = Heart rate (beat/min) × Stroke volume (mL/beat)



- The higher workload actually can ↓ stroke volume since the time is insufficient for the blood to flow into the ventricles

Regulation of heart rate

- The autonomic nervous system control the heart rate.



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~ The SNS ↗ heart rate:
- ↗ in sympathetic nerve activation → ↗ release of {adrenaline (hormone) / noradrenaline (neurotransmitter)}
- Leads to activation of β_1-adrenoceptors (on pacemaker cells)
- ↗ Na^+ influx by opening the F-type Na^+ channels
  → Depolarisation
  → More frequent pacemaker action
  → ↗ Heart rate

~ The PNS ↘ heart rate:
- ↗ in parasympathetic nerve activation → ↗ release of ACh (neurotransmitter)
- Leads to the activation of M_2 receptors (on pacemaker cells)
- ↗ K^+ efflux by opening K^+ channel
  → Hyperpolarisation
  → Less frequent pacemaker action
  → ↘ Heart rate

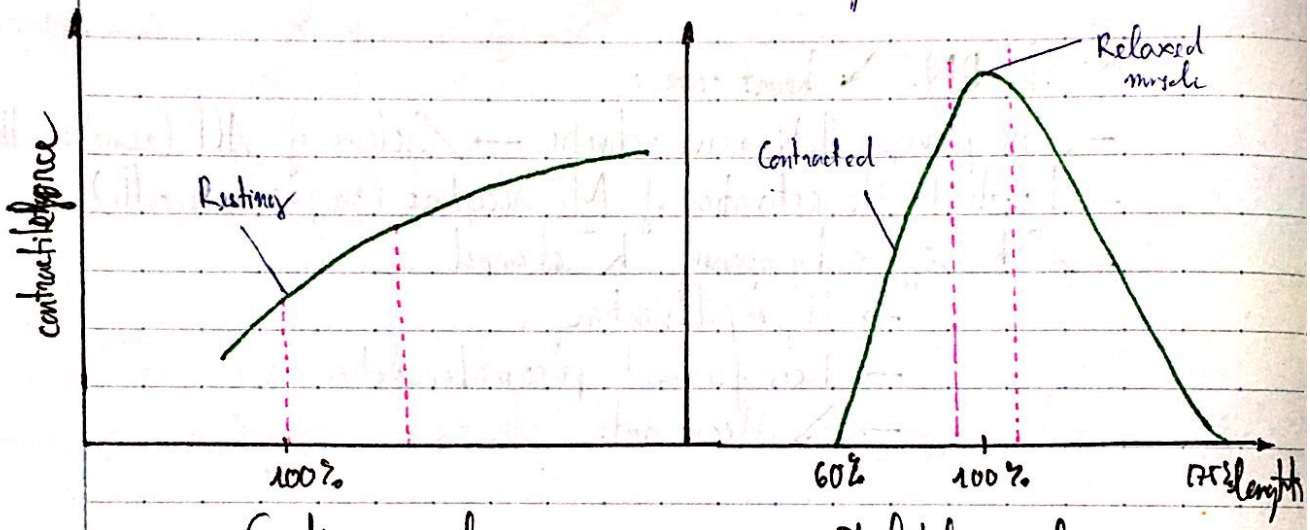
Regulation of stroke volume
- 3 key factors:
  - How much blood in the ventricle at the end of diastole (EDV)
  - How hard the heart contract (contractility)
  - How much pressure the heart needs to pump against (arteries' pressure)

- The SNS ↗ stroke volume by activating β_1 receptors → Ca^{2+} entry
  → more contraction

- **Frank-Starling mechanism**: relationship between EDV & stroke volume
  the heart will contract more forcefully when the ventricles are filled

w/ greater degree of blood
⟶ Increased EDV leads to increased stroke volume

- The reason for this mechanism:
  - Higher EDV ⟶ much greater stretch in muscle
  - The stretcher the muscle ⟶ the harder the contraction
  - The differante between skeletal muscle & cardiac muscle is that the length of cardiac muscle is not optimal for contrac as it in skeletal muscle ⟶ length - tension relationship



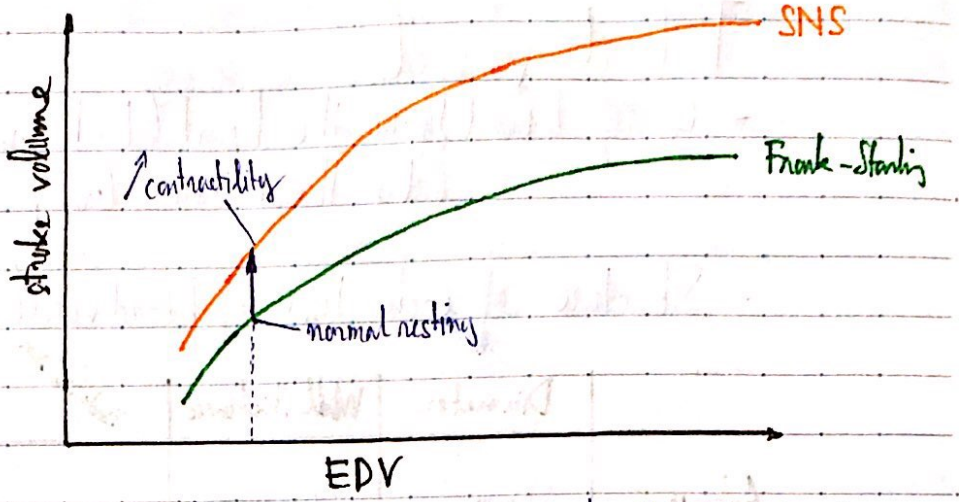
In skeletal muscle, the shortened length results in the decrease in contractility because of the interfere of small fillament (overlapping) & the Z lines touch the ~~Thick~~ thick fillaments

The lengthened muscle ↘ contractility because of the lack of cross-bridges that bind to actin.

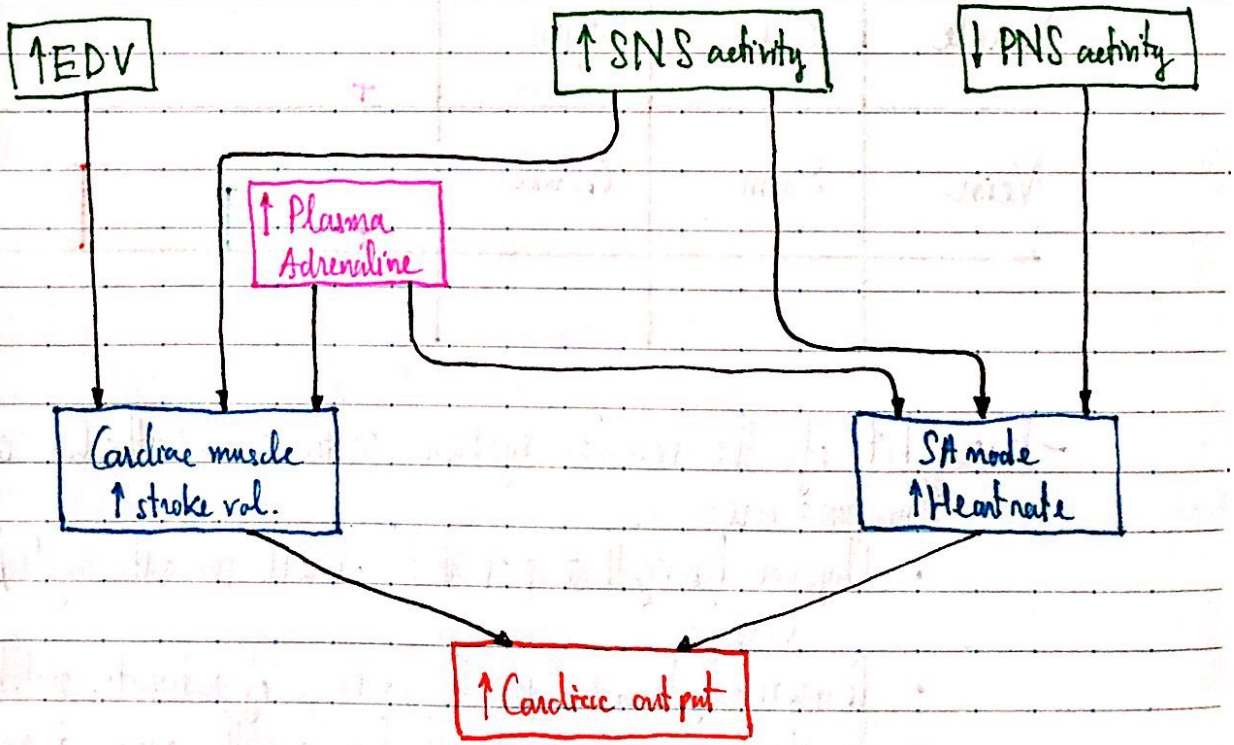
* Contractility ≠ contractile force

- Contractility: contraction in any given volume
  → $NS regulation
- Contractile force: the strength of contraction in different volume
  → Frank - Starling mechanism

- Relationship between Frank-Starling mechanism & SNS:



- It is very important for the SNS to increase both heart rate and the speed of contraction & relaxation since when increasing heart rate, the time for filling the ventricles decrease
  → Need quicker contraction & relaxation of ventricles.
  → Involve Adrenergic GCPR → ↑intracellular Ca^{2+}
  → Faster response



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III) The Vascular System

Blood vessels

- Convey blood { from the heart (high press.) to the body
  { to the heart (low press.) from the body

- Structure of each type of blood vessel are varied :

	Diameter	Wall thickness	Endothelium	Elastic tissue	Smooth muscle	Fibrous tissue
Artery	4 mm	1 mm	T	T	T	T
Arteriole	30 μm	6 μm	T		T	
Capillary	8 μm	0.5 μm	T			
Venule	20 μm	1 μm	T			T
Vein	5 mm	0.5 mm	T	T	T	T

- Every bit of the vascular system contains endothelial cells, their functions are:
  - Physical lining that prevent blood cell from adhering to ~~from~~ blood vessels.
  - Permeability barrier for the exchange of nutrients, metabolites & products
  - Secrete paracrine agents that acts on the adjacent smooth muscle cells (if had)

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- Mediate angiogenesis (new capillary growth)
- Formation & maintenance of ECM
- Produce growth factor in response to damage
- Secrete substances that regulate platelet clumping, clotting & anticlotting
- Synthesise active hormones from inactive precursors
- Secrete cytokines during immune response

- The arteries have a lot of smooth muscle & elastic tissue to reduce resistance when carrying blood. The elasticity also helps to maintain blood flow through the tissue during diastole

- Arterioles – the most important site of cardiovascular drug action. The smooth muscle contains many receptor that the drugs can act on. These smooth muscles also have a role in blood distribution.

- Capillaries are just endothelial tube for quick transfer

- Venules and veins pretty much have not so many things to do other than carrying the blood to the heart.

Blood flow & vascular resistance

- Perfusion: supply of blood to an organ

- Flow in a tube from point A to B depends on the pressure gradient from A → B & resistance

$$\text{Flow} = \frac{\Delta P}{\text{resistance}}$$

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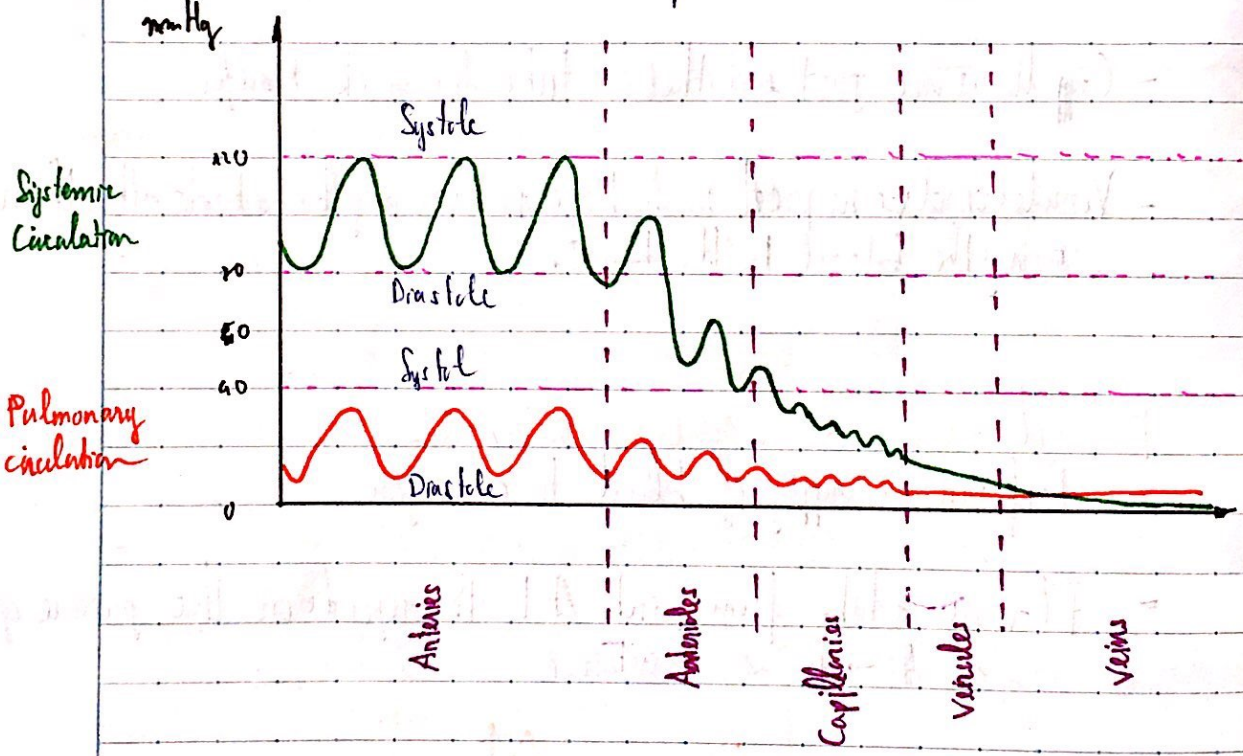
- Resistance is determined by 3 factors { length of the tube, viscosity of the fluid, diameter of the tube

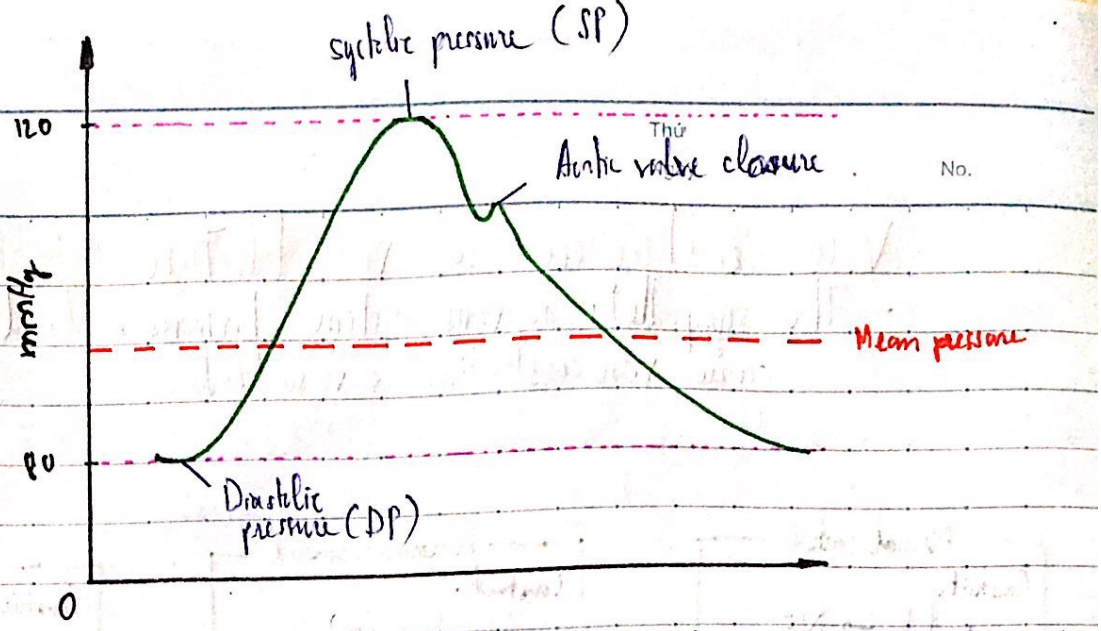
→ Poiseuille's law

$$\text{Resistance} = \frac{8\eta L}{\pi r^4}$$

- Vasculer resistance can change because of the arteriolar smooth muscle contraction & relaxation.
  → Blood flow determination is mostly dependent on the arteriolar diameter

- The flow also depends on the pressure between the heart & the organs.
  → Arterial blood pressure is calculated by the systolic pressure & diastolic pressure





- The difference between SP & DP is called **pulse pressure**, can be felt in the artery ở the neck or arm.

- Since the ~~pressure~~ arterial pressure changes throughout the cardiac cycle
  → Mean arterial pressure (MAP)

$$MAP = DP + \frac{1}{3}(SP - DP)$$

The MAP can represent for any artery as the pressure in the aorta or in other arteries is pretty much the same

- From there we can calculate the flow rate into an organ; as mention:

$$Flow = \frac{\Delta P}{R_{esistance}}$$

$$F_{organ} = \frac{MAP - \text{venous pressure}}{\text{arterial resistance}}$$

- Arterial resistance is regulated by { vasodilation / vasoconstriction

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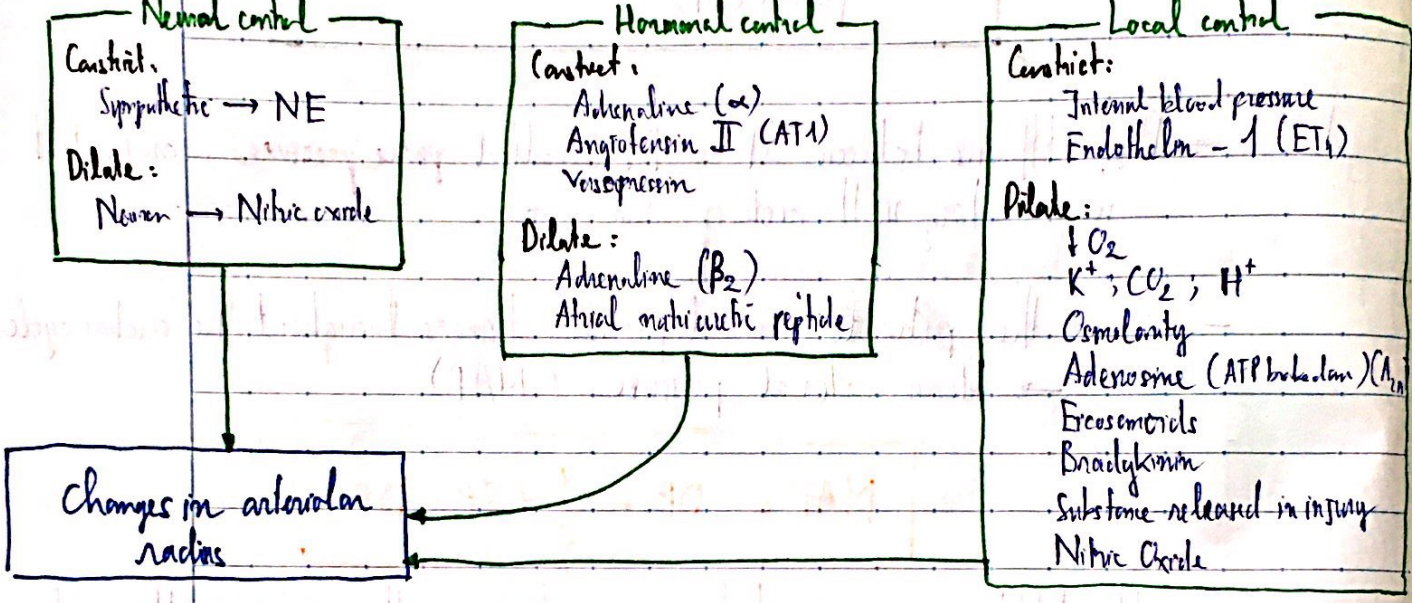
Vasoconstriction & vasodilation

- The sympathetic nervous system, hormons & local mediator cause vasoconstriction & vasodilation.



~ Local control

- The term local control → mechanism independent of nerve or hormones → self regulating
  → Autocrine, paracrine agents

Active Hyperemia

- When organ's metabolic activity ↓ → ↗ blood flow
  Eg. Exercise
- Due to local chemical change in ECF around the arterioles
- Active Hyperemia is most developed in skeletal muscle, cardiac muscle & glands.

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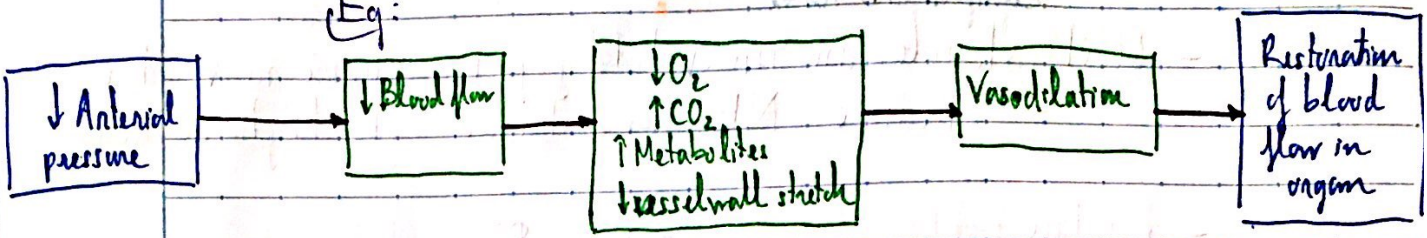
Flow Autoregulation

- The change of resistance to maintain blood flow is called autoregulation

Eg:



- Although the role of chemical factors in flow autoregulation are emphasised, smooth muscle in some organ can respond directly to stretch by contracting. These direct responses is due to the change in Ca^{2+} level, through the stretch-sensitive Ca^{2+} channels (Myogenic responses)

Reactive Hyperemia

- Occurs when an organ is totally locked of blood supply (by barrier, blockage) and an abrupt ↗ in blood flow when the obstruction is remove

- During blocking, the arterioles dilate since no O_2, chemical factors → Blood flow ↗

Eg: The finger turn bright red after removing the tight ring.

Response to Injury

- Tissue injury can release variety of substances to relax in the injured area. This is apart of inflammation.

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~ Extrinsic Controls

Sympathetic nerve

- Most arterioles are innervated by post-ganglionic nerve fibers.
  → Release NE → constriction by binding to α receptors
- Dilation can be achieved by reducing SNS activity
- SNS is rarely inhibited completely, but always cause some degree of constriction, contributing to intrinsic tone of the arterioles

Parasympathetic nerve

- No significant parasympathetic nerve innervation

Nonadrenergic, Noncholinergic autonomic neurons

- Some neurons don't release NE or ACh, but neither nitric oxide and other noncholinergic vasodilators
- Prominent in enteric nervous system (GI tract), penis.

Hormones

- Adrenaline is release from sympathetic nerve, combind to both α (constrict) and β_2 (dilate) receptors
  - Most: $\alpha > \beta_2$ → more constriction
  - Skeletal muscle: $\alpha < \beta_2$ → more dilation
- Angiotensin II constrict most of the arterioles
- Vasopressin "
- Atrial natriuretic peptide dilates.

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∞ Endothelial cells ↔ Vascular smooth muscle

- Endothelial cells can release paracrine agents that act on the adjacent smooth muscle cells.
  - Nitric oxide: dilation, in response to other mediators
  - Prostacyclin (PGI_2): dilation.
  - Endothelin 1 (ET-1): constriction

- Endothelial cells can also act on the arteries in response to shear stress (the force of blood flow to arterial wall)
  → Release NO, PGI_2., less ET-1
  → Arterial dilation
  → Flow-induced arterial vasodilation

How the blood can quickly return to the heart during exercise?

- ↗ skeletal muscle pump
- ↗ respiration → ↗ Pressure in veins
- ↗ "veno motor tone" by sympathetic nerve → smooth muscle in veins

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IV) Regulation of blood pressure

Blood pressure during exercise

- Total peripheral resistance ↓
  - Skeletal muscle dilate more than gut
  - Arterioles construct
  - Both dilation & contriction occur at the same time, depend on which organ need more blood.

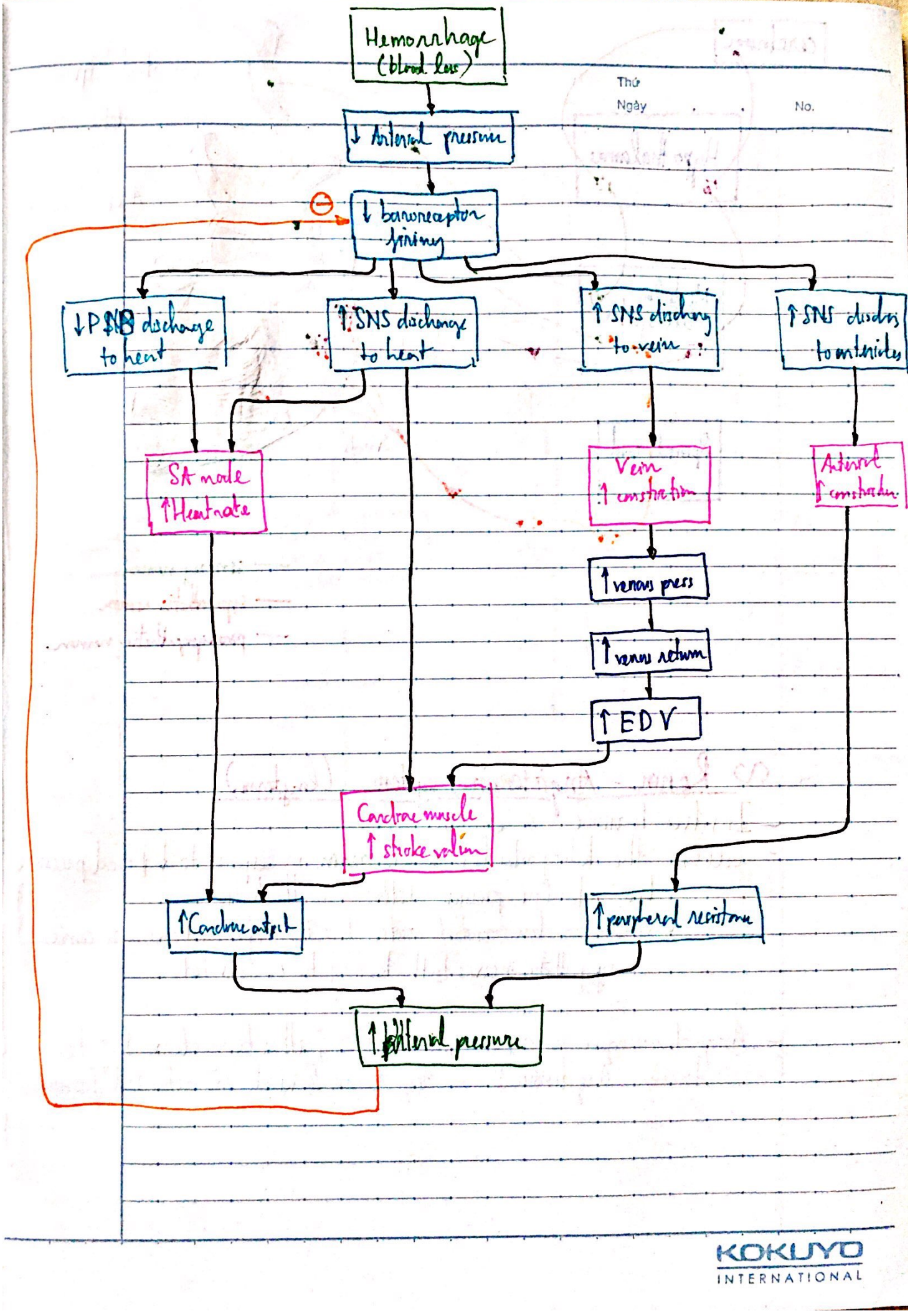
- Cardiac output ↑
  - ↗ Heart rate (200 bpm)
  - ↗ Stroke vol (30%) then ↓ if increase workload

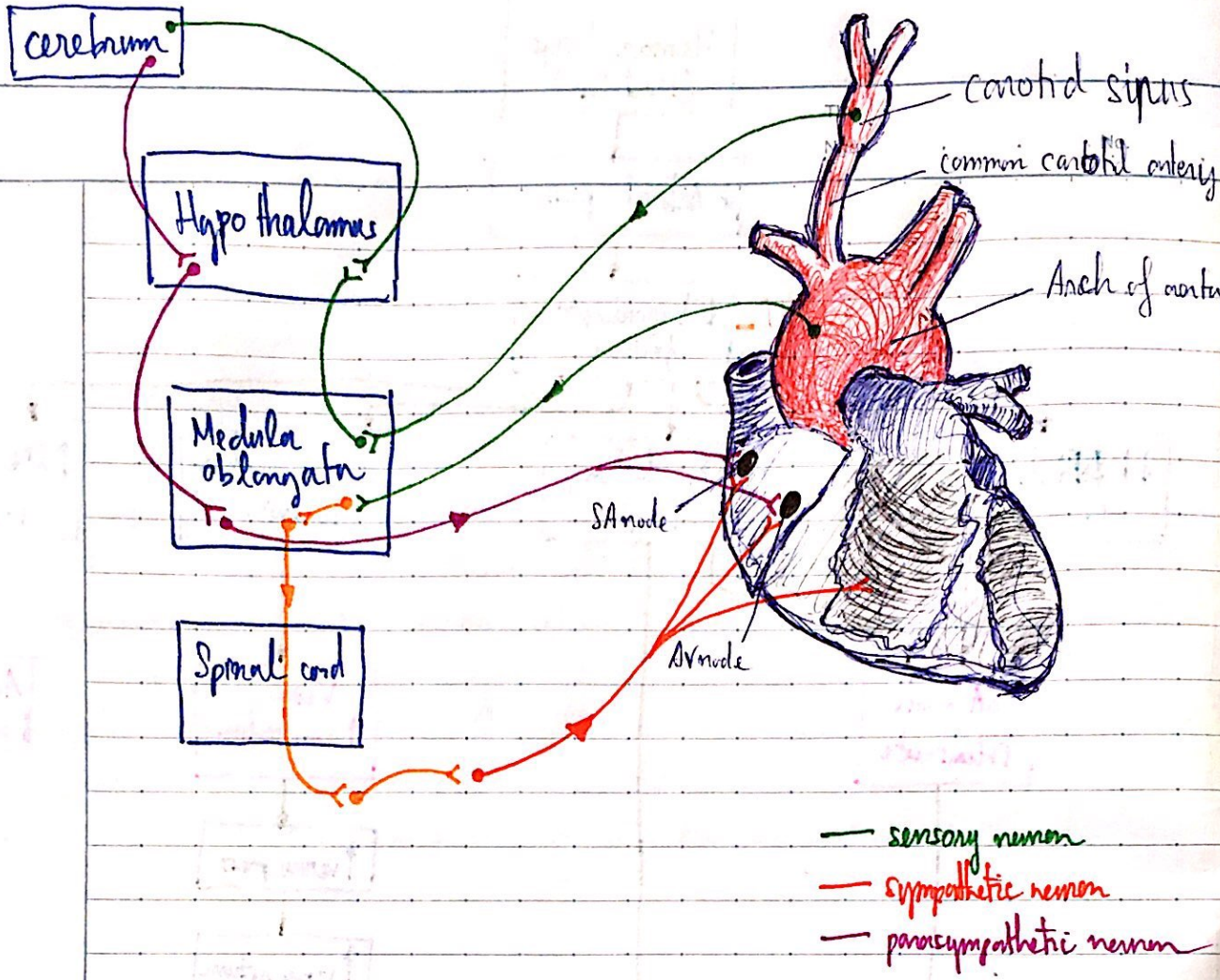
How?

Baroreceptor reflex (short term)

- Baroreceptors detect change in arterial pressure, bring the info to the Medulla oblongata, then the pressure is altered:
  - Change the frequency of AP in PNS nerve → heart rate
  - SNS nerve → heart rate + force
  - SNS nerve → vasoconstriction

- Sometimes, blood pressure need to rise (prepare for an important race)

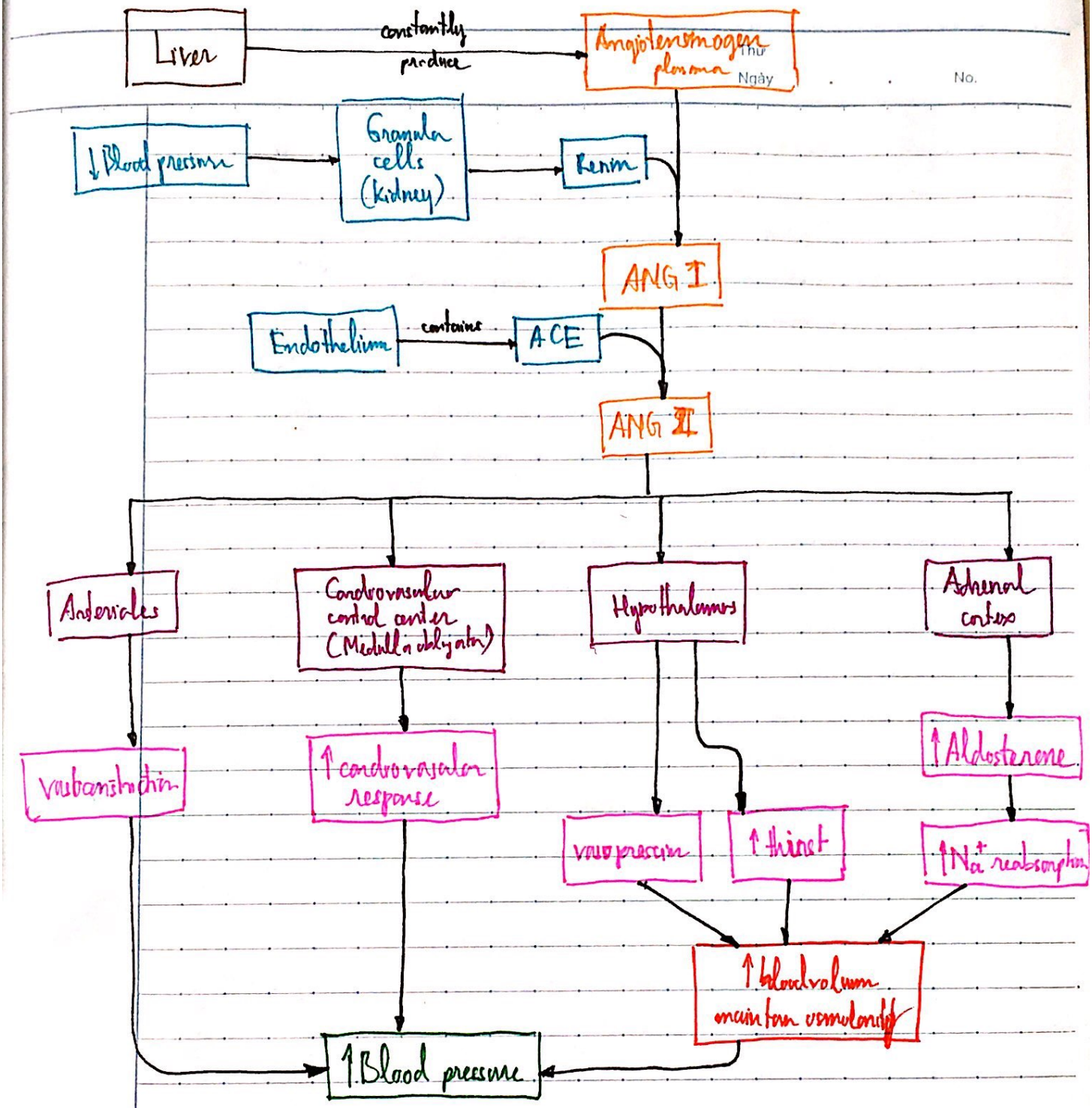




∿ Renin - Angiotensin system (long term)

- Involves hormone & enzyme
- Cells in the kidney arterioles secrete **renin** in response to ↓ blood pressure:
  - Low arterial pressure detection in the kidney
  - Cardiovascular control center detection of ↓ blood pressure cause sympathetic nerves to the kidney to be activated.

- Angiotensinogen is a zymogen that is further being cleaved of to become Angiotensin I & Angiotensin II which are activated forms



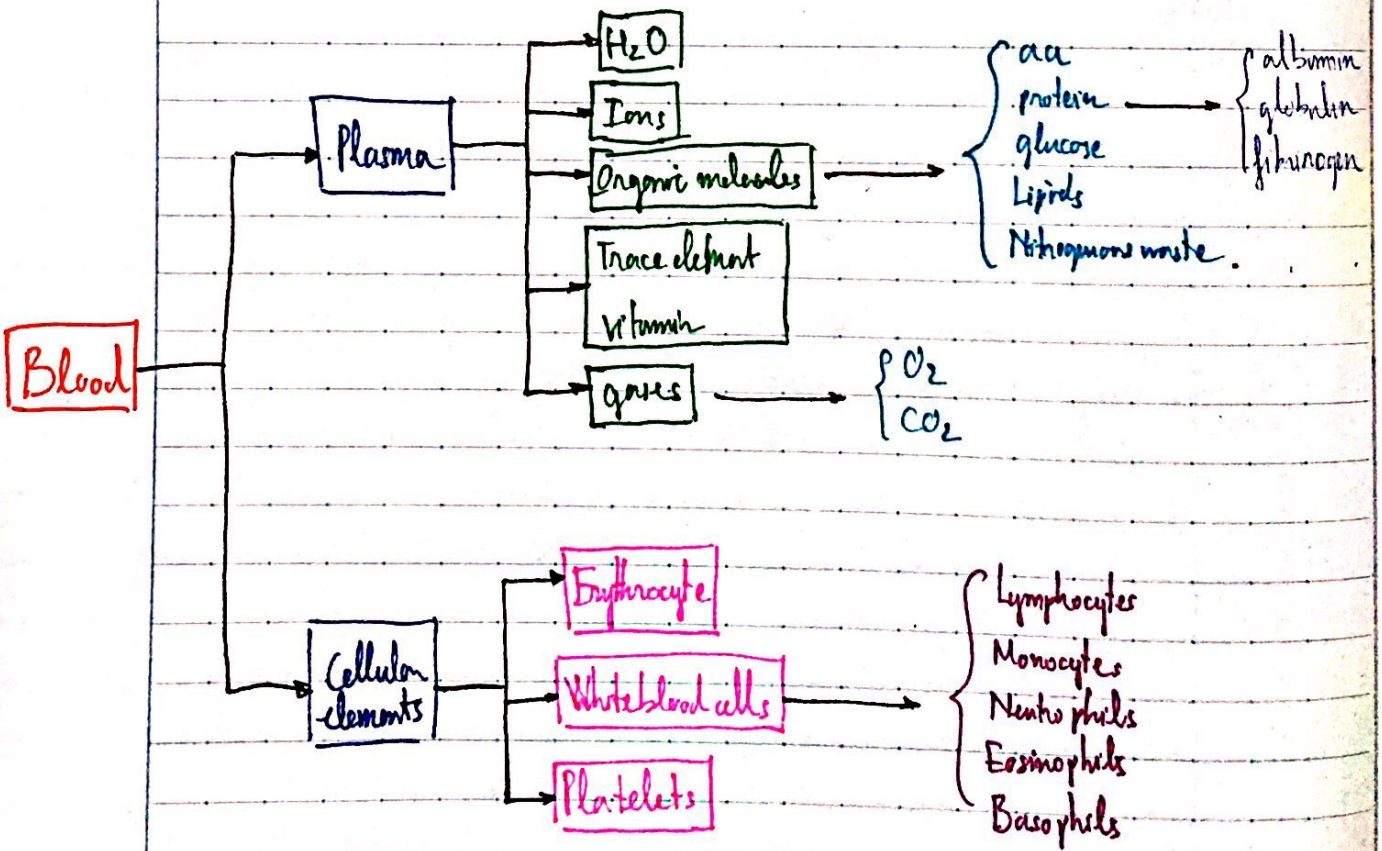
Week 10 8/15/2017

I) Blood

Blood

- Main function:
  - Transport of { O_2 , CO_2 ; Nutrients ; waste ; Hormones , messenger
  - Homeostasis { H_2O , electrolytes ; acid - base regulation ; t° regulation
  - Defence mechanism { antibodies, lymphocytes, phagocytes ; local reaction to injury & repair damage

- Main components:
  - Non-cellular & cellular



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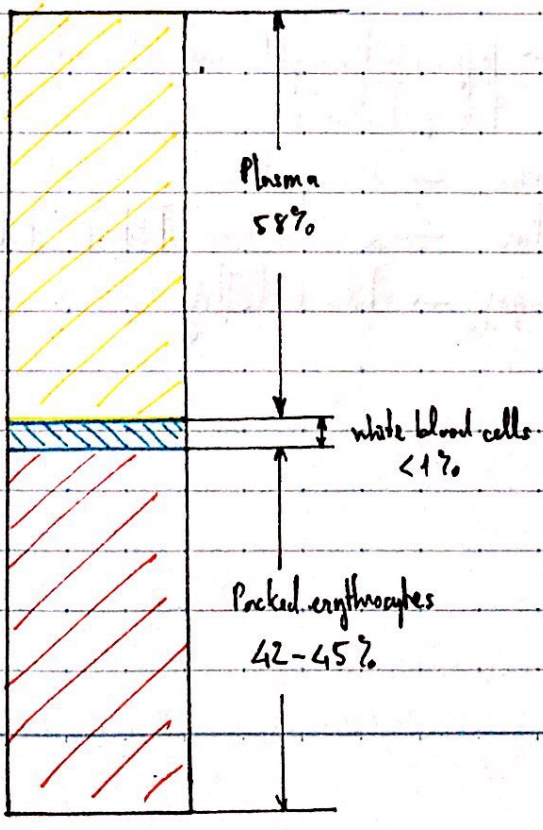
- Functions of each components:
  - Plasma: { > 90% H_2O
    > number of organic & inorganic substance
  - Cells: { Erythrocytes → O_2; CO_2
    Leukocytes → fighting diseases
    Platelets → blood clotting
  - Inorganic (< 1%) { Mostly Na^+, Cl^-, HCO_3^-, HPO_4^{2-}, Mg^{2+}, K^+, Ca^{2+}
    Buffering changes in pH, excitability & blood clotting

The haematocrit (packed cell volume)

- The contents of plasma are distributed evenly throughout plasma. However, centrifugation can separate these elements
  - Lighter plasma on top
  - Heavier cellular element to the bottom



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Plasma

- Main functions:
  - Medium for material carrying in the blood
  - High capacity to hold heat → distributing heat
  - H_2O has greate thermal stability → heat buffer

- Is made out of
  - Nutrients: { Glc, aa, lipid, vitamin
  - Wastes { creatinine (break down product in muscle), bilirubin (" " of haeme), urea (N waste from aa metabolism), uric acid (break down of purine metabolism)
  - Gases { O_2 ; N_2, CO_2
  - Hormones
  - Plasma protein → buffer, change pH, contribute to blood viscosity, transportation....
    { Albumin → transport
    Globulin → α, β (transport TH, Fe, chol), γ (
    Fibrinogen → blood clotting

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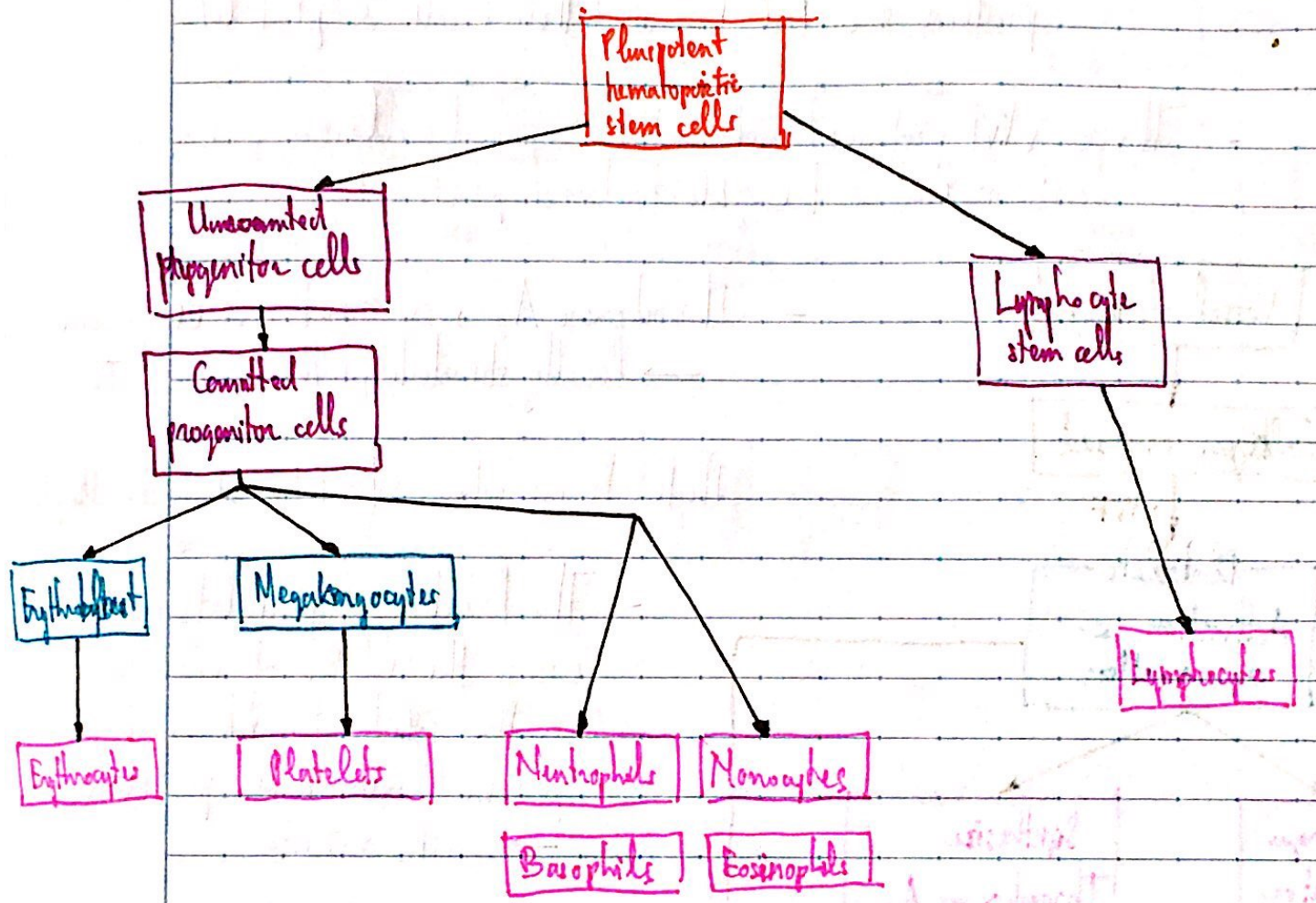
Haematopoiesis (blood cell synthesis)

- Stem cells are made in bone marrow, following stimulation of cytokines
- All blood cells are descended from a single cell type called pluripotent hematopoetic stem cell



- Proliferation & differentiation of various progenitor cells are stimulated by hormones & paracrine agents called hematopoietic growth factors, whose mechanism is very complex.

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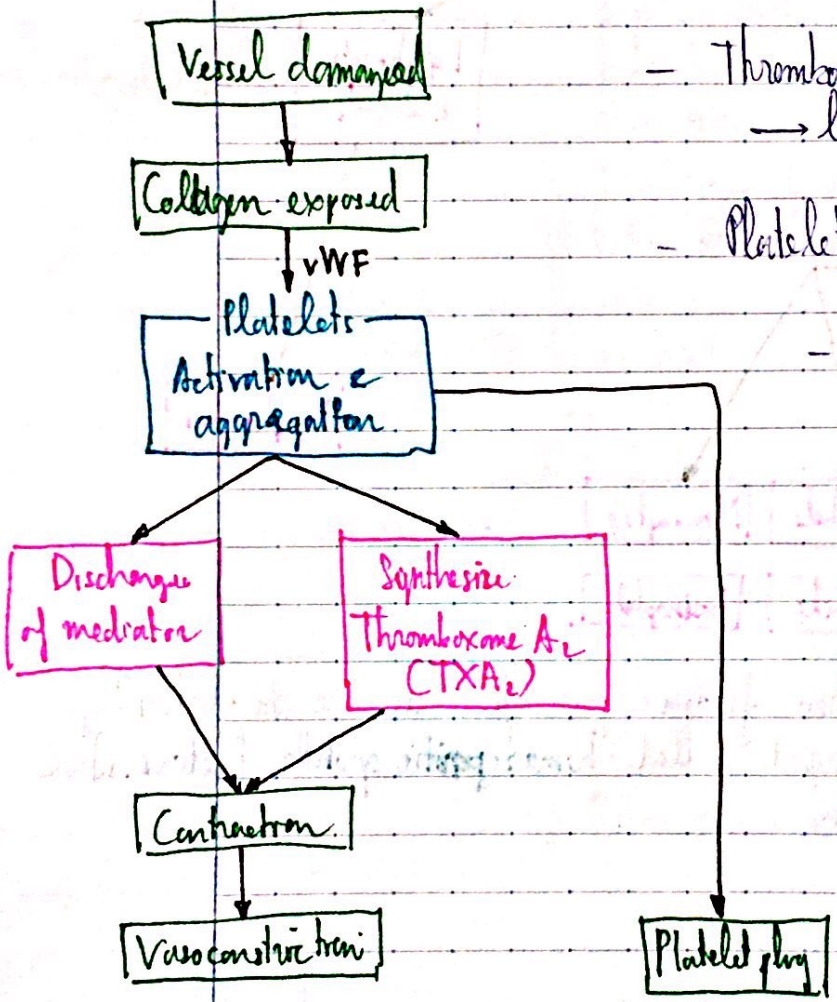
Platelet plug

- Stoppage of bleeding is called **hemostasis**
- Required adhesion to surface
  → von Willebrand factor (vWF), which is a plasma protein secreted by endothelial cells & platelets

- These vWF proteins bind to the exposed collagen, change its conformation & be able to bind platelets.



- Thromboxane A_2, a member of eicosanoid
  → locally stimulate platelet accumulation

- Platelets can also contract to strengthen the plug

- The binding of platelets to collagen cause the release of vesicular content in the platelets, which have positive feedback in platelet aggregation
  → quick action

- The platelet plug is locally activated, not spreading out because of the mechanism of adjacent undamaged endothelial cells:
  In platelets, there is enzyme that create TXA_2 from arachidonic acid

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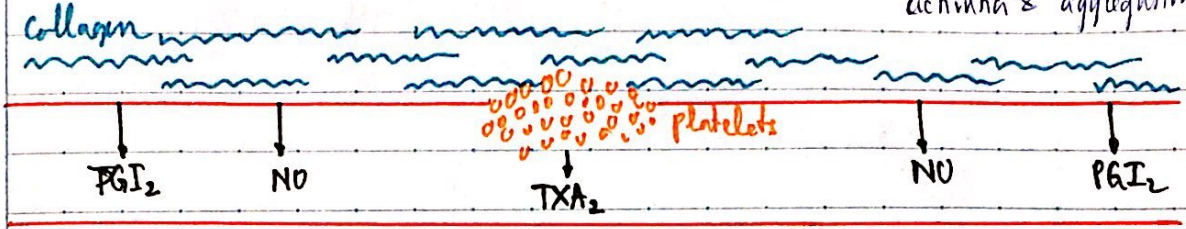
In endothelial cells, there is an enzyme that creates Prostacyclin (PGI_2)
→ platelet accumulation inhibitor

- The endothelial cells can release N oxide { vasodilator
inhibitor of platelet adhesion activation & aggregation.



Erythrocytes (Red Blood cells)

- Small, flat, disk-shape, biconcave & flexible
→ appropriate for the function of transporting O_2 & CO_2
  - Large surface area
  - Thinness of the cells → fast diffusion
  - Flexibility → mvt. w/o rupture of capillaries

- Each erythrocyte is full of hemoglobin molecules { O_2 transport
CO_2 transport & buffer

- Mature erythrocytes have no organelles → spaces for hemoglobin
There are a few remaining enzymes:
  - Glycolytic enzymes: generating energy → maintain osmolarity
  - Carbonic anhydrase: CO_2 buffer, transportation

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- O_2 is poorly soluble → 98% O_2 is carried by erythrocytes
The amount of O_2 depends on:
  - % saturation of hemoglobin
  - How much hemoglobin / L of blood

Erythropoiesis (RBC production)

- RBC cannot live long due to the lack of vital mechanism + can't divide
  → constantly replace

- Requires: { amino acid, carbohydrates, lipids
  Iron, folic acid, B_{12}

~ Iron

- Iron is important in erythropoiesis:
  → Hemoglobin molecules
- Small amount of Fe is lost via urine, faeces, sweat ...
  → Need to be replaced
- Fe storage is important → protection from anemia (liver, ferritin)
- Fe is carried in blood by protein transferrin, takes Fe to bone ma

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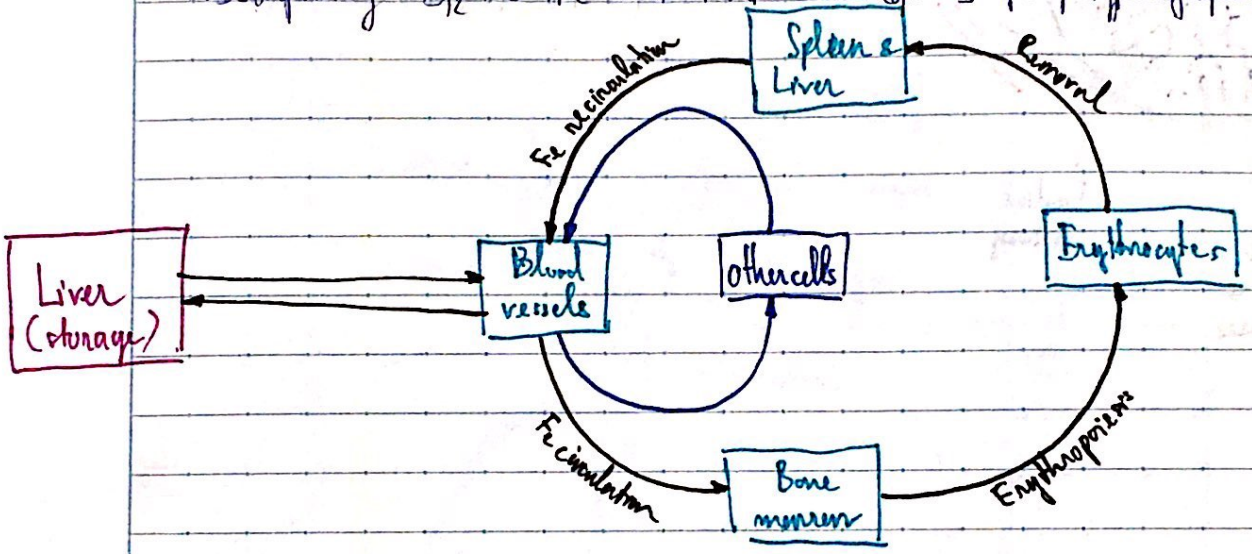
~ Folic acid & vitamin B_{12}

- Folic acid is a vitamin required for synthesis of nucleotide base Thymine
  → Deficiency of folic acid leads to the impairement of all cells in the body but mostly erythrocyte

- B_{12} is required for the action of folic acid
  Absorption B_{12} in the GI tract also requires specific type of protein



~ Regulation

- Neither Fe, folic acid nor B_{12} contains signal for production rate regulation
  → Protein **erythropoietin** secreted by the kidney
  → Act on bone marrow to stimulate erythrocyte progenitor cells & differentiation

- O_2 blood to the kidney determines erythropoietin secretion rate:
  less O_2 to the kidney, ↗ erythropoietin to stimulate production of RBCs
  Eg: high altitude, anemia, lung diseases ...

- Testosterone also stimulates erythropoiesis → Men have higher hematocrit than women.

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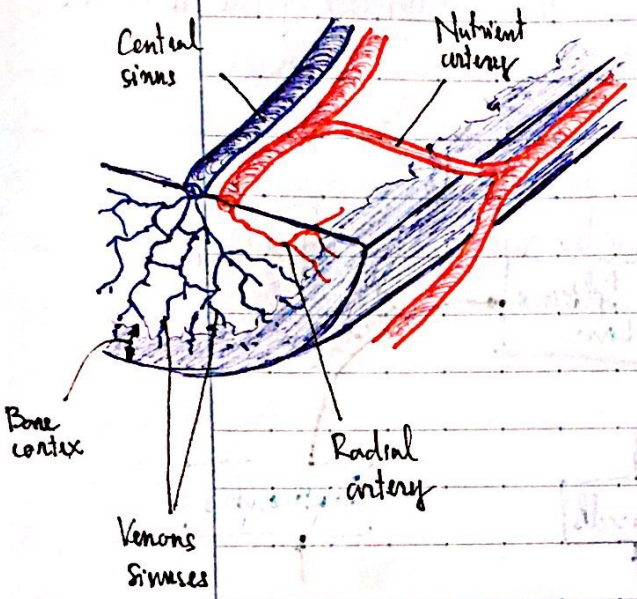
Bone marrow

- Where hematopoiesis occurs



- Proliferation & differentiation of blood stem cells happen in the bone marrow, then cells are released into the venous sinuses.

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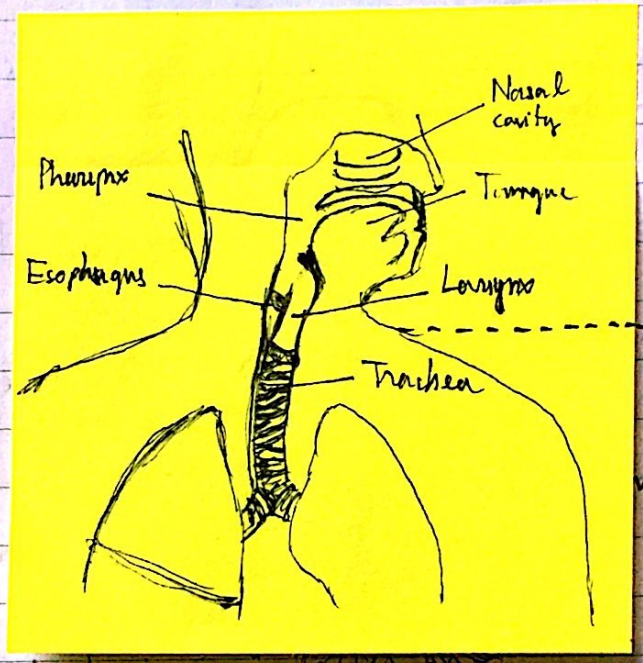
II) Respiration

Anatomical divisions

- 2 parts:
  - Upper respiratory tract: Nasal cavity; pharynx; larynx
  - Lower respiratory tract: Trachea; bronchi; bronchioles, alveoli



Upper respiratory tract

- Consists of the nasal cavity, pharynx (throat), larynx
  - Nasal cavity: [folded tissue → slowdown air, must warm wet environment, filteration
  - Pharynx: common pathway for air & food
  - Larynx: [protects the entrance to trachea; vocal cords are found.

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II) Respiration

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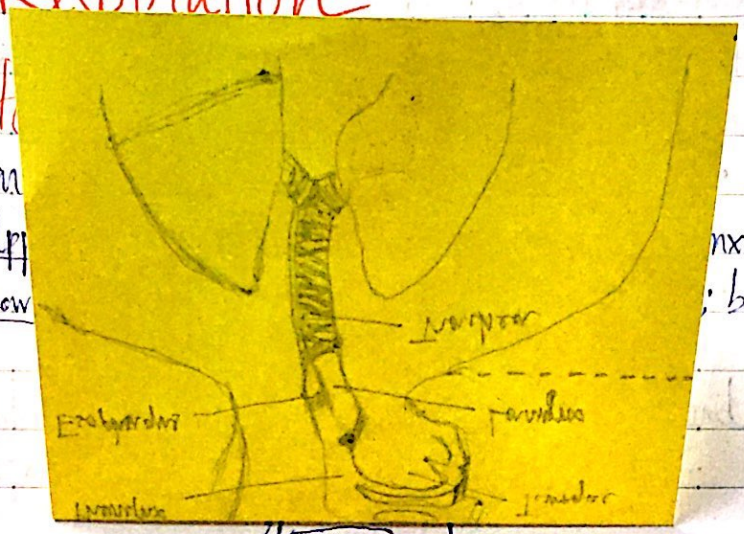
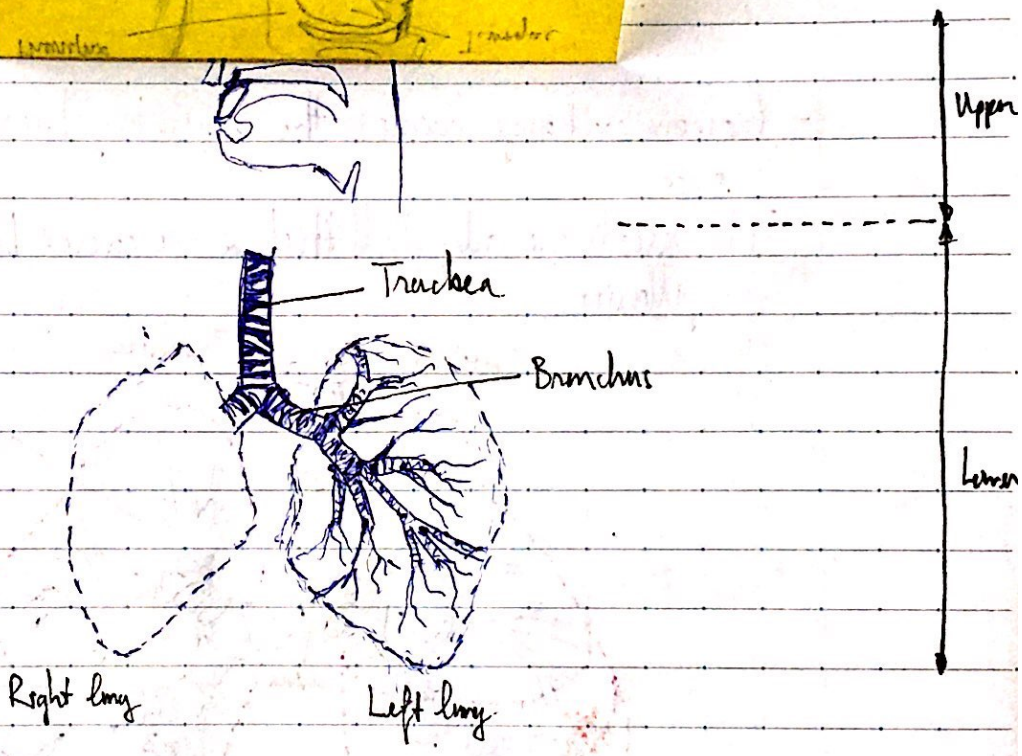
nx; larynx
: bronchioles, alveoli





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  - Larynx: [protects the entrance to trachea
    [vocal cords are found.

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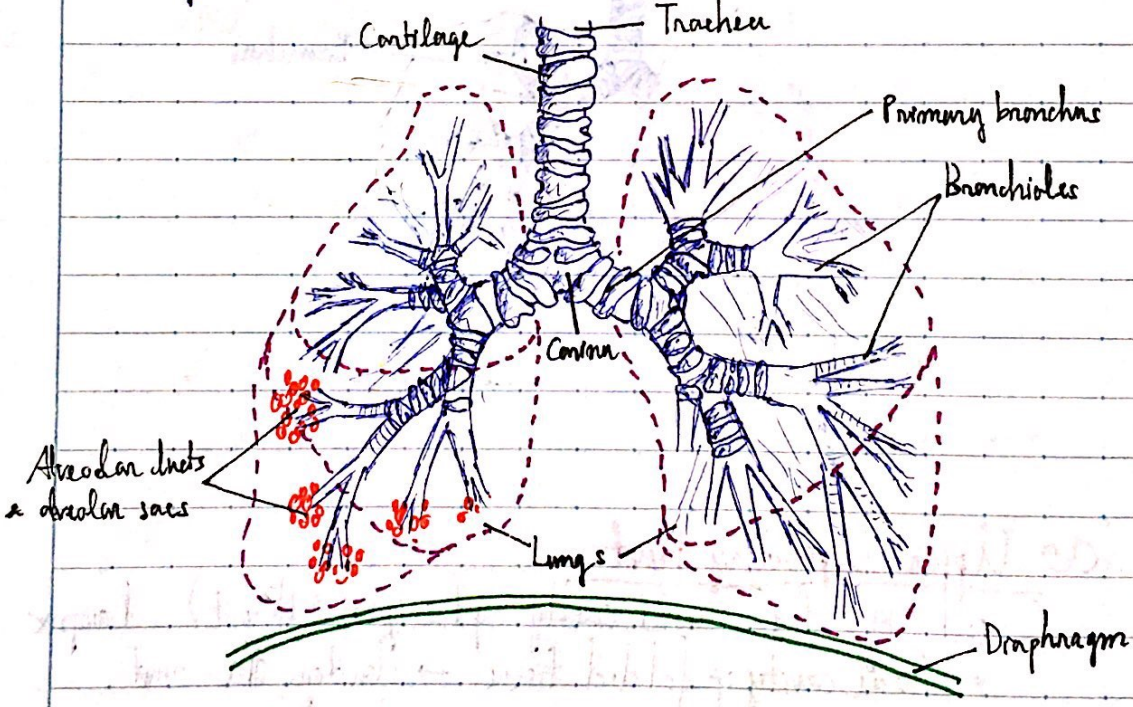
~ Lower respiratory tract

- Consists of: trachea, bronchi, bronchioles, terminal & respiratory alveolar sacs
  - **Trachea**: rigid tube, 1 way → cartilage-supported
  - **Primary bronchi**: initial branching, also rigid
  - **Terminal bronchioles**: smallest branches, leading to alveoli

- The bronchioles are embedded in the connective tissue framework → diameter changes according to the lung volume

- Gaseous exchange occurs in the respiratory bronchioles (little) & alveolar sacs
  The alveoli are only 1 cell thick & are covered by continuous sheet of capillaries



- The drawing above also expresses the conducting zone of the respiratory tr

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Functional divisions

- Beyond the larynx, the respiratory tract can be divided into 2 zones:
  - Conducting zone: top of trachea → beginning of respiratory bronchioles
  - Respiratory zone: respiratory bronchioles → alveoli

Zone	Name	N°
Conducting zone	Trachea	1
	Bronchi	2
	↓	
	Bronchioles	16
	↓	
	Terminal bronchioles	6×10^4
Respiratory zone	Respiratory bronchioles	5×10^5
	Alveolar ducts	
	Alveolar sacs	8×10^6

~ Conducting zone

- Provides low-resistant pathway for air flow
- Defend against microbes, toxics
  → Cilia, mucus, macrophages
- Warm & moistens the air by extensive vasculature
- Vocal cords

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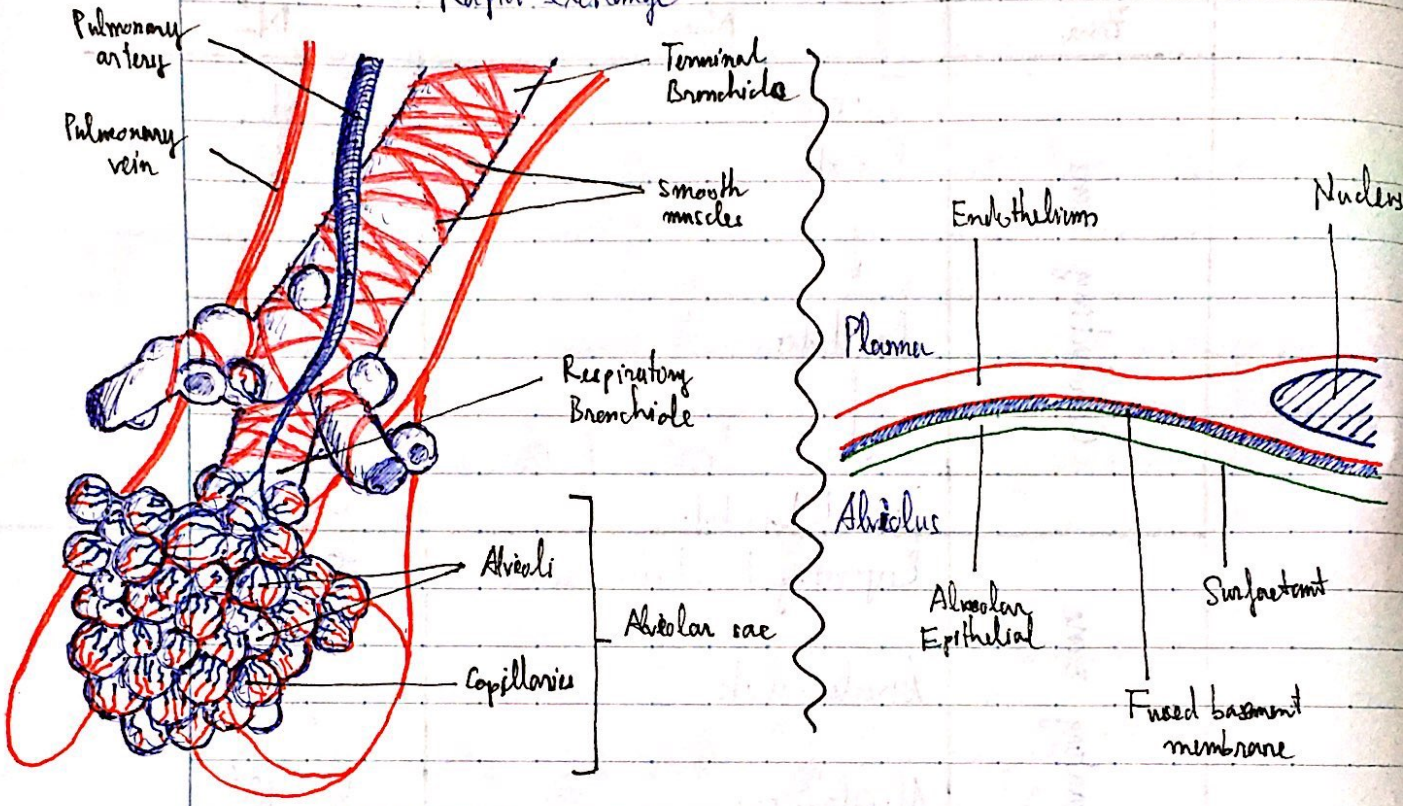
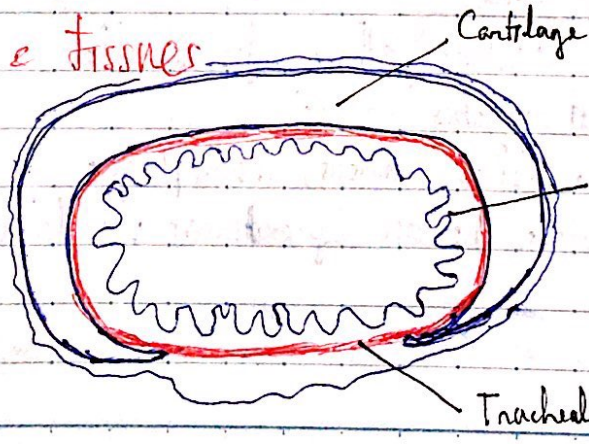
~ Respiratory zone

- Gaseous exchange
- Air-blood barrier is only 2 cells thick { alveolar cell / endothelia cell

→ Rapid exchange



Cells & tissues



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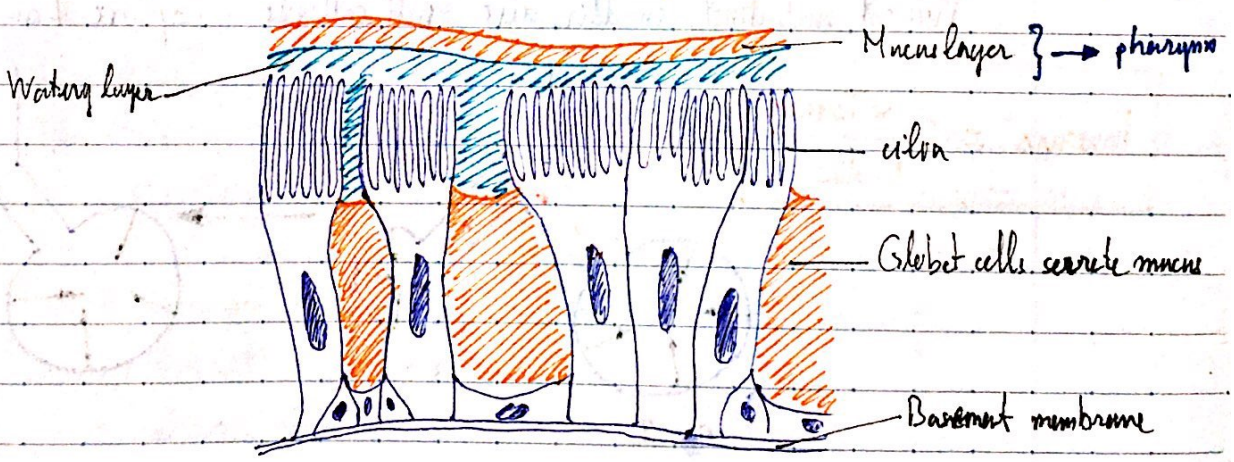
- The cartilage provides rigidity & support.
  The C shape allows the esophagus to move in abit
  Can also be found in the bronchi, but become patchy & gradually disappear

- The smooth muscle → diameter regulation
  When the muscle constrict → narrow the airway

- The mucosa lines the lumen of the airway
  Consists of { ciliated columnar epithelial cells
  mucus - secreting cells
  glands
  There is also an extensive vasculature, supporting membrane & matrix
  Further to the respiratory tree, the mucosa disappear & epithelial cells lose cilia & become more cuboidal

- The ciliated epithelial cells & the mucus are important
  → mucus escalator for filtering air
  → cilia must moves the layer of water & mucus toward the pharynx



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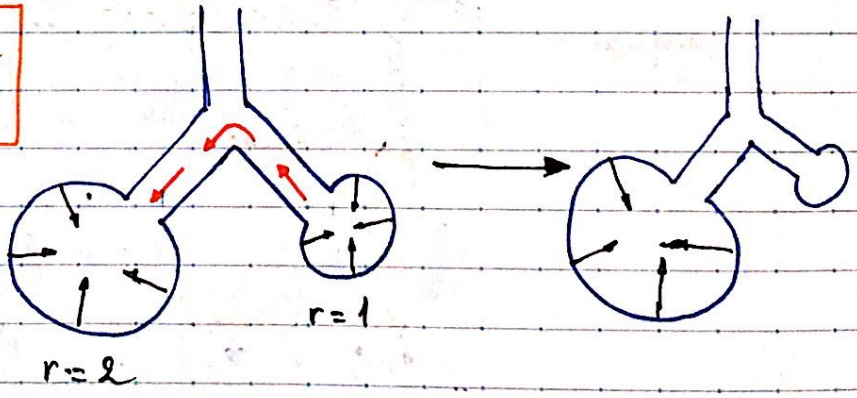
- 2 types of alveolar epithelial cells:
  - Type 1: thin & flat
    - main site of gaseous exchange
  - Type 2: smaller
    - secrete surfactant → help alveolar cell to expand when inhale

Type 2 can replicate & differentiate into type 1 when there is damage but not ideal for gas exchange

- There are many elastin fibers & macrophages in the alveoli.

- The alveoli are highly compliant (stretchy) & elastic
  The compliance is opposed by elasticity & surface tension provided by H_2O in the alveolar fluid (all the tube & tissue in lungs are lined w/ H_2O)
  H_2O attraction → hard to inflate alveoli
  → Surfactant { ↓ H_2O attractant force
  ↓ alveolar surface tension
  Without surfactant, smaller alveoli will collapse (Laplace Law)

$$\text{Pressure} = \frac{2 \times \text{Tension}}{\text{Radius}}$$



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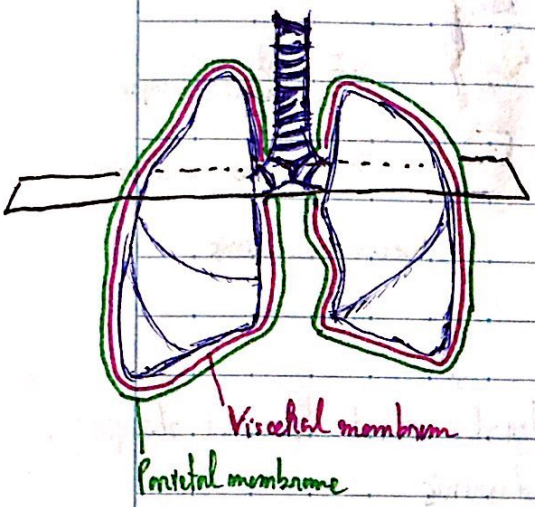
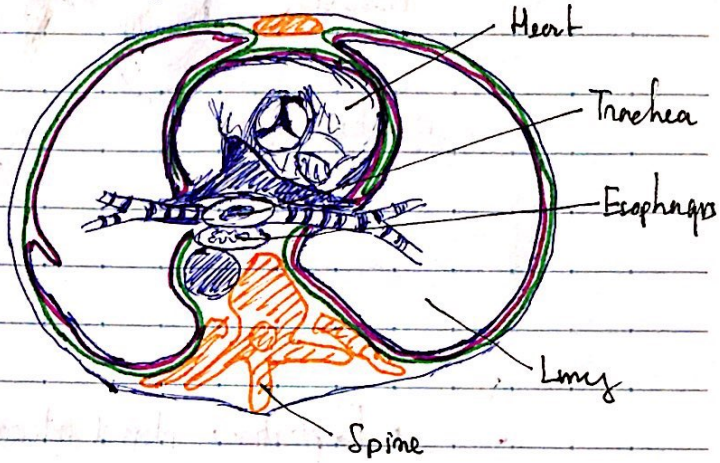
Lungs & pleural membrane

- The space between the lungs & the thorax (chest) is filled by a sac called pleural sac
  - Parietal membrane lines thoracic wall } by connective tissue
  - Visceral membrane lines the lungs





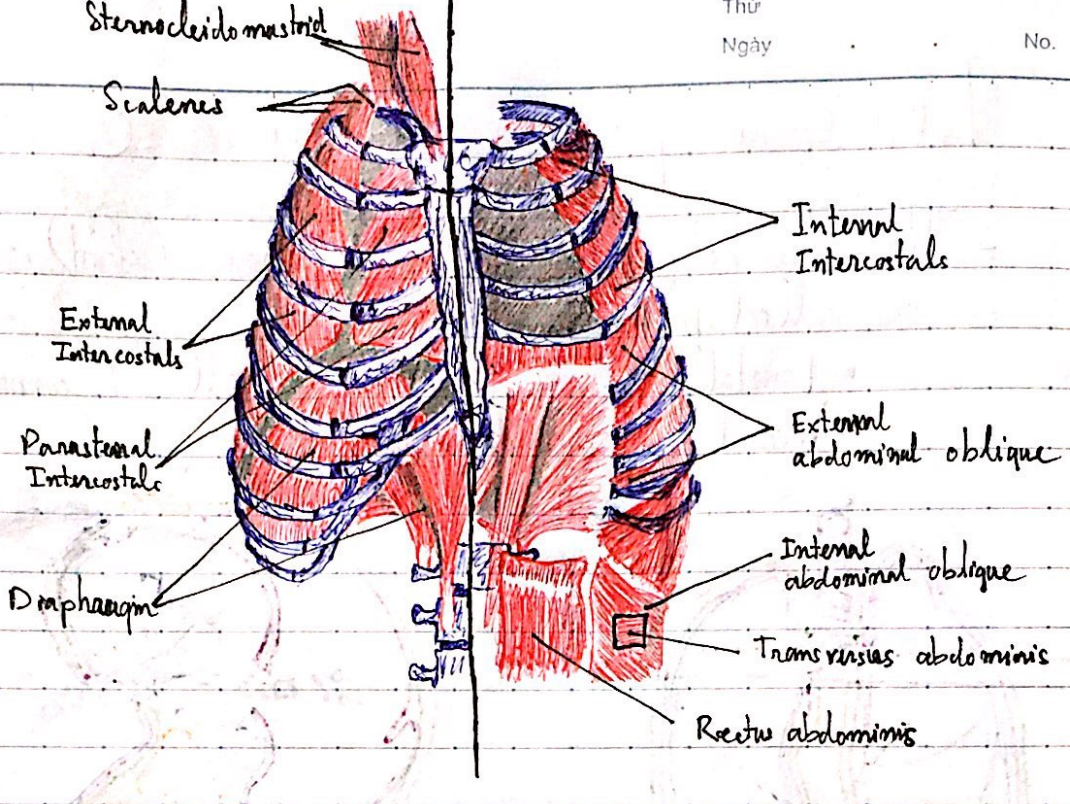
Muscles of inspiration & expiration

- Breathing must be innitated neurally because all muscle involvig are skeletal
  → Ventilation relies on muscle contraction by somatic neurons

- The diaphragm makes the greatest contribution to breathing
  - Contract → inhale
  - Relax → exhale

- There are other muscles of inspiration & expiration
  - Inspiration: parasternal & external intercostals ; scalenes, pectoralis minor ; sternocleidomastoid muscle

Inspiration | Expiration



- Expiration: internal intercostals ; internal & external abdominal obliques ; transversus & rectus abdominis

- These muscles contract & relax to change the thorax volume → inspiration & expiration.

- The diaphragm can alone control ventilation at rest
When more forceful ventilation is required → skeletal muscle:
  - Inspiratory muscles contract → ↗ thoracic vol.
  - Expiratory muscles contract → push organ. up against the diaphragm → ↓vol

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III) Ventilation

Competing pressure

- Total atmospheric pressure: 760 mmHg

$0,8 N_2$
$0,2 O_2$
Ar H_2O
CO_2

→ $P_{O_2} = 160$ mmHg

- Ventilation is the mvt of air into and out of the lung
  - → Bulk flow (like blood) from high to low pressure

$$F \propto \Delta P / R$$

  - → Follow Boyle's Law of gas volume

Important pressure

- P_{ATM}: Atmospheric pressure = 760mmHg at almost any time
- P_A: Intraalveolar pressure, which remain inflated partially
  The pressure can change due to volume change.
- P_{PL}: Intrapleural pressure, negative value w/ respect to P_A < P_{atm}
- P_{TP}: Transpulmonary pressure, gradient between the pleural space & the alveoli = $P_A - P_{PL}$
  This pressure usually has Positive value

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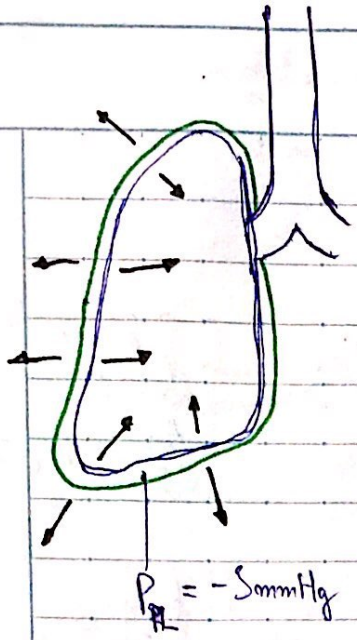

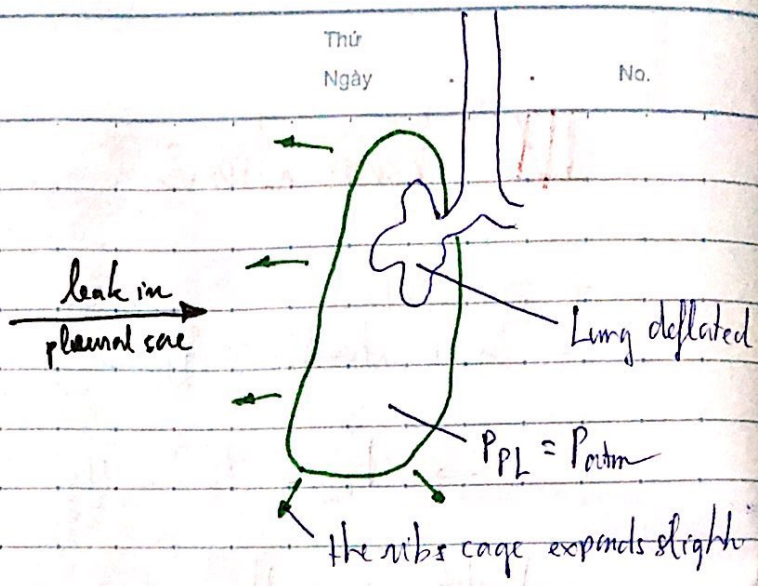

Mechanism of breathing

Brainstem respiratory centers

~ Inspiration

- Inspiratory muscles contract → V_{thorax} ↑
- P_{PL} ↓
- P_{TP} ↑
- → V_{lung} ↑
- P_A ↓
- Air enters lungs ($P_A < P_{atm}$)

~ Expiration

- Expiratory muscles contract → V_{thorax} ↓
- P_{PL} ↑
- → P_{TP} ↓
- V_{lung} ↓
- P_A ↑
- Air exit the lungs ($P_A > P_{atm}$)

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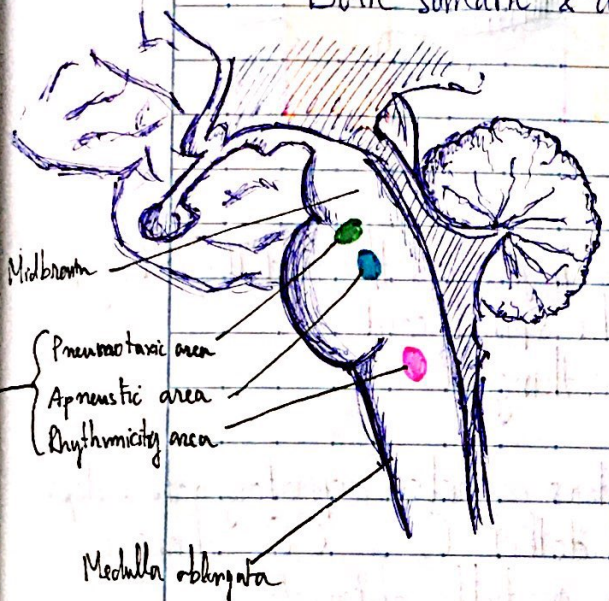
Control of ventilation

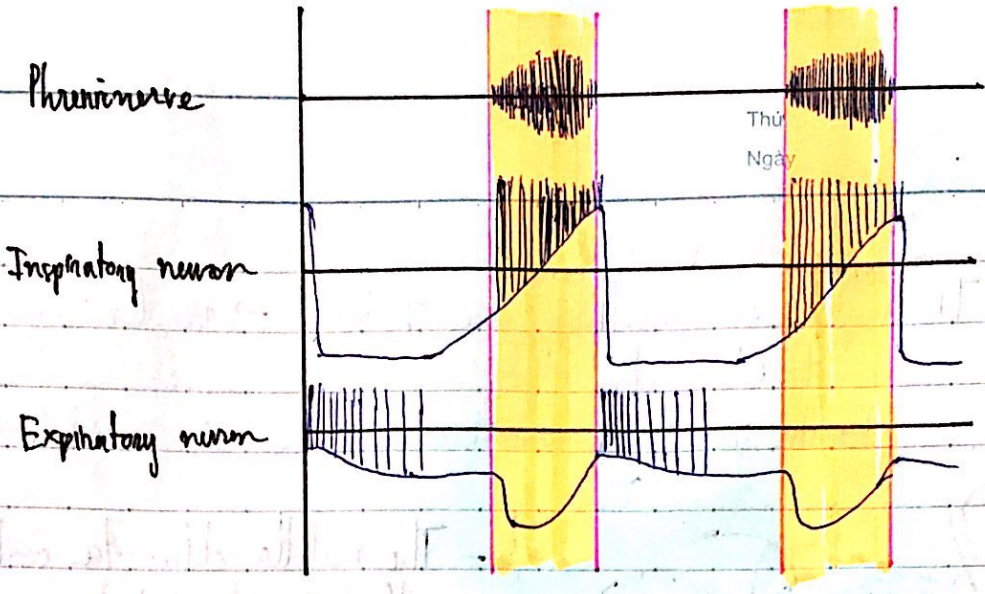
- The muscles of breathing are skeletal → need neuronal activation to contract
  Both somatic & autonomic processes are involved



- The medulla oblongata contain a center called dorsal respiratory group (rhythmicity area) which has intrinsic pacemaker activity (DRG)
  → stimulate phrenic nerve
  → diaphragm contracts

- The ventral respiratory group (VRG) of the medulla oblongata has expiratory & inspiratory actions
  Usually active when more forceful contraction required.
  - Specific VRG subregions → activate accessory expiratory muscles
  - Intermediate VRG subregion → inspiratory muscles
  - Rostral VRG inhibits the DRG → assist expiration.

- Inputs from the pons region modulate activities from the medulla oblongata & influence DRG and/or VRG where required.
  Pons contains subregions that help to control pattern of breathing & reflexes
  - Pneumotaxic area → DRG switches off → inhibit inspiration
  - Apneustic area → on → excite inspiration

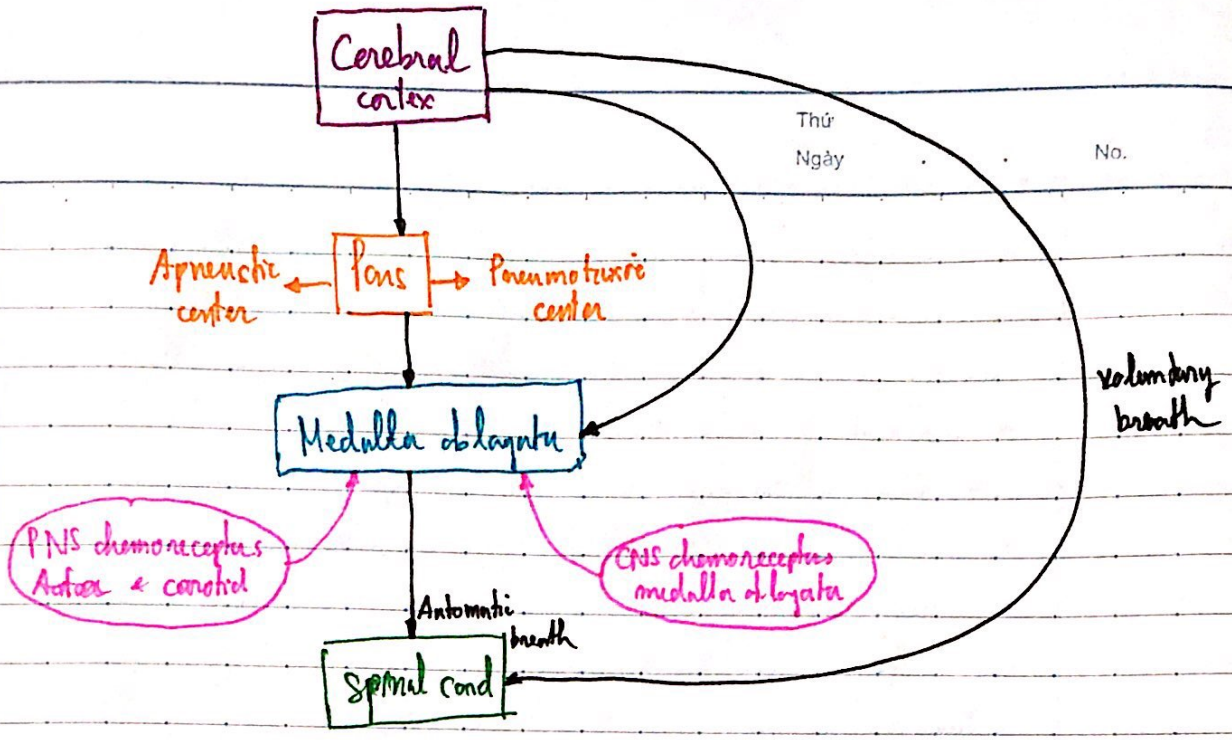


- Inputs from the cerebral cortex influences the medulla oblongata, pons & motor neurons in the spinal cord
  → have control over breathing

- A reflex based on chemoreceptors controls respiratory rate & depth
  → Chemoreceptors that detect O_2 & CO_2 changes
  - CNS chemoreceptors in medulla oblongata
  - Peripheral chemoreceptors at aorta & carotid sinus

- Changes in CO_2 (via changes in pH):
  - ↗ $[H^+]$ → stimulate inspiratory neuron
  - ↘ O_2 → " , but P_{O_2} need to fall to ~ 50 mmHg before the reflex is triggered

⇒ CO_2 = driving force.



* Note: • The central chemoreceptor doesn't detect pCO_2
• The peripheral does

Week 11 : 15/5/2017

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I) Gas exchange

Partial pressures

- Dalton's law → pressure ∝ concentration
  ↳ total pressure = sum partial pressures

Eg : Air { 78.8% N_2 / 21% O_2 / 0.2% CO_2 } → Partial pressures { P_{N_2} = 599 mmHg / P_{O_2} = 159.6 mmHg / P_{CO_2} = 1.5 mmHg }

- When calculating the partial press. → need to take humidity into account since when the air reaches the alveoli, it should be saturated w/ water vapor.

P_{H_2O} = 47 mmHg

→ Partial pressures { P_{N_2} = 561 mmHg / P_{O_2} = 149.7 mmHg / P_{CO_2} = 1.456 mmHg }

- The contribution of O_2 to overall mixture in the alveoli is further reduced because the inspired air mixed w/ air remaining in the conducting zone → more CO_2 than atmosphere air.

→ Alveolar pressure (seal) { P_{N_2} = 569 mmHg / P_{O_2} = 104 mmHg / P_{CO_2} = 40 mmHg }

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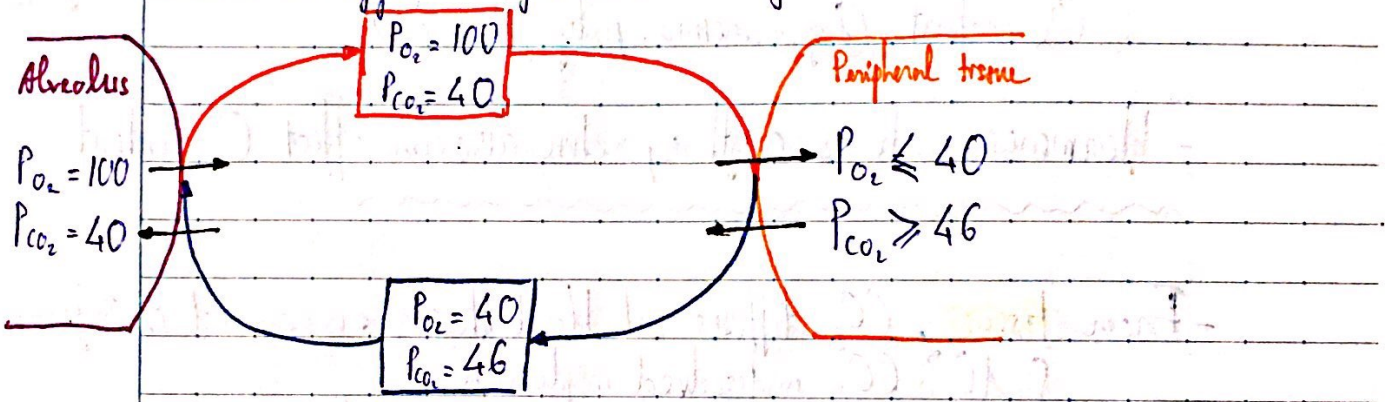
- Gasses need to be dissolved to move in the blood.
- Henry's Law: amount depends on:
  - Solubility of a gas
  - T° of the fluid
  - Partial pressure of the gas (variable)

Blood P_{CO_2} & P_{O_2}

- Capillaries form a sheet of blood almost totally surrounding the alveoli
  → Efficient gaseous exchange



Hemoglobin (Hb) O_2 & CO_2 transport

- Hb can be found in erythrocytes (RBC)
  - Hb ↗ O_2-carrying capacity of blood
  - Hb promotes O_2 diffusion into plasma because O_2 attached to Hb doesn't contribute to P_{O_2}
  - Different Hb structure have different affinities to O_2
    Eg: fetal Hb contains 2 γ subunits instead of 2 β subunit
    → higher affinity to O_2
  - Hb buffers H^+ & CO_2

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- Hb is a positive-cooperating "enzyme"

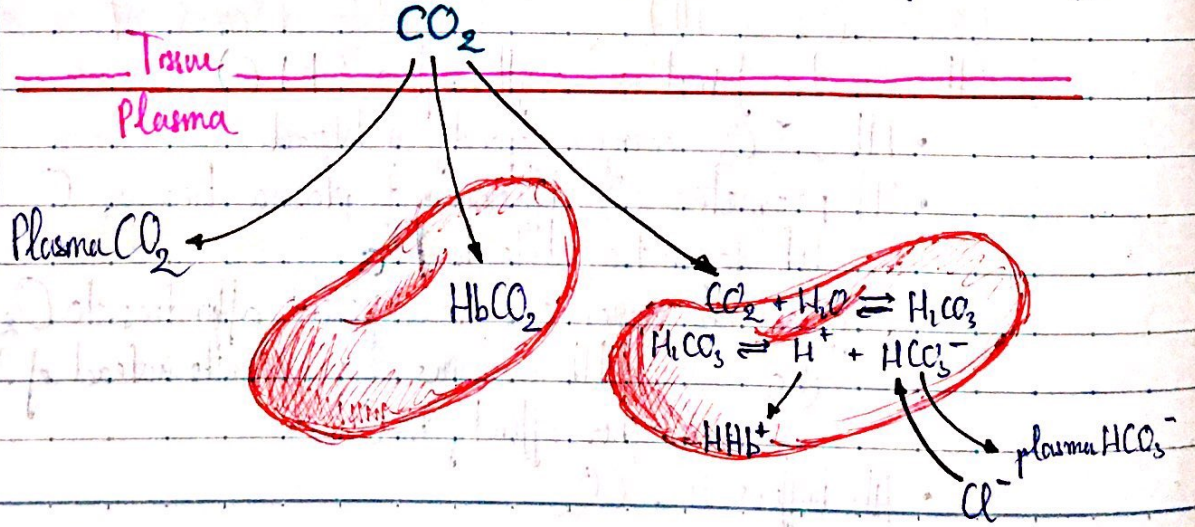
* More info about Hb in Week 2 (2.1)

- O_2 content: amount of O_2 carried in the blood
  and is influenced by { Hb concentration
  O_2 saturation (% binding site occupied)
  → Affected by alveolar P_{O_2}

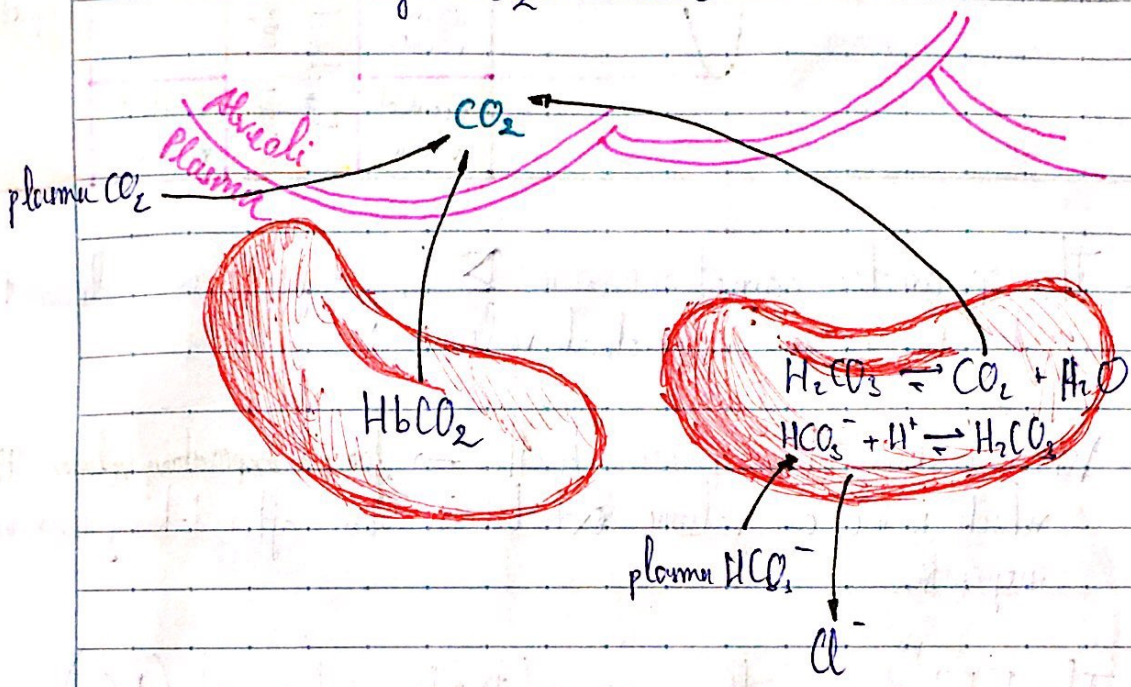
- Disorders that affect Hb structure or number of RBCs will eventually affect O_2 content (Eg: anemia, polycythemia)

- Hormones such as erythropoietin also can affect O_2 content

- From tissue, CO_2 diffuses into blood stream & is carried in 3 forms
  { 10% CO_2 is dissolved in plasma
  20% CO_2 is carried as carbamino Hb ($HbCO_2$)
  70% CO_2 is converted into H^+ & HCO_3^- → $HHb^+ + HCO_3^-$
  HCO_3^- is moved to the plasma by transporter (Cl^- exchange; Cl shift)



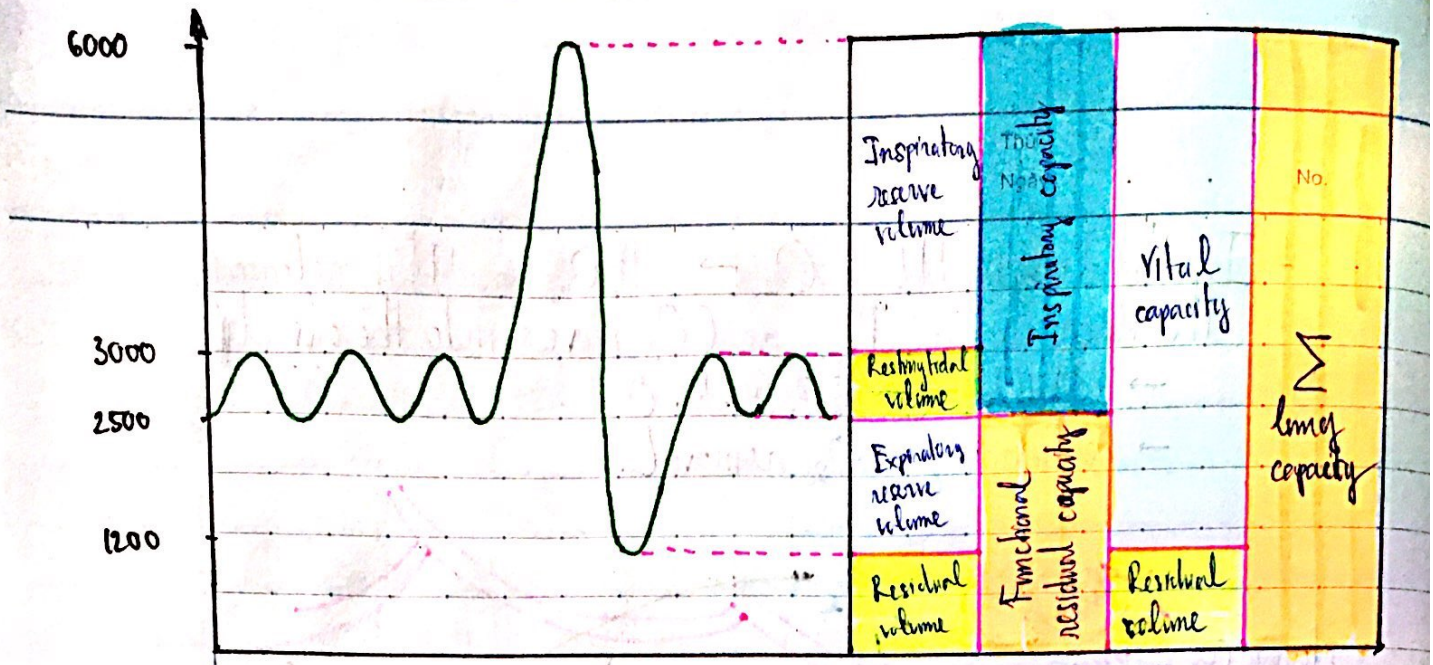
- In the lung, $Hb + O_2 \rightarrow HbO_2$ & H^+ is released
  the decrease in P_{CO_2} as CO_2 moves into the alveoli
  → $H_2CO_3 \rightleftharpoons CO_2 + H_2O$
  → enhancing CO_2 removal.



* More info:
- Carboxyl Hb : $HbCO$
  Methemoglobin : Hb with Fe instead of Fe^{2+} → cannot bind w/ O_2
  Myoglobin : Mb, similar to Hb, specific for muscle tissue

Measuring pulmonary function

- Use peak flow meter & spirometer
  - Peak flow meters: maximal rate of expiration
  - Spirometer : air flow



- The spirometer cannot measure Σ lung capacity since it cannot directly measure residual volume

- When looking at respiratory health → forced expiratory volume (FEV1) which is the air volume exhaled in 1 sec after taking maximal inspiration

The FEV1 is usually express relative to vital capacity (VC)
→ FEV1 / VC as the % of vital capacity in 1 sec

- A healthy individual should have FEV1/VC > 80%

- "Obstructive" respiratory disorder (eg: asthma, chronic obstructive pulmonary disease (COPD))
→ ↗ resistance in airway
→ FEV1/VC decreases

- "Restrictive" respiratory disorder (eg: broken ribs → ↓ lung expansion, edema, tuberculosis)
→ both FEV1 & VC reduce
but FEV1/VC may look normal

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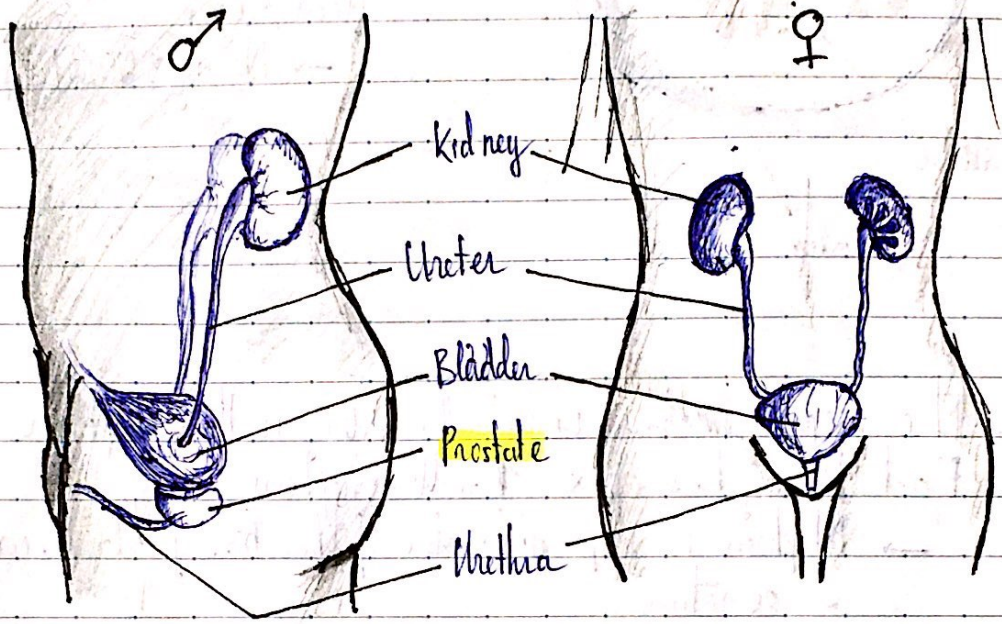
II) Kidney

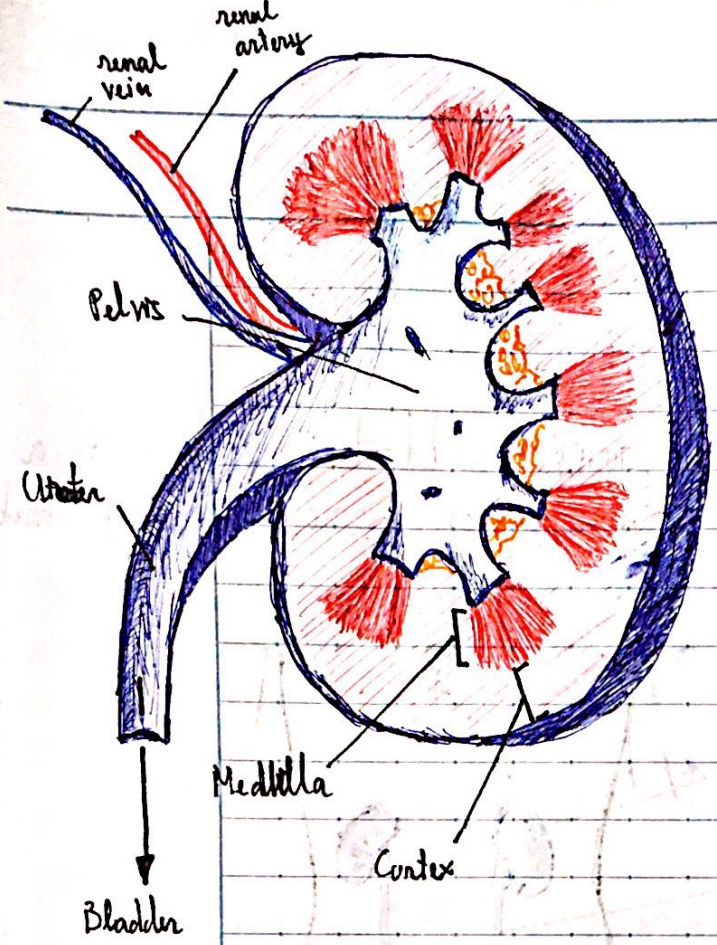
Anatomy

- There are 2 kidneys, 2 ureters, 1 bladder & the urethra
The main function : form, store & excrete urine & waste produ
of metabolism



- The kidneys lies against the posterior wall of the abdominal cavity, one on each side of the vertebral column
Each kidney is covered in a tough connective tissue capsule which is norm
covered in fat
The attachment of kidney to the renal veins, arteries, nerves & ureter are all on the inner-facing side of each kidney.

- 2 main roles of kidney :
  - Regulation of H_2O & ionic balance
  - Removal of metabolic waste products & chemicals from blood



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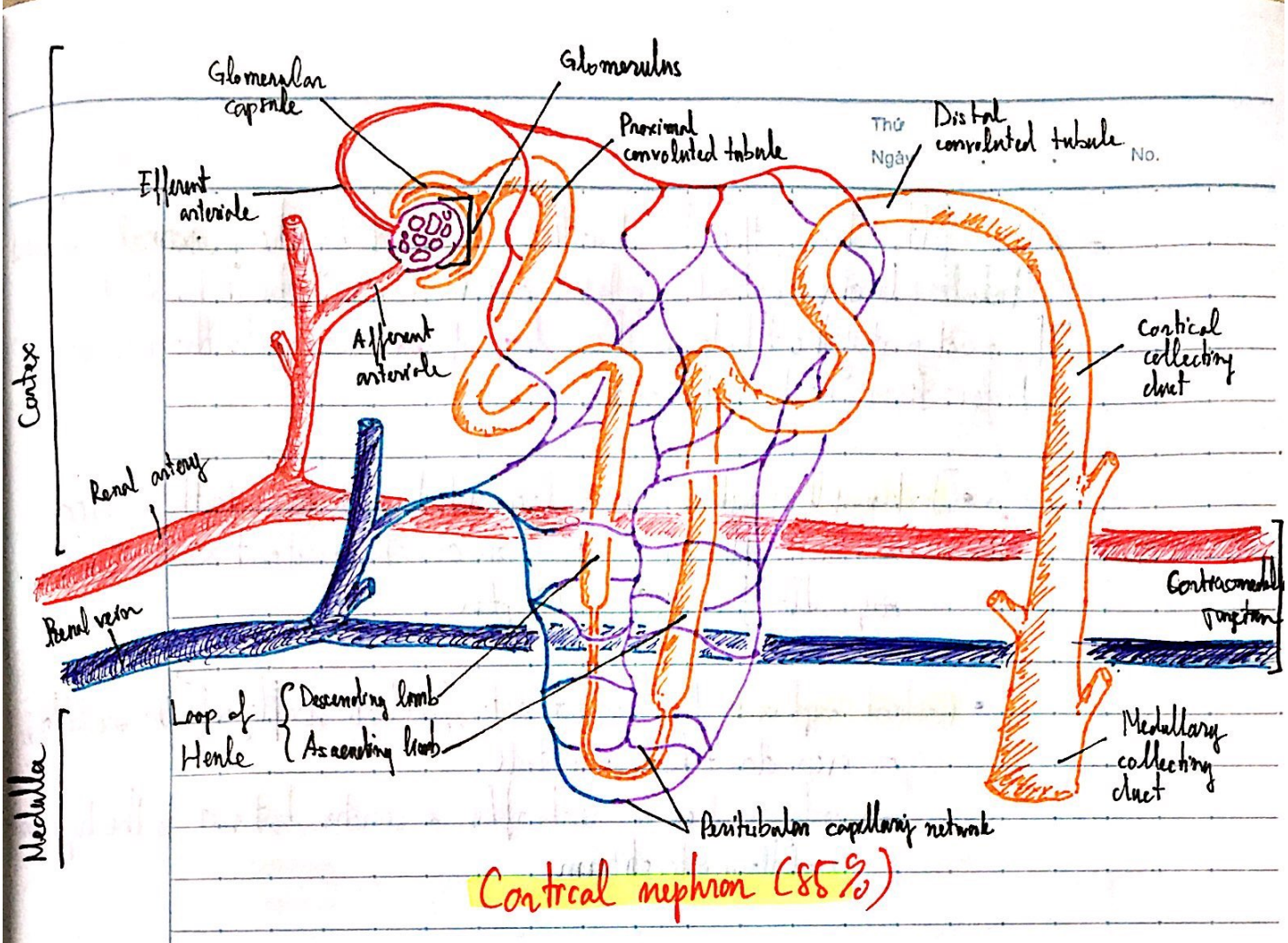
- Together the kidneys account for abont 0.5% body weight, but receive 25% of cardiac output (1.3L/m) cause 7% of O_2 consmption

- The kidneys will process around 78L of blood / hour
  → Nearly 2000L per day

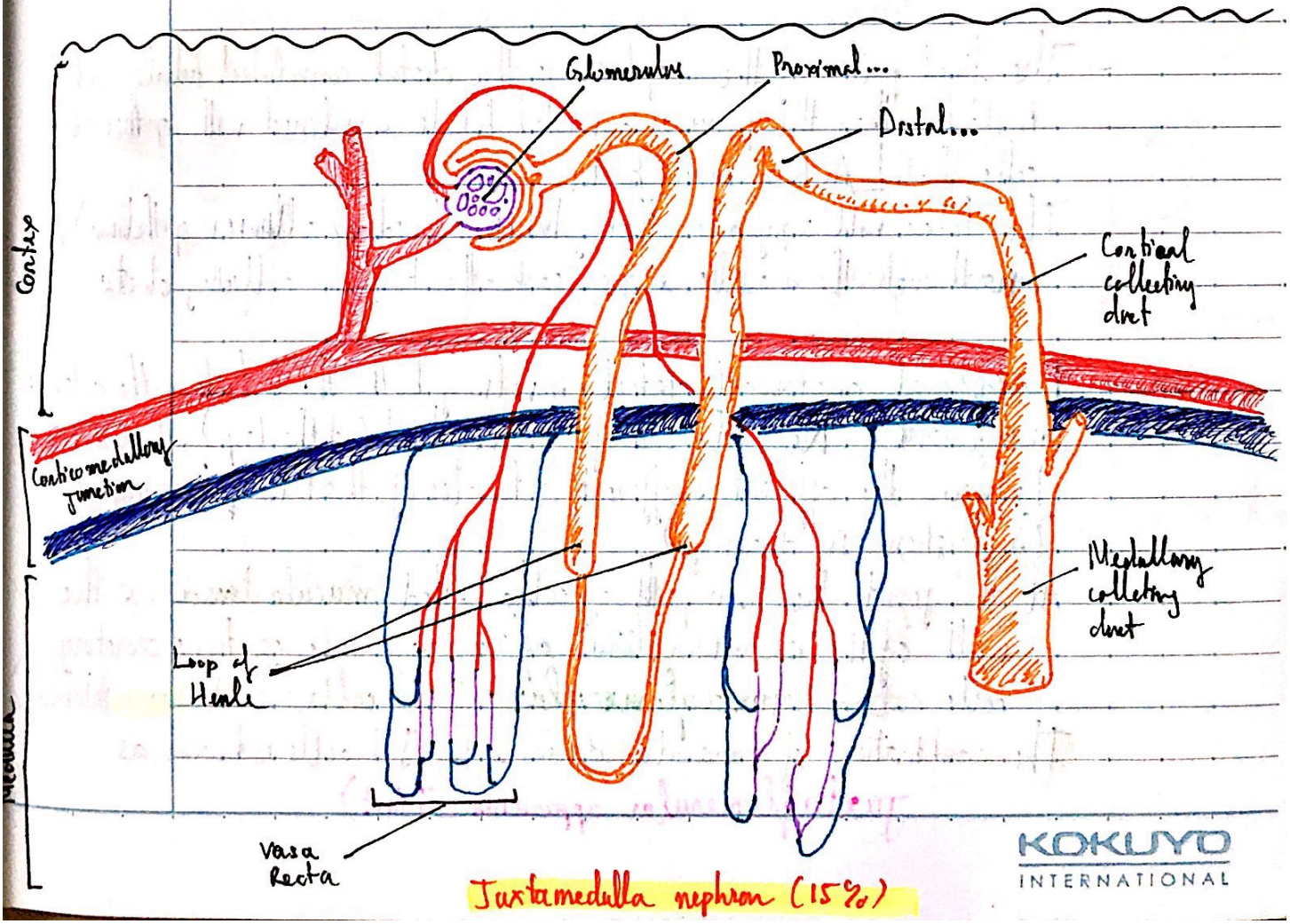
- The major functional unit of the kidney is the nephron
  Each kidney has appx. 1 million nephrons
  → Nephron is responsible for filteration of blood, urin production & secretion

- The major structures within the nephron are glomerulus, loop of Henle, distal tubule & collecting duct

- Most of the nephron is contained in the renal cortex. Filteration of blood from the renal arteries occurs from fine capillaries within the glomerular capsule (Bowman's capsule). The capsule is lined with squamous epithelium.
  On the interior surface of the capsule, the epithelial lining forms a membrane which is in close proximity to the endothelium of the capillary loops
  → Site for filteration



Cortical nephron (85%)



Juxtamedulla nephron (15%)

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- After filteration, the fluid is then drained by the proximal convoluted tubule (lined w/ cuboidal epithelial cells which have a brush border)
The next part of the tubule is the loop of Henle, runs into the medulla before turning back to the cortex.

  - Juxtamedullary nephrons have a loop which runs deep into the medulla
    → responsible for creating an osmotic gradient in the medulla
    ~~responsible~~ for H_2O reabsorption

  - Cortical nephrons' loop do not enter/penetrate deeply into the medulla, or even don't have any at all
    → only involve in reabsorption & secretion but not to the hyperton medullary interstitium

- The final portion of the nephron is the distal convoluted tubule, which is shorter than the proximal convoluted tubule & is lined with epithelial cells that LACK a brush border
The tubes will empty into collecting tubules (lined w/ cuboidal epithelium), runs through the medulla & join each other to form collecting ducts

- 1 additional anatomical detail involving both the tubule & the arterioles is important: Near the end of ascending limb (of the loop), it passes between the afferent & efferent arterioles of that loop's own nephron (not shown in drawings)
At this point there is a patch of cells called macula densa, & the wall of the ~~ascending limb~~ afferent arteriole contains secretory cells called juxtaglomerular (JG) cells. (secrete renin into blood)
The combination of macula densa & the JG cells is known as
juxtaglomerular apparatus (JGA)

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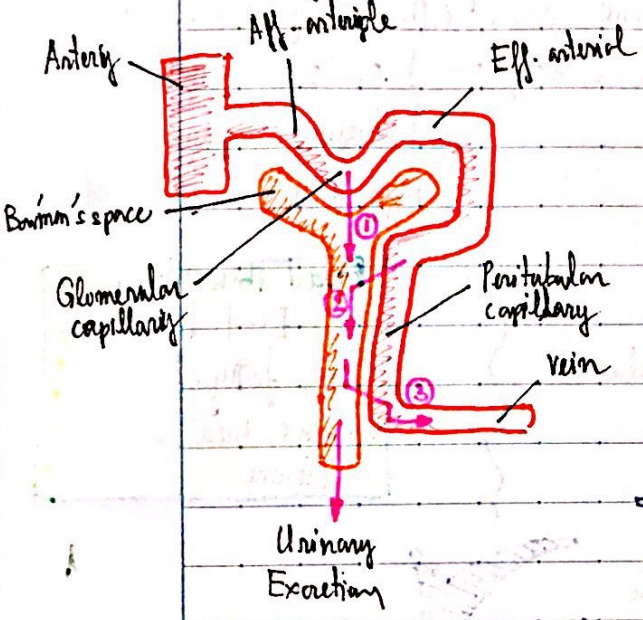
Basic renal processes: Filtration & reabsorption

- Main output of the kidney is urine, which is produced by filtration of blood & selective reabsorption



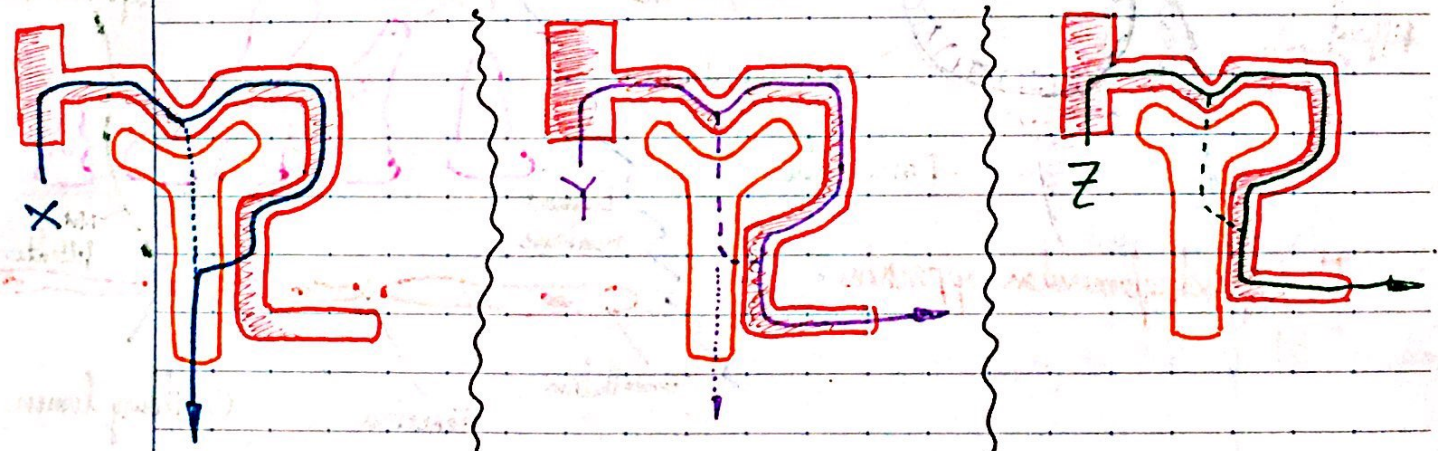
① Glomerular filtration

② Tubular secretion

③ Tubular reabsorption

⇒ 3 basic components of renal function

Depends on the particular substance → varied processes:



Substance X is filtered & secreted but not reabsorbed

Substance Y is filtered, then a fraction is reabsorbed.

Substance Z is filtered, then completely reabsorbed.

Excretion = Filtered + secreted − reabsorbed

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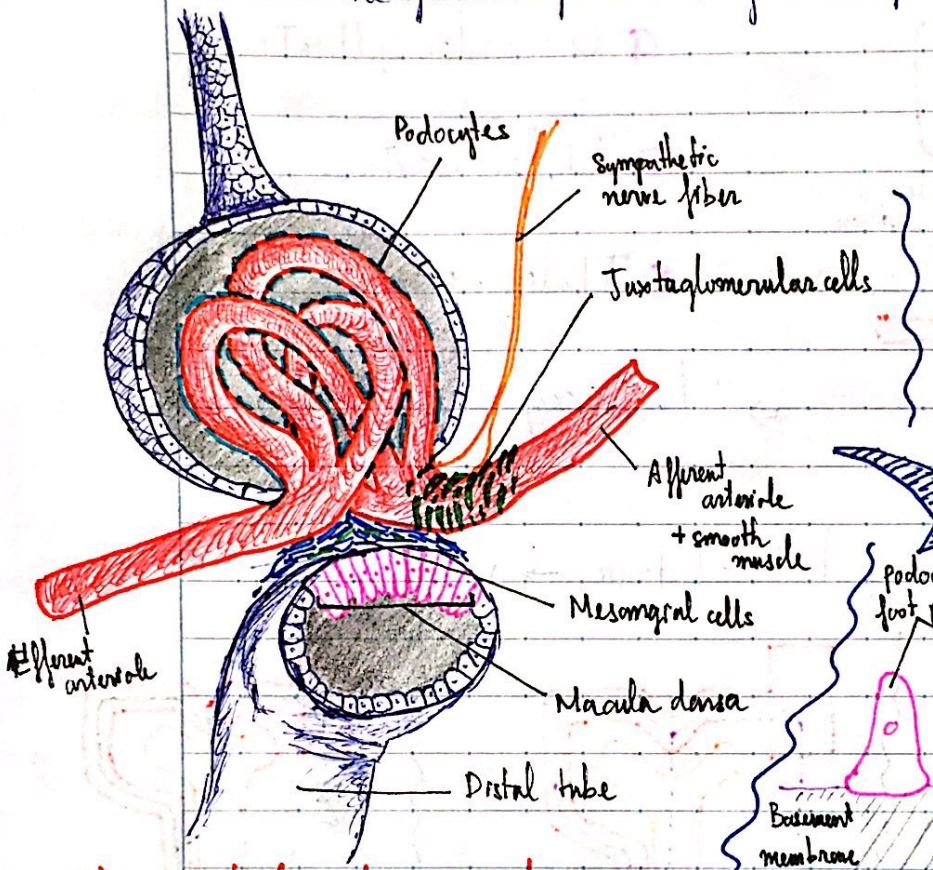
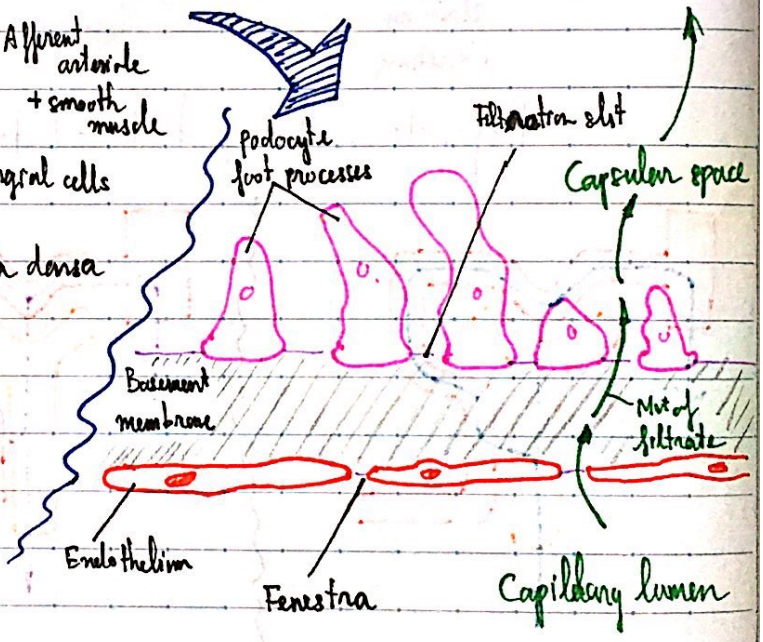
Glomerular capsule – Glomerular filteration

– Initially blood is filtered in the glomerulus :
- The filtrate is cell-free, except for protein, contains all substances in almost same concanthation as plasma (ultrafiltrate)
- The filtrate passes through 3 layers : { endothelium, basement membrane, epithelial cells (podocytes)

Passed thru filter : H_2O; Electrolytes, Glucose aci; fatty acid, vitamins, urea, uric acid creatinine



The juxtaglomerular apparatus



– The podocytes of the Bowman's capsule cover the capillaries. The filteration slits allow the filtrate to flow into the capsule. On the capillaries there are holes called fenestrae which also allow the movement of fluid to Bowman's capsule / space.

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- Substances in the blood through capillary fenestrae between endothelial cells, pass the basement membrane, then through the podocyte filtration slits and enter the capsular space
From here, the filtrate is transported to the lumen of proximal convoluted tubule

- The filtrate normally contains all plasma substances with same concen as in plasma except protein
Such proteins as albumins & globulins are excluded from the filtrate

The only exception for the generalisation that all non-protein compound have the same concentration is that some molecules could bind to plasma proteins → cannot be filtered

Loop of Henle – Tubular reabsorption

- Ion reabsorption using osmotic gradient
- 2 general mechanisms:
  - Na^+ reabsorption actively in all tubular segment except the ascending limb of Henle's loop
  - H_2O reabsorption by diffusion and is dependent on Na^+ reabs

~ Primary Active Na^+ reabsorption

- By K^+/Na^+ - ATPase pump
- The active transport of Na^+ out of the cell keeps the intracellular concentration low (compared to tubular lumen)
  → Net effect: Na^+ move out of the lumen to the tubular epithelial cells.

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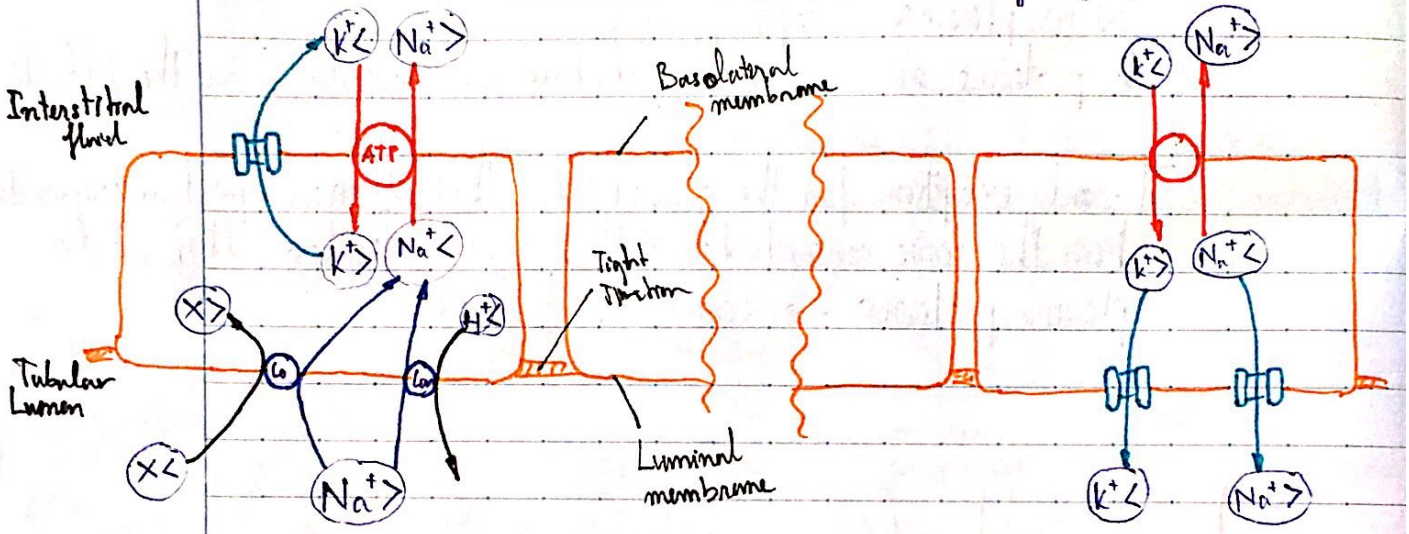
- This mechanism varies from segment to segment depending on which channels or transporters that are presented

Eg: • <u>Proximal tubule</u> use a cotransport in the entry step of with variety of protein, or countertransport with H^+

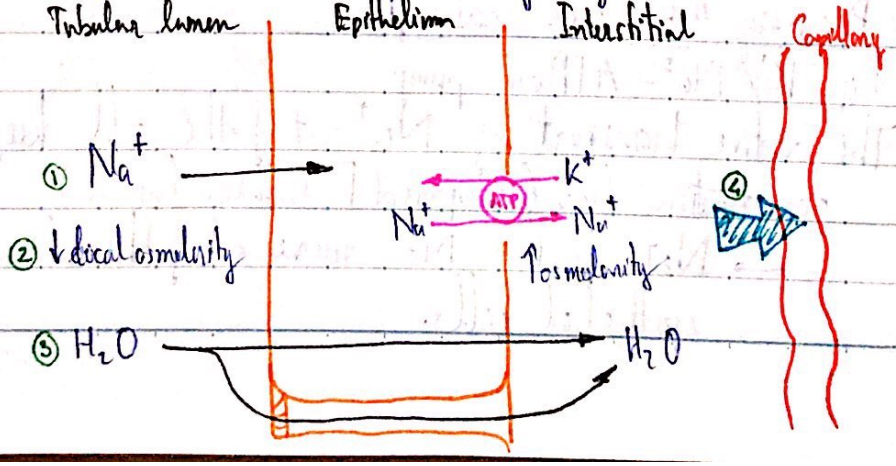
• <u>Cortical collecting tubule</u> primarily by diffusion thru Na^+ ch



- The movement of ion in the basolateral membrane is the same in all segments, using Na^+/K^+ ATPase pumps

∿ Coupling of H_2O reabsorption to Na^+ reabsorption

- H_2O follow Na^+/Cl^- passively by osmosis:



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1. Na^+ is transported to the interstitial fluid across epithelial cells
   Other solutes (glucose, aa, HCO_3^-) are dependent on Na^+ reabsorption & also contribute to overall osmosis
2. The removal of solutes from the lumen → ↓ local osmolarity
   The appearance of solutes in the interstitial fluid → ↑ local osmolarity
3. H_2O diffuses from the lumen out to the interstitial fluid
4. From there, H_2O, Na^+ & everything else dissolved in the interstitial fluid move together by bulk flow into peritubular capillaries

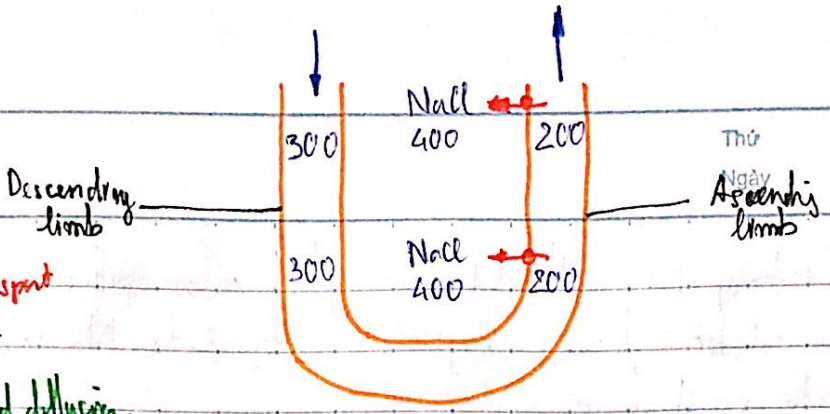
- H_2O mvt across the epithelium only occurs if the epithelium is H_2O permeable, and the permeability is varied greatly due to physiological control.
  → the role of ADH (vasopressin; antidiuretic hormone)

- ADH stimulate the insertion into the luminal membrane of a particular group of aquaporins made by collecting duct cells
  → ↑ADH → ↑ H_2O permeability → less urine
  ↓ADH → ↓ " → more urine

⇒ Any solutes loss must be accompanied, but not true for the opposite

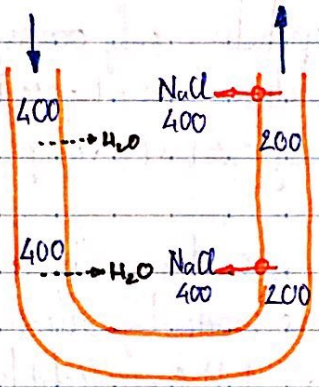
~ The countercurrent multiplier system

- The ascending limb of the Henle's loop contains $Na^+/K^+/2Cl^-$ transporters which pump Na^+ & Cl^- out of the lumen to the interstitial fluid, creates a hyperosmotic environment.
  The descending limb is relatively impermeable to H_2O
  → the interstitial fluid is hypertonic compared to the ascending limb

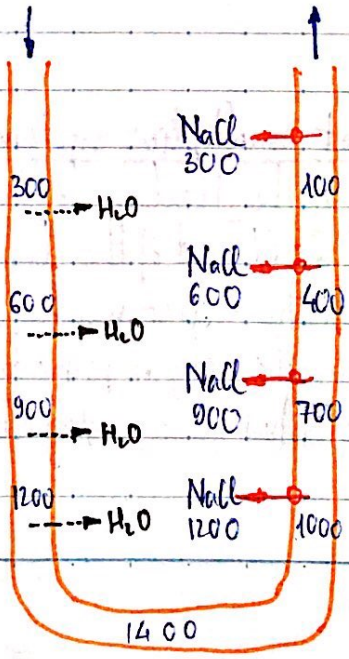


→ Active transport
- - - → diffusion
→ Facilitated diffusion

- The descending limb is quite H_2O - permeable, & doesn't absorb NaCl
  → H_2O diffuse into the more concentrated fluid (interstitial)
  The interstitial fluid osmolarity is maintained during this equilibration because the ascending limb continuously pumps NaCl to maintain concentration difference between it & interstitial fl

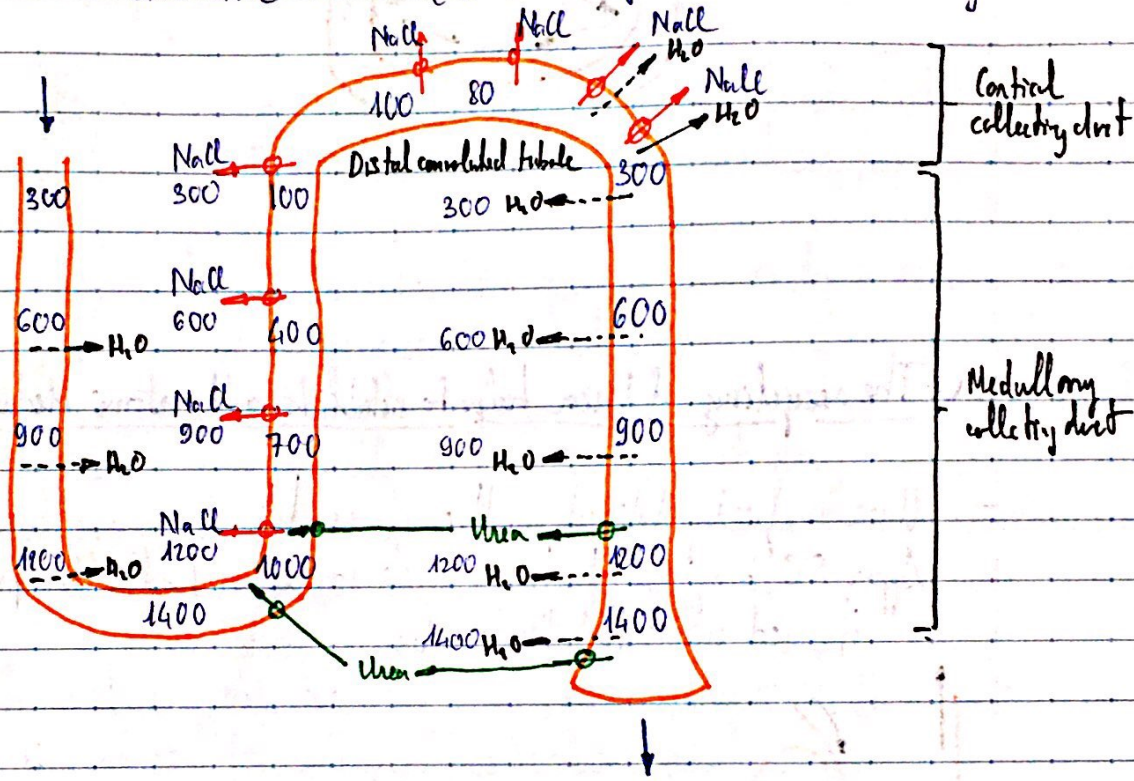


- The "multiplying" aspect: the osmolarity is "multiplied" as the tube goes deeper into the medulla:



- Continue to the collecting duct. Urea reabsorption & trapping contributes to the maximal medullary interstitial osmolarity

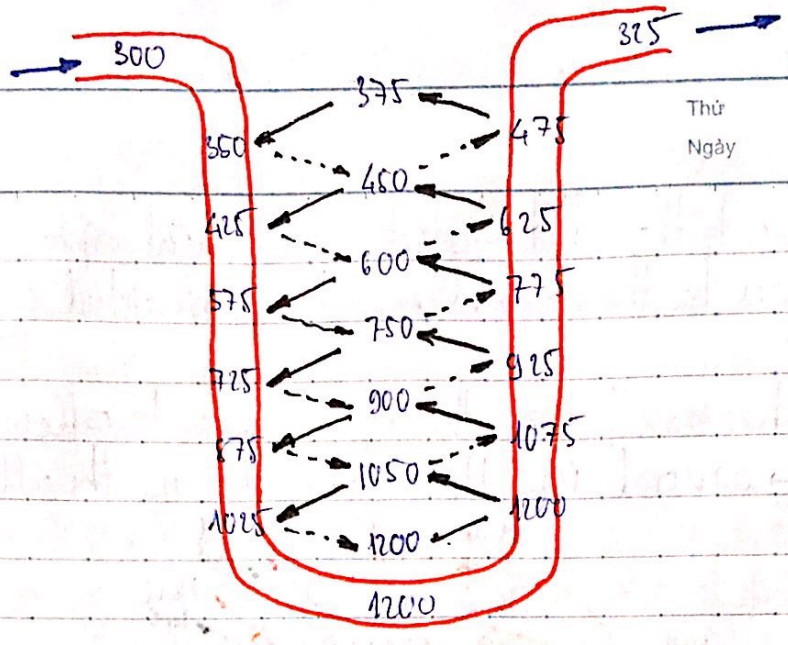
ADH has no effect on the segment prior to collecting duct
→ crucial in H_2O reabsorption in the collecting duct



~ The medullary circulation

- The capillaries does not eliminate the osmotic gradient, even though these capillaries does indeed get NaCl (& other ion) and remove water passively as they go deeper to the medulla.

This is because of the hairpin loop structure of the vasa recta
At the same time, both the salt & H_2O being reabsorbed from the loop of Henle & collecting duct are carried away in equivalent amount



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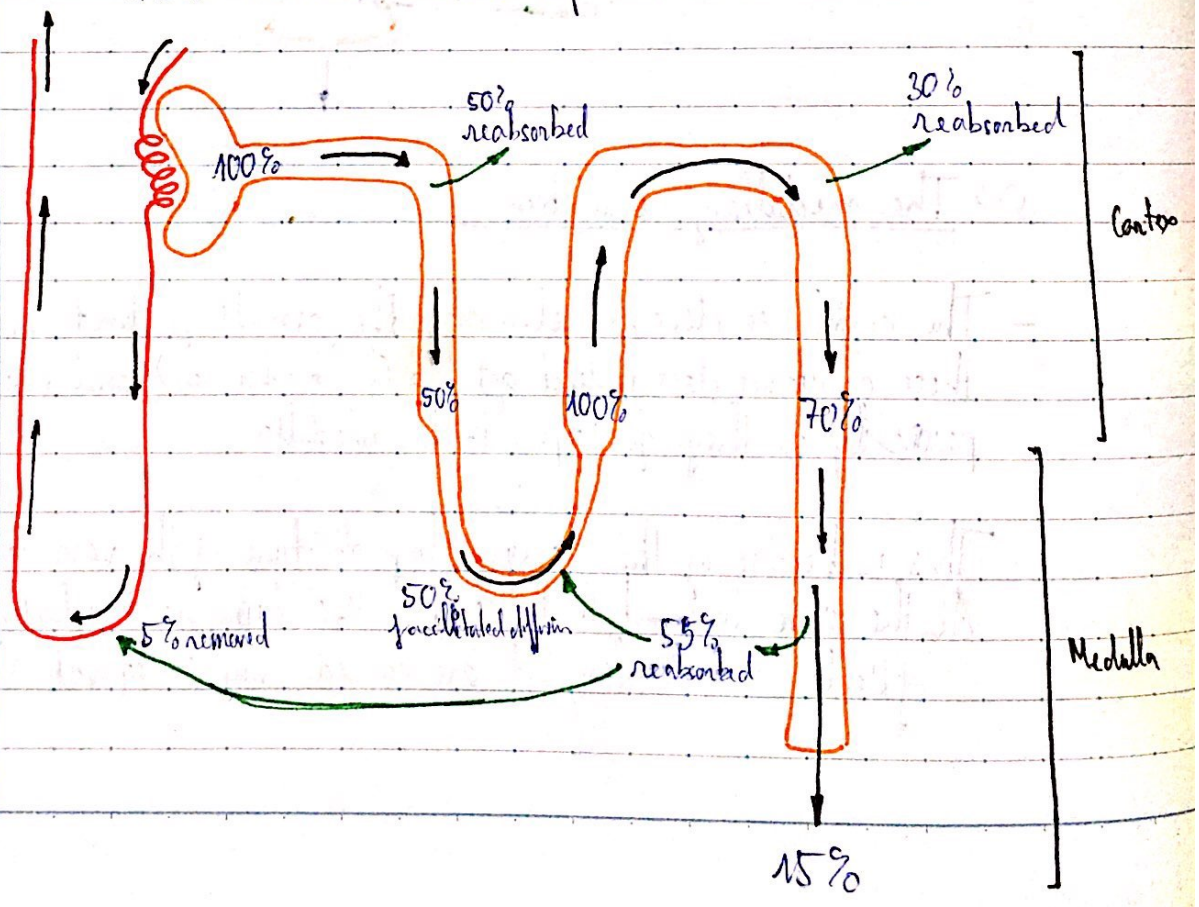
~ The recycling of Urea helps to establish a Hypertonic Medullary Interstitium

- Urea is freely filtered in the glomerulus.
  Appx 50% of the filtered urea is reabsorbed in the proximal tubule, the rest enters the Henle's loop



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Distal tubule & collecting duct

- Several distal tubules empty into a single collecting tubule, which then further combine into a collecting duct.

This part of the nephron are under the influence of hormones which can regulate the reabsorption of solutes.

Eg: • Calcitriol & PTH ↗ Ca^{2+} reabsorption
• Aldosterone affects Na^+ reabsorption

- The distal tubule lies in the vascular rich cortex & receives about 16% of the original glomerular filtrate.

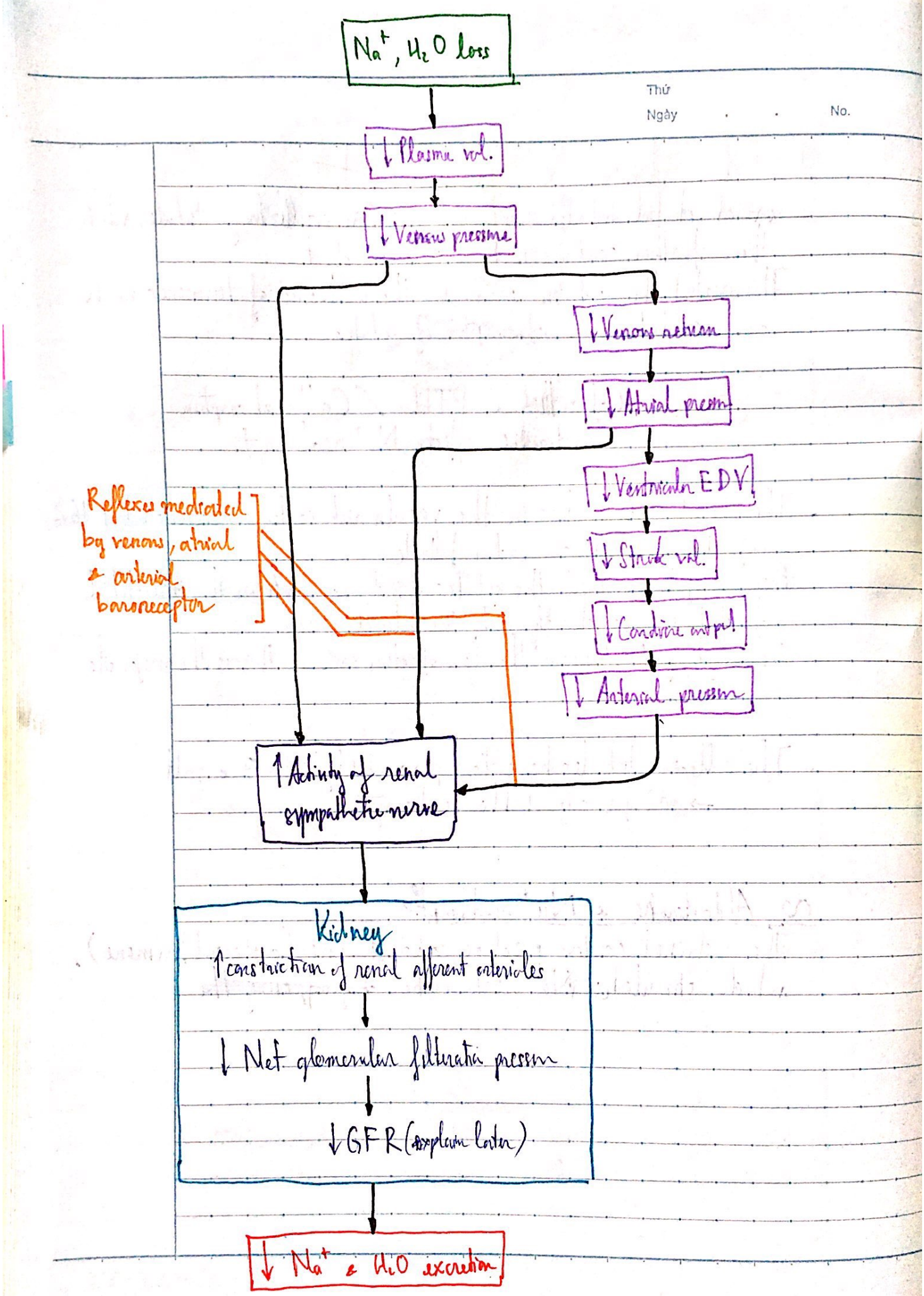
Because of its location, the solutes don't accumulate in the interstitial fluid but move directly into the blood stream

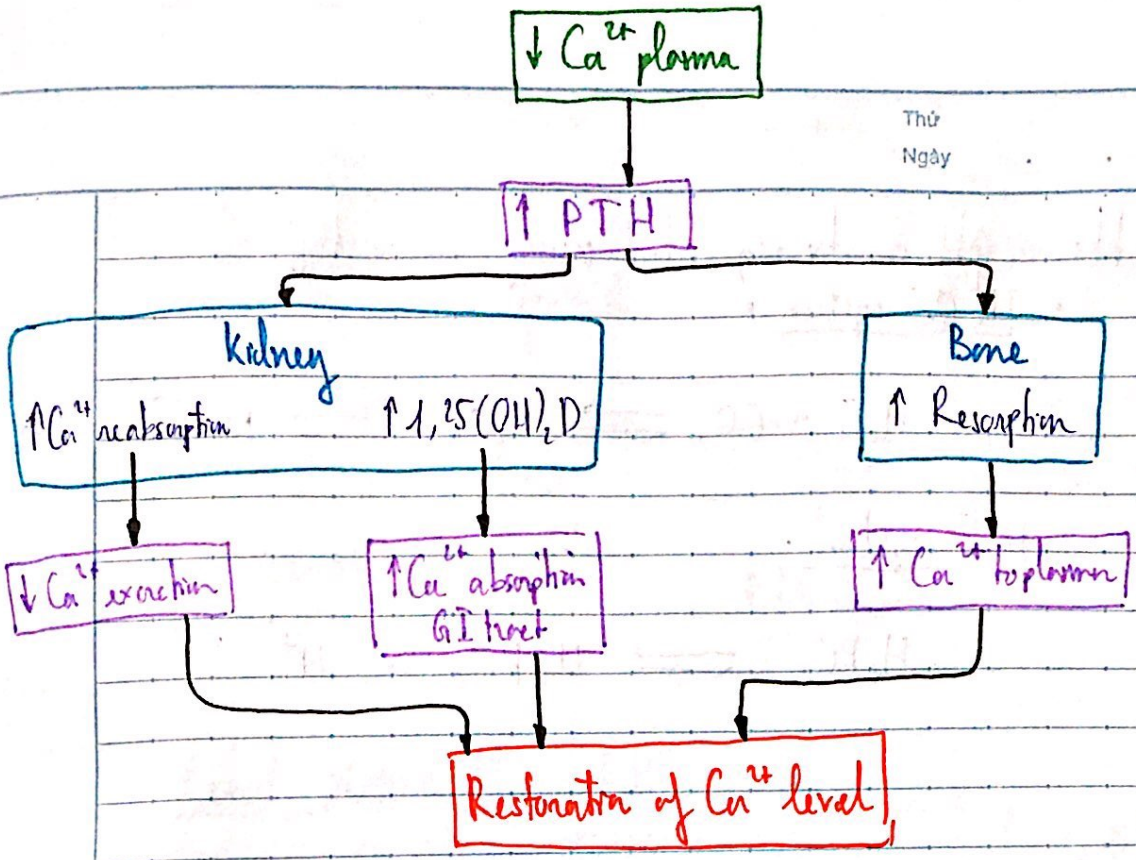
Reabsorbing Na^+ means the loss of other ion → this is the major site of K^+ loss

- The collecting tubules have low permeability to H_2O & salt
→ site for adjustable reabsorption

∿ Aldosterone & Na^+ reabsorption

- The adrenal cortex produce aldosterone (a steroid hormone), which stimulates Na^+ reabsorbtion ~~by affecting the~~





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Regulation of pH

— Kidney are good at long term regulation of plasma secretion, & this can be necessary when there are change in plasma pH

- Respiratory alkalosis can occur when there is an ↑ in ventilation
- Metabolic alkalosis can occur when there is excessive ingestion of absorbable antacids or persistent vomiting or in association w/ hypokalemia
- Respiratory acidosis " ↓ in ventilation
- Metabolic acidosis " methanol or acid are ingested, or after severe &/or prolonged diarrhea or heavy muscular work

— When there is an imbalance in pH, the respiratory rate is initially adjusted to rebalance pH. If the balance is not restored → renal system is activated

The renal system is slower at adjusting blood pH, but has higher capacity & can be sustained

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- Plasma pH can be regulated using common buffers:
  - HCO_3^- system:

$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

  - PO_4^{3-} system:

$$H_3PO_4 \rightleftharpoons H_2PO_4^- + H^+$$

Measuring function

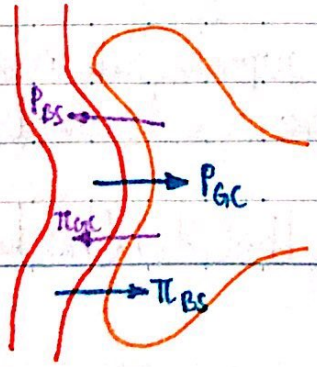
~ Glomerular filtration rate (GFR)

- The volume of fluid filtered into Bowman's space per unit time is known as GFR

GFR is not only determined by permeability of the corpuscular membrane & surface area for filtration, but also by net filtration pressure

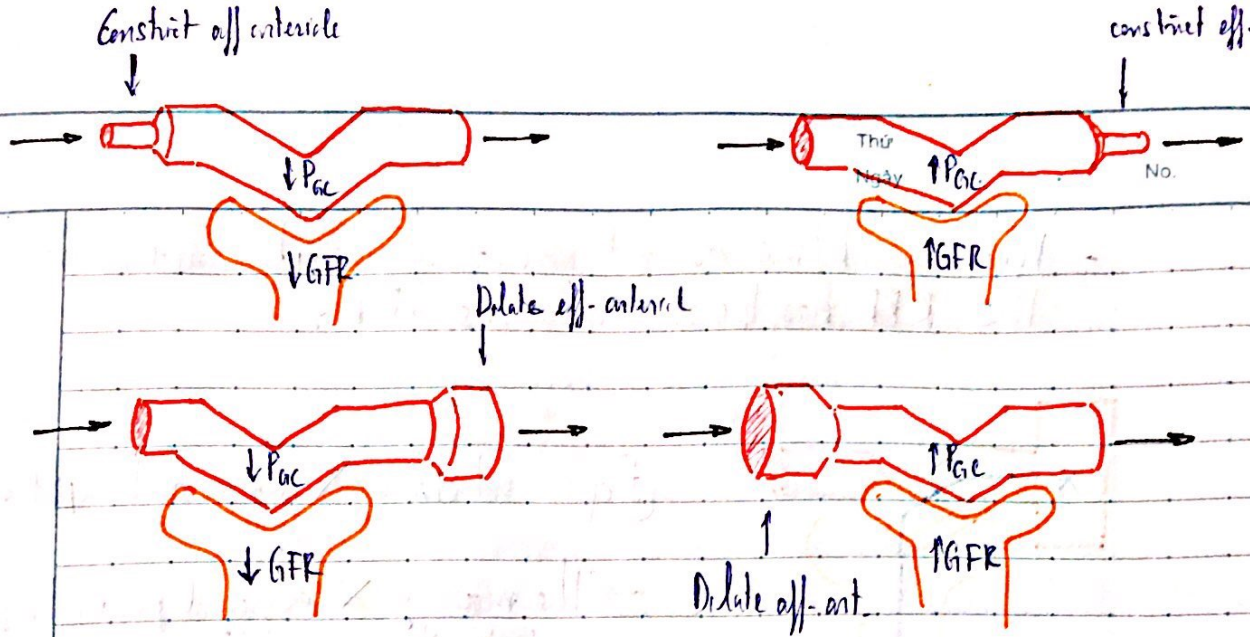
- GFR is not a fixed value, but can be subjective to neural & hormonal input, which cause change in net glomerular filtration pressure

- Net glomerular filtration pressure



Where
- P_{GC}: glomerular capillary hydrostatic pressure
- π_{GC}: osmotic force due to protein (GC)
- P_{BS}: Bowman's space hydrostatic pressure
- π_{BS}: osmotic force due to protein (BS)

$$\rightarrow NGFP = P_{GC} - \pi_{GC} - P_{BS} + \pi_{BS}$$



∿ Renal plasma flow (RPF)

- Understand renal clearance first: the vol. of plasma from which that substance is completely removed by the kidney per unit time

$$\text{Clearance of S} = \frac{\text{Mass of S excreted / time}}{\text{Plasma conc. of S}}$$

→ Other expression:

$$C_s = \frac{U_s V}{P_s}$$

C_s : clearance of S
U_s : urine conc. of S
V : urin vol. per unit time
P_s : plasma conc. of S

- Renal plasma flow ≈ when the substance is filtered, but neither reabsorbed nor secreted (since these processes can alter the clearance.)
No substance like this presents in plasma → intravenous inulin & para amino hippurate (PAH) is used for precise RPF, then GFR

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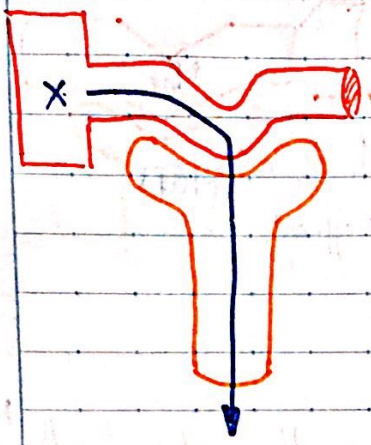
- When a substance does not undergo reabsorption and secretion, the RPF has the same value as GFR:



Eg: substance X is not reabsorbed & secreted

→ The mass of X excreted per unit time is equal to the mass filtered during the same time period.

→ Generalization: when the clearance < GFR → that substance undergoes reabsorption and vice versa.

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III) Male & Female urinary tract
Benign Prostatic Hyperplasia (BPH)

Male & Femal urinary tract

- For anatomy, see 18 pages before this
- The urinary system consists of the upper & lower urinary tract
  - Upper tract consist of organs & tissues above the bladder (kidney & meter), this is same for ♂ & ♀
  - Lower tract " below the bladder (urethra). This is different in ♂ & ♀
- The kidney produce urine, which is stored in the bladder until expelled out of the body thru the urethra.

Function of prostate gland

- The prostate is a walnut-size gland found in male, located between the bladder & the penis

It is an accessory gland which indirectly facilitates fertilization by ↗ sperm motility & providing nourishment via the expulsion of fluid into the urethra

- The prostate has 4 main constituents:
  - Proteolytic enzymes
  - Acid phosphatase
  - Zinc
  - Citric acid.

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- The prostate gland is made up of a series of ducts surrounded by smooth muscle, akin like sponge.

The smooth muscle surrounding the ducts are innervated by sympathetic nerves that release NA to mediate contraction of prostatic smooth muscle via α_{1A} adrenoreceptors on smooth muscle cells
Just prior to ejaculation, the sympathetic nerves are activated to release NA to contract the prostatic smooth muscle which squeezes the prostatic secretions contained in the prostatic ducts out of the gland and into the urethra where it mixes w/ sperm & seminal fluid to form semen.

The prostate & BPH

- Before puberty & into adolescence & early adulthood, males typically have very strong urinary stream. As men grow older, their urinary stream tends to become weaker
→ This dev is age & androgen dependent.

- BPH affects men at different ages but the onset is usually after 40
  - 50% in their 50s
  - 90% in their 80s

Although BPH is not life threatening, can still affect life quality

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BPH Diagnosis

- Is carried out by a medical practitioner using a Digital Internal Rectal Exam (DIRE).
  As the prostate grows, it is not allowed to grow outward.
  → grows inward to constrict the urethra & pushes up on the bladder to cause urinary symptoms.
  The severity of the symptoms is not related to prostate size, but due to the hardness or tone of the prostate
  → The DIRE to see the hardness, not the size.

- The severity of urinary symptoms is assessed using questionnaire, w/ some categories: nocturia, daytime frequency, hesitancy, ...

Management of BPH

- Lower Urinary Tract symptom (LUTs) can be due to a number of causes. Very mild symptoms are usually associated w/ anxiety, and in ♂, moderate to severe symptoms are usually due to BPH.

Other factors producing similar symptoms but requiring different treatments are most likely to be prostate cancer or overactive bladder and are managed properly.

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Mechanism of action of drugs used to treat BPH

~ Treatment of mild to moderate LUTs by BPH w/ α-blockers

- Medications blocking α_1-adrenoceptors are the most effective pharmacological treatment for ♂ w/ mild to moderate LUTs.

Adrenoceptors have 3 major subtypes (α_1, α_2, β_2) which are further divided. The distribution of these receptors is not homogenous

- Prostate smooth muscle, has α_{1A} & α_{1D} adrenoceptors.
The α_{1A}-adrenoceptors are more abundant in the prostate, while α_{1D}-adrenoceptors are more expressed in vasculature
→ Agents which target α_{1A}-adrenoceptors have greater effect in the prostate & less cardiovascular side effects.

~ Non-selective α_1-adrenoceptor antagonist

- α_1-adrenoceptor antagonists relax prostatic smooth muscle to ease the pressure off the urethra to allow a smoother flow of urine.
The same mechanism is present in vascular smooth muscle
→ Side effects: { weakness, fatigue
postural hypotension
dizziness

- These side effects are sometimes advantageous if the patient suffers from high blood pressure, as in common in many aging men
→ Non-selective α_1-adrenoceptor antagonist can be used to treat both disorders simultaneously.

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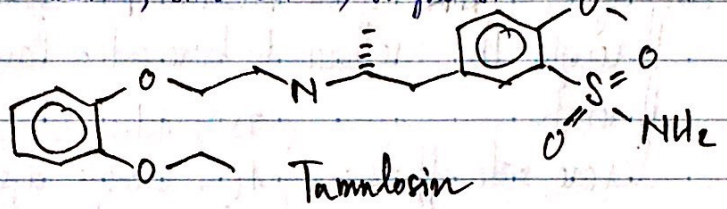
- Pharmacentical treatment of BPH in the absence of hypertension or hypertension is managed w/ other mechanism requires more specific adrenoceptor antagonist

~ Uroselective pharmacotherapy

- Selective α_{1A} - adrenoceptor antagonists are classed as uroselective since α_{1A} - adrenoceptor antagonist predominantly act on prostatic smooth muscle
Vascular smooth muscle contains higher proportion of α_{1B} & α_{1D} - adrenoceptor
→ less cardiovascular side effect.
Eg : tamulosin, silodosin, alfuzosin



Tamulosin

~ Hormonal pharmacotherapy (prostate shrinkers)

- Steroid 5α-reductase inhibitor are disease modifying rather than symptomatic treatment.
5α-reductase is an enzyme present in the prostate gland that convert testosterone to more potent dihydrotestosterone (DHT)
→ 5α-reductase inhibitor inhibits the conversion of testosterone
→ shrink the prostate

- Problem w/ this treatment is the delayed onset of action (6-12 mth), & they also shown to decrease the lvls of prostate specific antigen (PSA), which may prevent the early detection of prostate cancer.
Eg : finasteride, dutasteride.

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- The side effects { erectile dysfunction
  loss of libido
  ejaculation disorder
- This class of med is also used to treate men baldness

Treatment of severe BPH → surgery

~ Transurethral resection of the prostate (TURP)

- Usually, TURP is an invasive procedure where a needle is inserted through the urethra to bore out a large space for urine to pass through.
  Severe side effects: { 75% retrograde ejaculation
  10% erectile dysfunction
  1% incontinence

~ Radial prostectomy

- The whole prostate is removed.
  More common to treat localized prostate cancer, but also for enlarged prostate
  Severe side effects: { 85% erectile dysfunction (removal of nerves)
  5% incontinence

~ Transurethral needle ablation (TUNA)

- Interstitial radio frequency needle placed through the urethra into the lateral lobe of the prostate.
  → produce heat - induce coagulation necrosis (tissue heated to 110°C/5min)
- Quick & less evasive than surgery
- Low incidence of incontinence & erectile dysfunction

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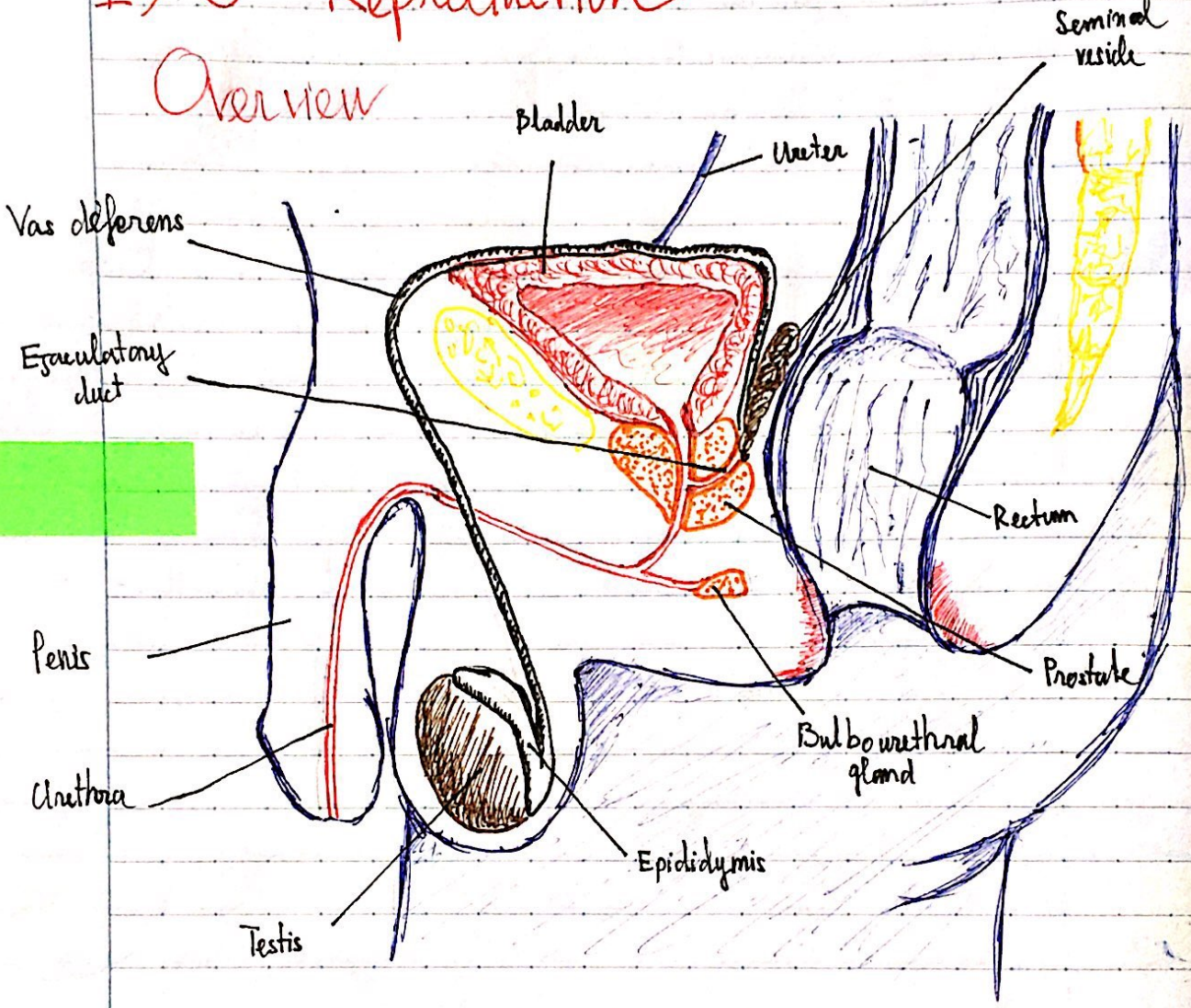
∞ Transurethral microwave therapy (TUMT)

- Transurethral insertion of catheter into bladder
Microwave antenna positioned w/in prostate
Microwaves heat & destroy hyperplastic prostatic tissue
1 time treatment.

Week 12 Thứ Ngày 22/5/2017 No.

I) ♂ Reproduction

Overview



- The ♂ reproductive system includes two testes; the system of ducts that store & transport sperm to the exterior; the glands that empty into these ducts; & the penis constitute the ♂ accessory reproductive system.
  - Testis: { produce sex steroid hormone (testosterone)
    sperm synthesis in the seminiferous tubules
  - Epididymis: 3 parts, where store sperm (a rest)
    eject sperm by contraction (ejaculation)

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Accessory glands

- Seminal vesicle : secretes seminal fluid during ejaculation
- Prostate : secretes prostatic fluid during ejaculation
- Bulbourethral : secretes lubrication

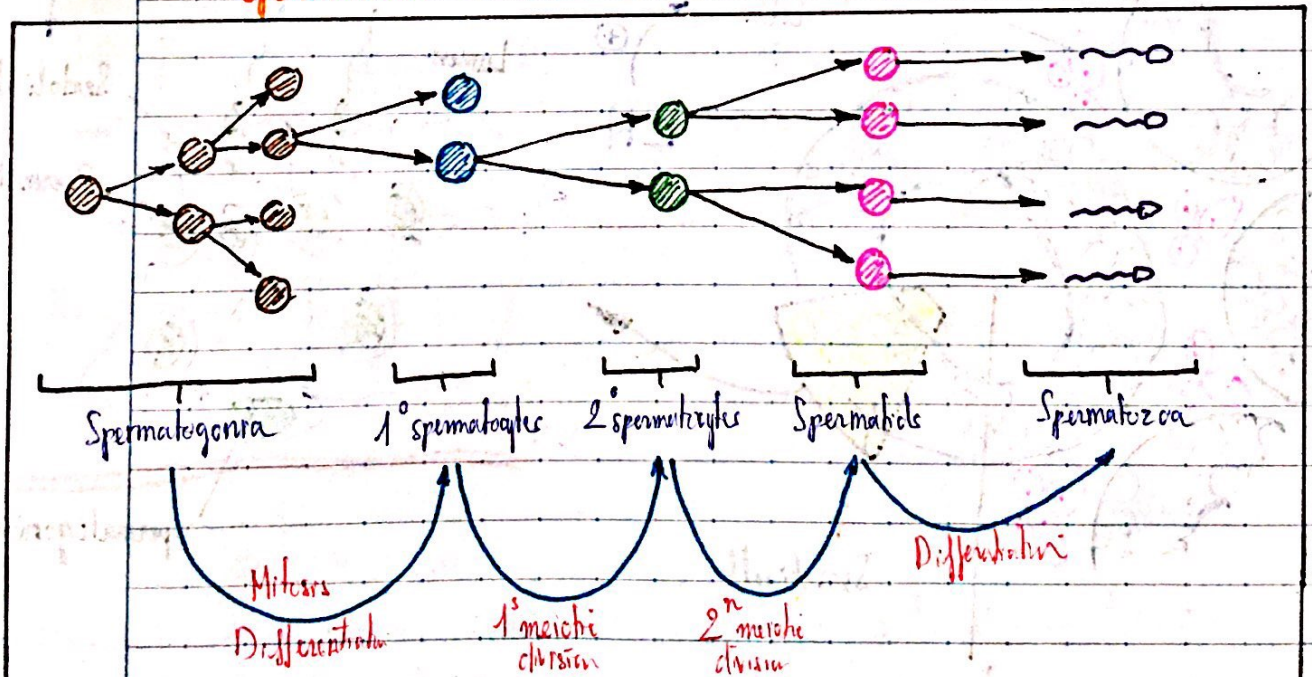
Testis

The principle organs of the ♂ rep. system is the testes
Main function : [spermatogenesis
[androgen (♂ sex hormones) secretion

~ Spermatogenesis

- Spermatogenesis is the formation of sperm & occurs in the numerous seminiferous tubules within the testes.

Within the seminiferous tubules sperm develops from spermatogonia into primary spermatocytes, then thru 2° spermatocytes into spermatids



N° chromosome per cell	46	46	23	23	23
Chromatid per chromosome	2	2	2	1	1

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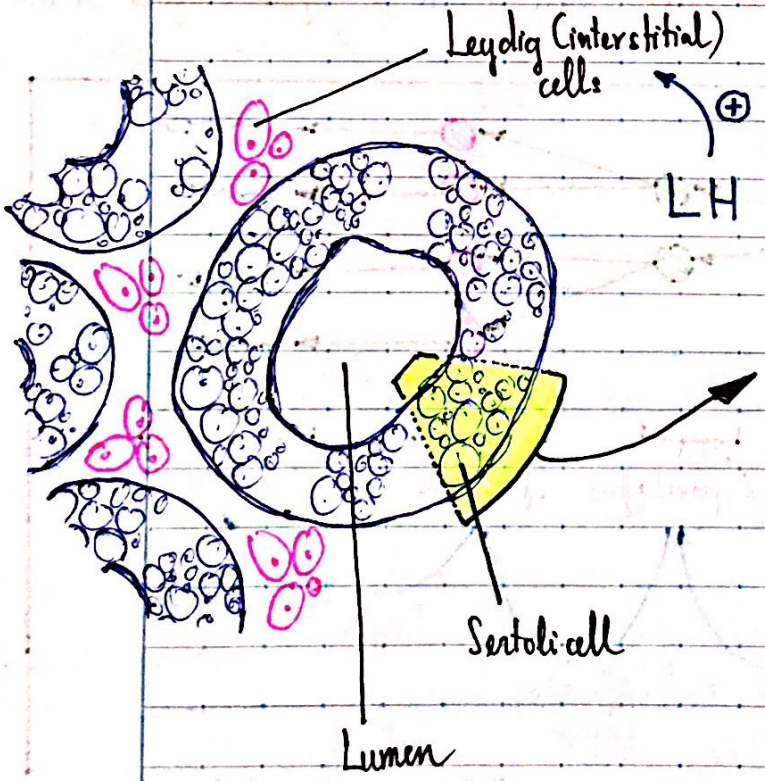
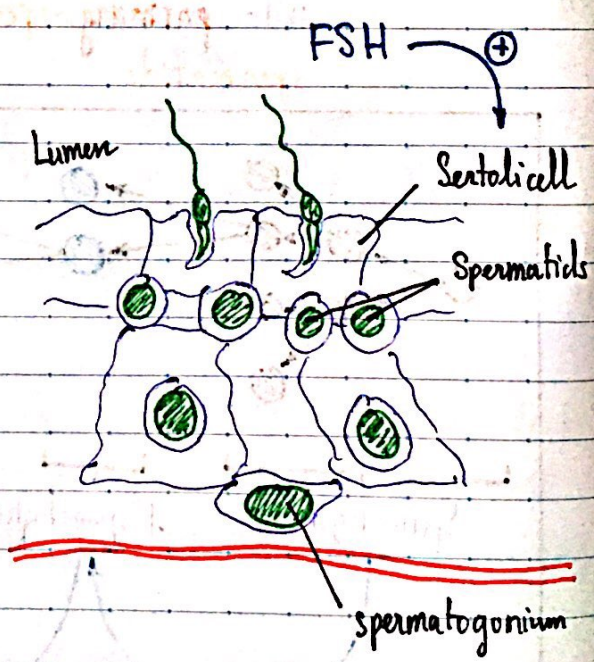
Ngày . . No.

- The site for spermatogenesis are seminiferous tubules, as mentioned. In the center of each tubule is the fluid-filled lumen containing mature sperm cells, spermatozoa.
The tubular wall is made of developing germ cells & another cell type called Sertoli cells.

- The Sertoli cells join to each other by tight junctions, which then form a ring of interconnected Sertoli cells to become blood-testes barrier, which prevents the movt of many chemicals in the blood to flow into the lumen
→ proper condition for germ all dev. & diff.

- The Sertoli cells also respond to FSH & testosterone to produce chemical messengers, which act as paracrine agents to stimulate proliferation & differentiation of germ cells.





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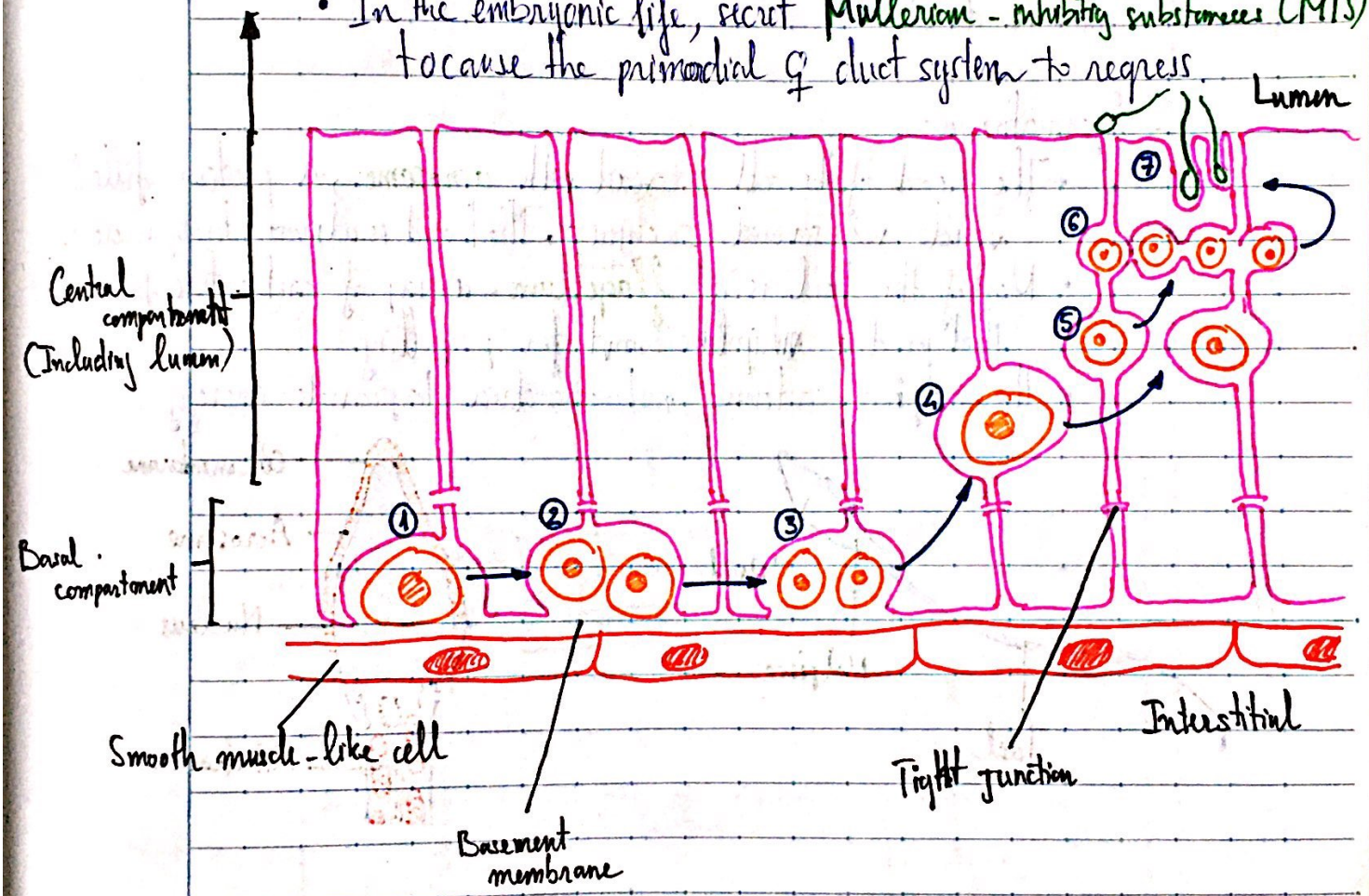
- In general, the summary of the function of Sertoli cells:
  - Sertoli cell barrier (blood-testes barrier)
  - Nourish developing sperm
  - Secrete luminal fluid, including androgen-binding protein
  - Response to stimulations to alter sperm proliferation & diff.
  - Secrete hormone inhibin, which inhibits FSH secretion of the pituitary
  - Secrete paracrine agents that influence the function of Leydig cells
  - Phagocytize defected sperm
  - In the embryonic life, secret Müllerian-inhibiting substances (MIS) to cause the primordial ♀ duct system to regress.



1. Spermatogonium
2. Spermatogonia after division, stay in the basal compartment
3. Primary spermatocytes
4. The primary spermatocytes move to the central compartment, enlarge

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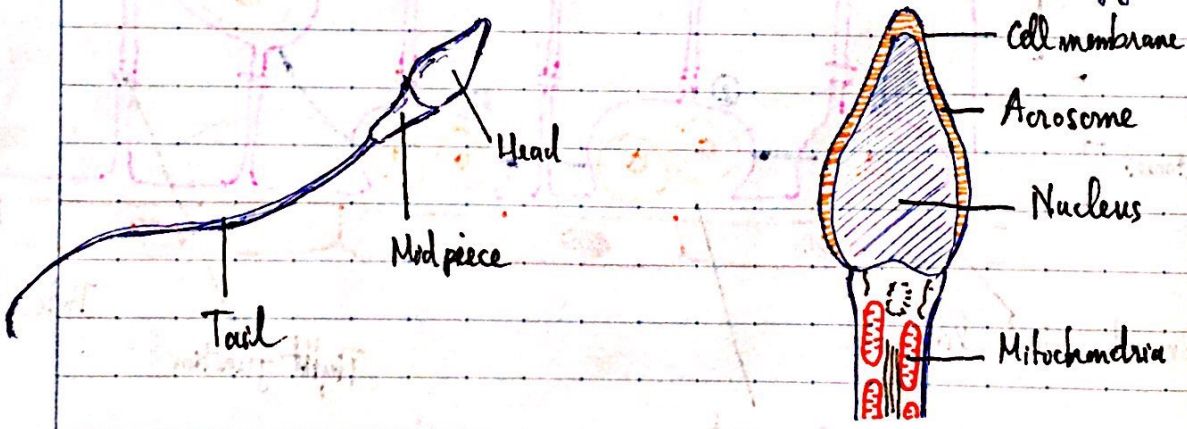
5. Primary spermatocytes divide into secondary spermatocytes
6. Secondary spermatocytes will then further divide into spermatids
7. Spermatids diff. into spermatozoa. This step involves the loss of cytoplasm

- The final phase of spermatogenesis is the diff of the spermatids into spermatozoa
This process requires extensive cell remodelling, including elongation but no more division

- Spermatozoa:
  - The head of the cell is covered with **acrosome**, a protein-filled vesicle w/ several enzymes. The head is almost entirely nucleus.
  - Most of the tail is a **flagellum** - a group of contractile filaments that produce whiplike mvt for propelling
  - The midpiece contains mitochondria to provide energy



- One important aspect of spermatogenesis is that not all daughter spermatogonia will be converted into primary spermatocytes
One of the cells exits the pathway to remain spermatogonium that will later enter exactly the same division, and so on
→ Supply of undifferentiated spermatogonia doesn't reduce

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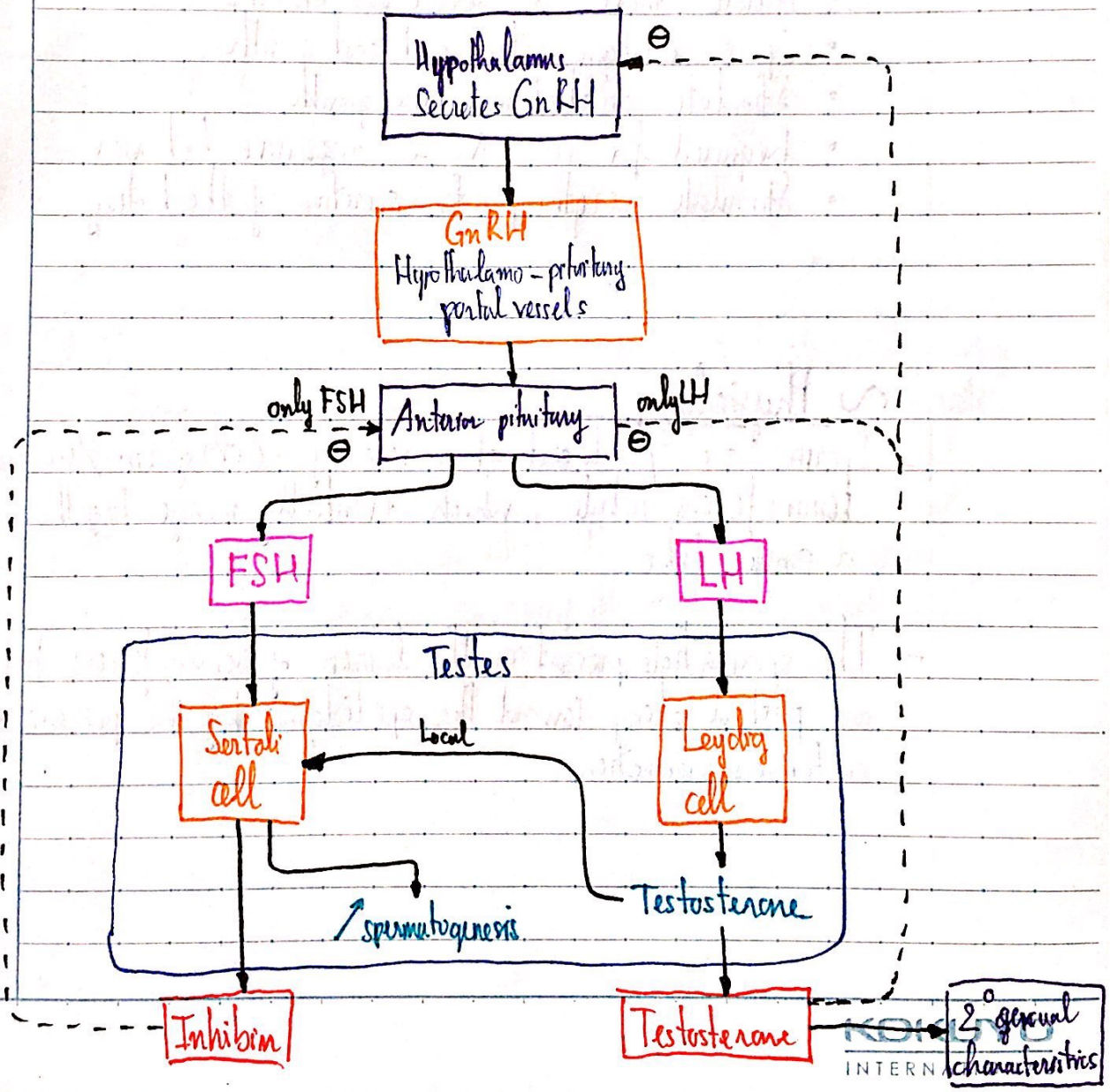
~ Androgen hormones secretion

- The Leydig cells are located between the seminiferous tubules of the testes, and are the main source of androgen hormones.

- The primary role of testosterone is the maturation of genital organs. Testosterone is also involved in development of secondary sexual characters including growth of body hair, deepening of voice ...

- The Leydig cells are stimulated to produce testosterone in response to Luteinizing hormone (LH) from the anterior pituitary



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- In some cells / tissues, testosterone is converted in to the more active form
  Eg: • Prostate: Testosterone is converted to DHT by 5α-reductase
  • Brain: Testosterone is converted to estradiol

- Summarized roles/effects of testosterone in ♂
  • Required for initiation & maintenance of spermatogenesis
  • Decrease GnRH secretion of hypothalamus
  • Inhibit LH secretion via anterior pituitary
  • Induces diff. of male accessory reproductive organs & maintain
  • Induce male 2° sexual characteristics
  • Oppose estrogen action & breast growth
  • Stimulate anabolism, bone growth
  • Required for sex drive & aggressive behavior
  • Stimulate erythropoietin secretion of the kidney.

~ Physiology

- Sperm are produced at a rate of 2000 sperm/sec in the seminiferous tubule, which eventually merge together into a single tube

- The spermatids present in the lumen of seminiferous tubules are pushed along toward the epididymis by the pressure of continuous production

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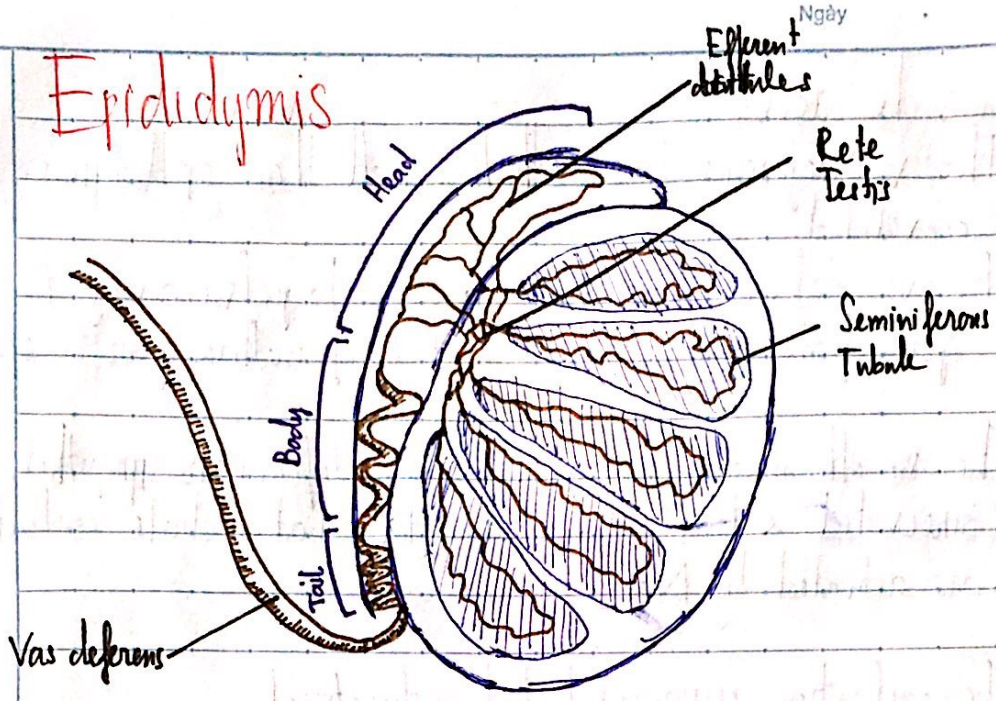
Epididymis



- The epididymis is located at the posterior side of the testis, has 3 sections:
  - Caput epididymis (Head)
  - Corpus epididymis (Body)
  - Cauda epididymis (Tail)

- The head & tail have ciliated spontaneous contractile cells lining the lumen which moves the sperm forward at constant rate
  These 2 sections also where sperm maturation occurs

- The tail of epididymis is where the mature sperm is stored
  This region is surrounded by sympathetically innervated smooth muscle, which plays a role in ejaculation

- Both the testes & the epididymis operate at a lower temp. than human body temp.
  - Spermatogenesis : 35°C
  - Cauda epididymis : 32°C

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Vas deferens

- The vas deferens has a thicker wall than epididymis, and is not convoluted.

The vas deferens runs from scrotum to pelvic cavity to carry sperm from storage site to the base of urethra prior to ejaculation

- The smooth muscle surrounding the vas deferens is sympathetically innervated & has α_1 - adrenoceptors that mediate contraction & are activated by NA

The contraction is powerful but unidirectional.
This is the tube which is cut in a vasectomy to cause sterility.

Semen

- Glandular secretions from prostate & seminal vesicle contain: proteolytic enzymes, acid phosphatase, Zn, citric acid, prostaglandins.

The sperm are suspended in the seminal fluid → semen

- Function of semen:
  - Nutrition
  - Buffers for protecting sperm from acidic vaginal secretion
  - Chemicals that ↗ sperm motility
  - Bulbourethral contributes a small volume of lubricating mucoid secretion

Aging

- As men age, the glands continue to secrete testosterone
  → continue to stimulate
  → ongoing growth to accessory organs

Thứ
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→ Based on anatomy, the growth of these organ could lead to the dysfunction of urinary system, especially prostate.
→ BPH.

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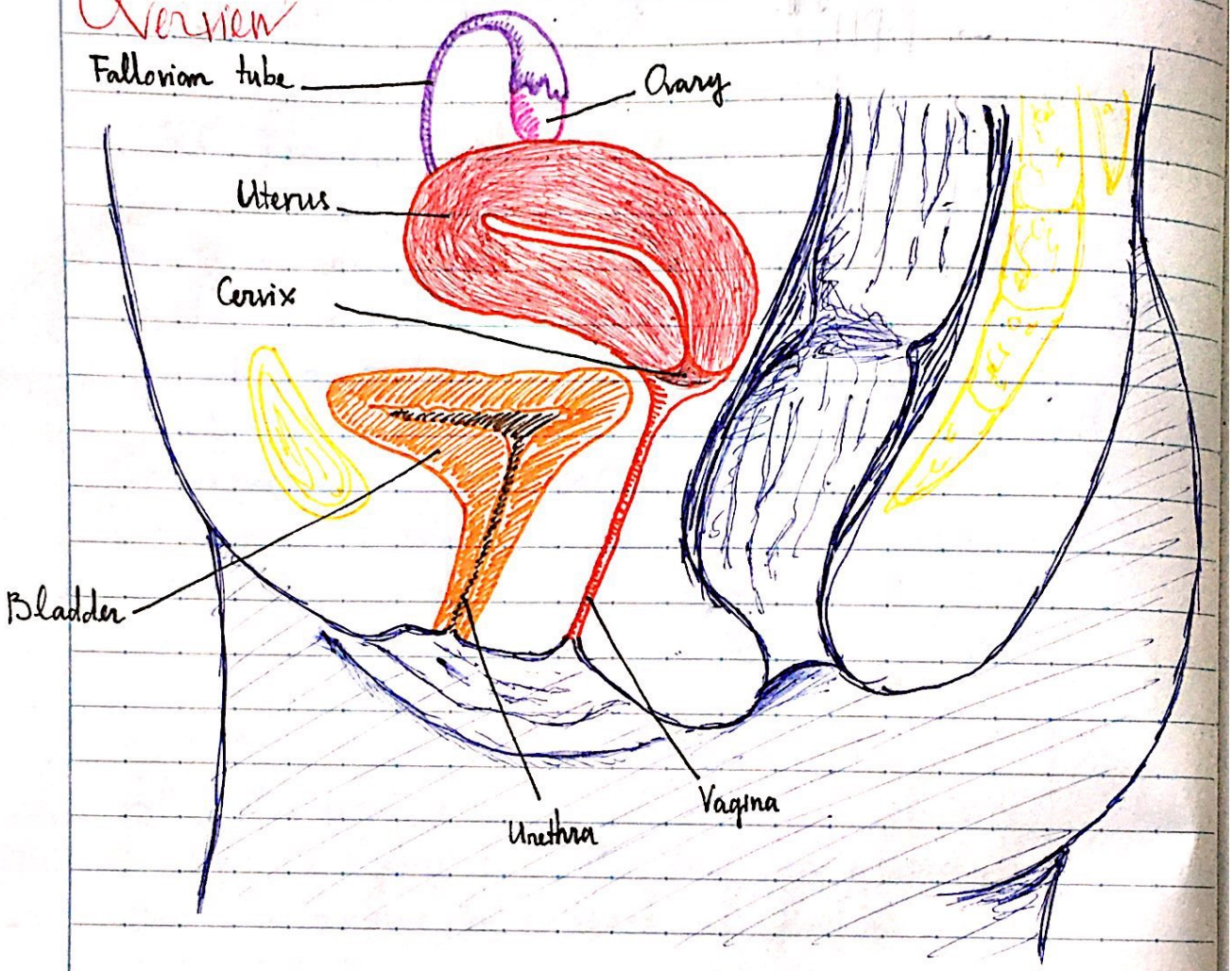
II) ♀ Reproduction

Overview



- The ♀ reproductive system includes 2 ovaries & the ♀ reproductive tract - 2 fallopian tubes (oviducts), the uterus, cervix & vagina

Unlike in ♂, the urinary & reproductive system are separate from each other.

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♀ reproductive physiology

- At birth, the ovaries already contained 2-4 million eggs
  During gestation, the fetal ovaries generated these eggs through oogenesis
  Within the ovary the eggs are contained within a structure known as follicle.
  However, only about 400 eggs will be ovulated during a woman's lifetime
  → By age 50 there will be no more eggs remained.

Ovarian functions

- Like the testis in ♂, there are several functions
  - Oogenesis – production of gametes during fetal period
  - Maturation of oocytes
  - Ovulation – expulsion of mature oocytes
  - Secretion of ♀ sex hormone (estrogen & progesterone) as well as inhibin

∽ Oogenesis

- During early age in utero development, the primitive germ cells, or oogonia (same as spermatogonia in ♂), which undergo numerous mitotic divisions for 3 months after conception

- During fetal life, all oogonia develop into primary oocytes which then begin their meiotic divisions by replicating DNA.
  However, they don't complete the division in the fetus.
  → Stay still : meiotic arrest.

* egg refers to germ cells at any stages

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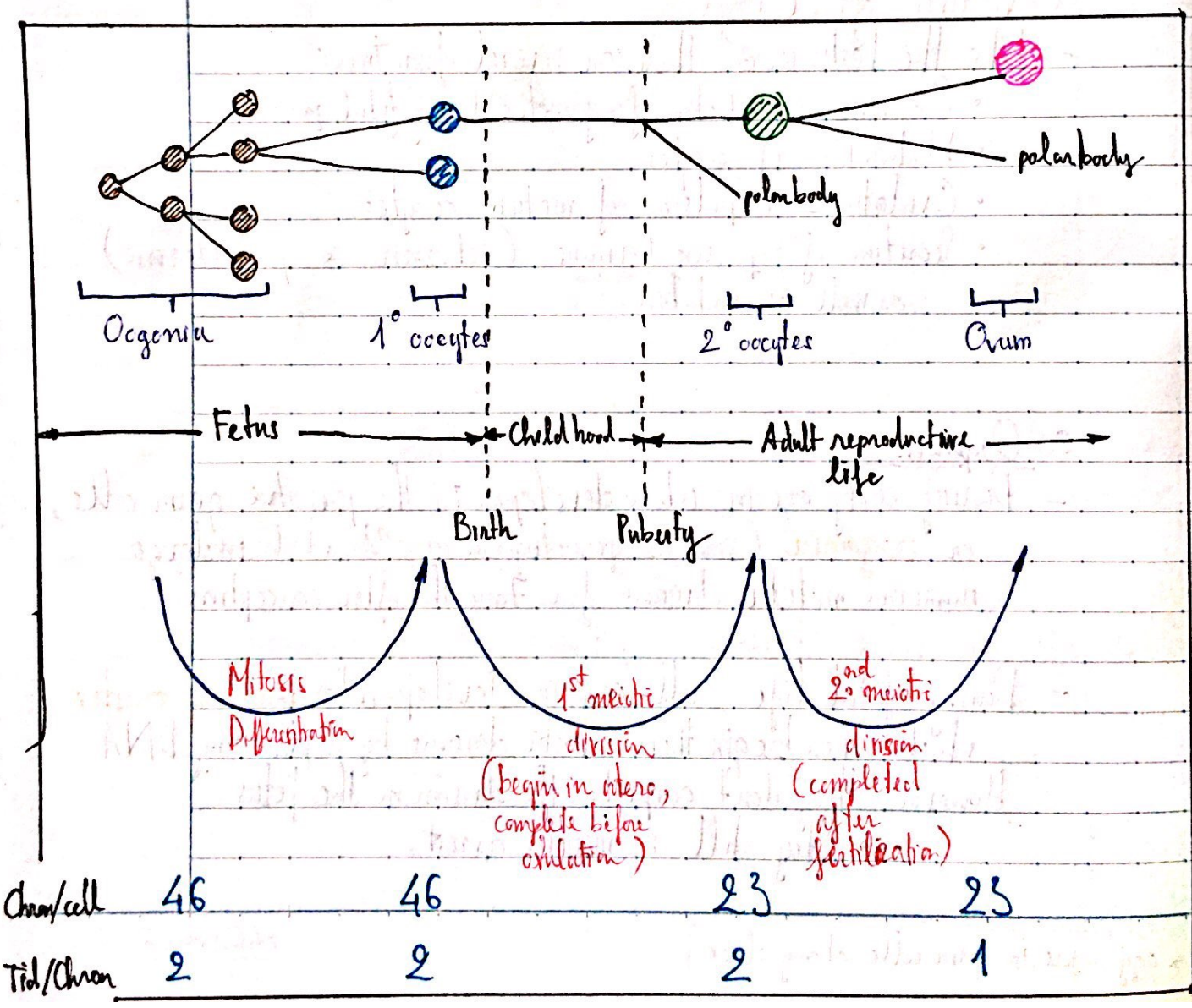
- This state continues until puberty & the onset of renewed activities in the ovaries.
The primary oocyte divides into 2 **secondary oocytes**, but 1 of the daughter cells retains all the cytoplasm virtually. The other cell will become the first **polar body**

- The second meiotic division is exactly the same, occurs in the fallopian tube after ovulation, but only if the secondary oocyte is fertilized (penetrated by a sperm)
The process will create an **Ovum** and again the second polar body.



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∞ Follicle growth

- Throughout their life in the ovaries, the eggs exist in structures called **follicles**, which begin as **primordial follicles**, which consist of a 1° oocyte surrounded by a single layer of cells called **granulosa cells**.

- Further dev of primordial follicle stage is characterized by an ↑ in oocyte size, proliferation of granulosa cells & the separation of the oocyte from the granulosa layer by the material called **zona pellucida**
The granulosa cells secrete estrogen, small amount of progesterone just before ovulation & inhibin
Despite the zona pellucida, the granulosa cells still form gap junction w/ the oocyte for nutrients, chem mess.

- As the follicle grows, connective tissue cells surrounding the granulosa cells diff → form 2 layers called **theca**, which play important role in estrogen secretion by granulosa cells.
Shortly after this, the oocyte reaches the full size, & a fluid-filled space begins to form, the **antrum**

- Beginning of each menstrual cycle, some preantral & early antral begin to dev into larger antral follicle, and only 1 dominant follicle continues to dev.
The other follicles undergo **atresia**, or apoptosis

- The dominant follicle enlarges & became a **mature follicle**.
The oocyte is separated from follicular wall by **cumulus oophorus**

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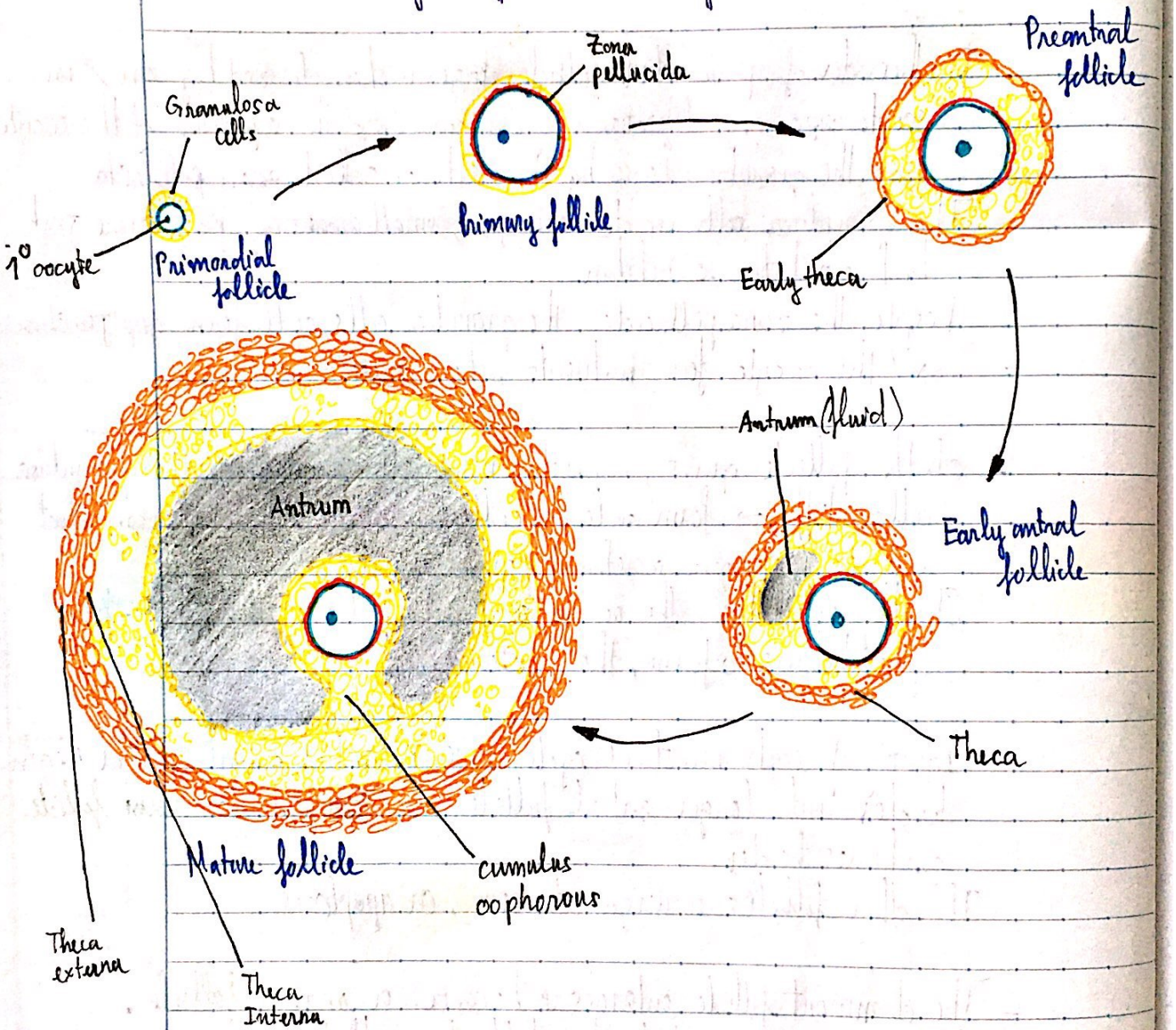
- Ovulation occurs when the thin wall of the follicle & ovary ruptures at the site where they join.
The 2° oocyte, surrounded by zona pellucida & granulosa cells & the cumulus, is carried out of the ovary & onto the ovarian surface (day 14 of menstrual cycle)



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~ Formation of Corpus Luteum

- After the mature follicle discharges its antral fluid & egg, it collapses around the antrum & undergoes rapid transformation. The granulosa cells enlarge & the gland-like structure formed is called corpus luteum which secretes estrogen, progesterone & inhibin

- If the egg (now in fallopian tube) is not fertilized, the corpus luteum reaches its max dev. in 10 days & the degenerate rapidly.

- The loss of corpus luteum function → menstruation & new cycle.

~ Site of Synthesis of Ovarian Hormones

- Ovarian hormone synthesis site can be summarized:
  - Estrogen: by granulosa cells & release into the blood during follicular phase
    after ovulation, synthesized by corpus luteum
  - Progesterone & others: small amount by granulosa cells just before ovulation but the major source is corpus luteum
  - Inhibin: both granulosa cells & corpus luteum.

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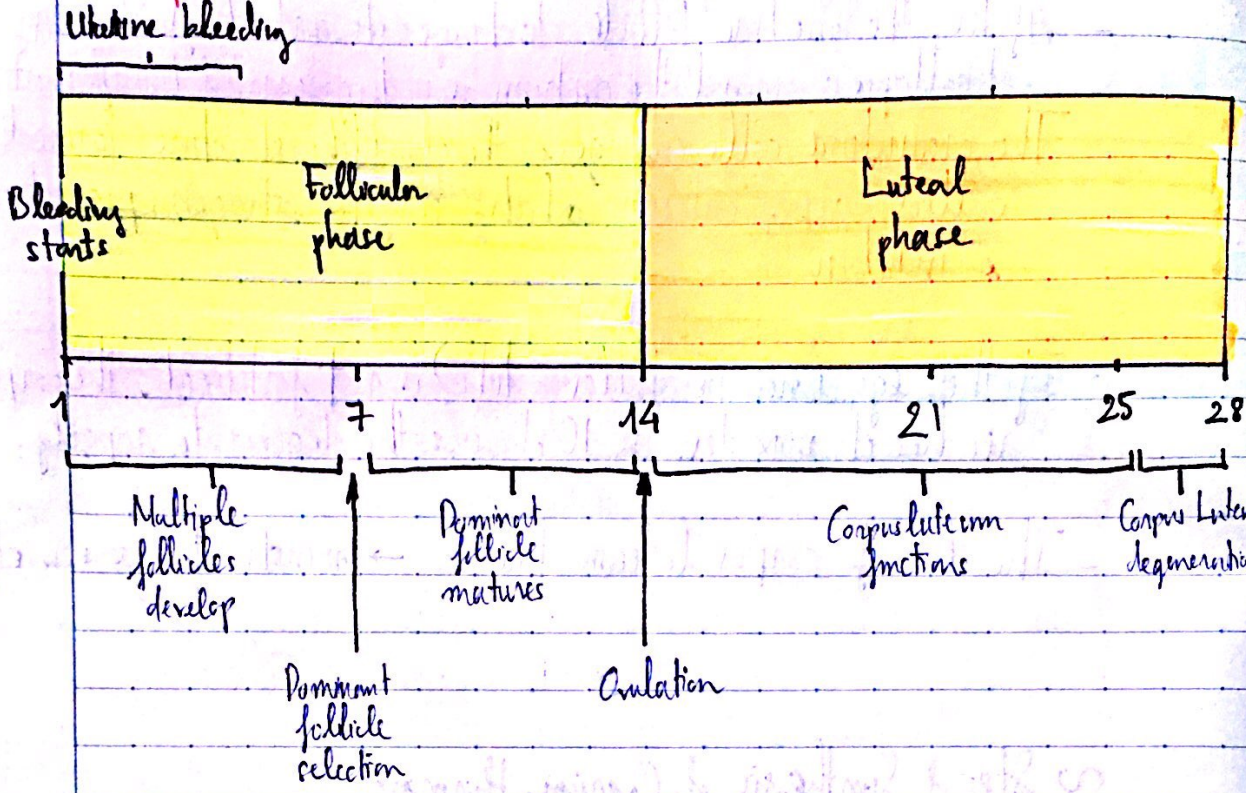
Steps in ovulation



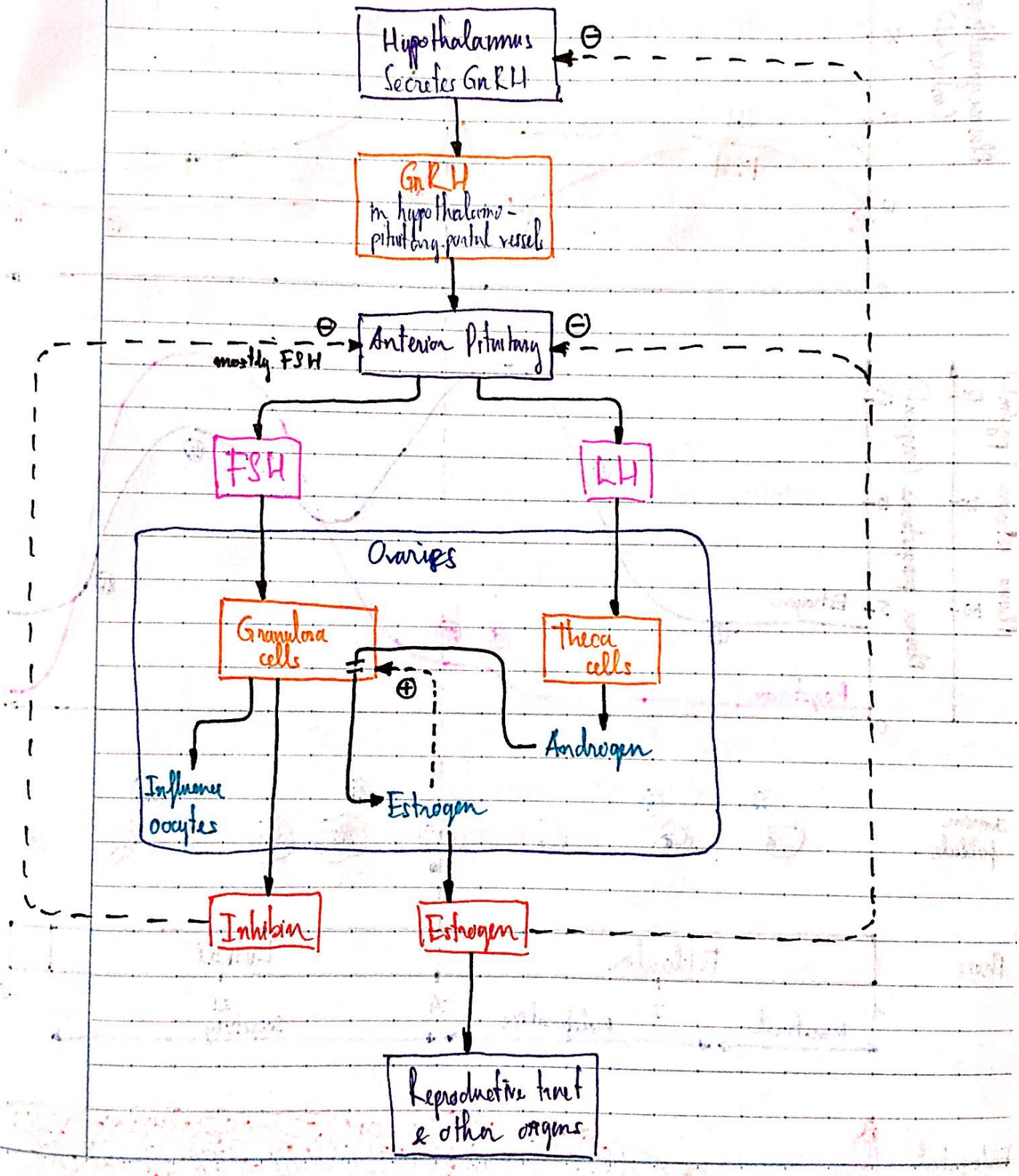
- The ovulation event marks the fertile period when the egg is available to be fertilized.

Selection of dominant follicle

- The dominant follicle survives while the others degenerate due to the ↗ sensitivity to FSH (produced from anterior pituitary). As FSH concentration ↘ in this event, the follicles that cannot response to FSH start to undergo atresia
  → 1 left is the dominant one

- The dominance in response to FSH is due to the ↗ number of FSH receptors.

- There is a parallel process with LH but FSH is thought to be more important in this process.



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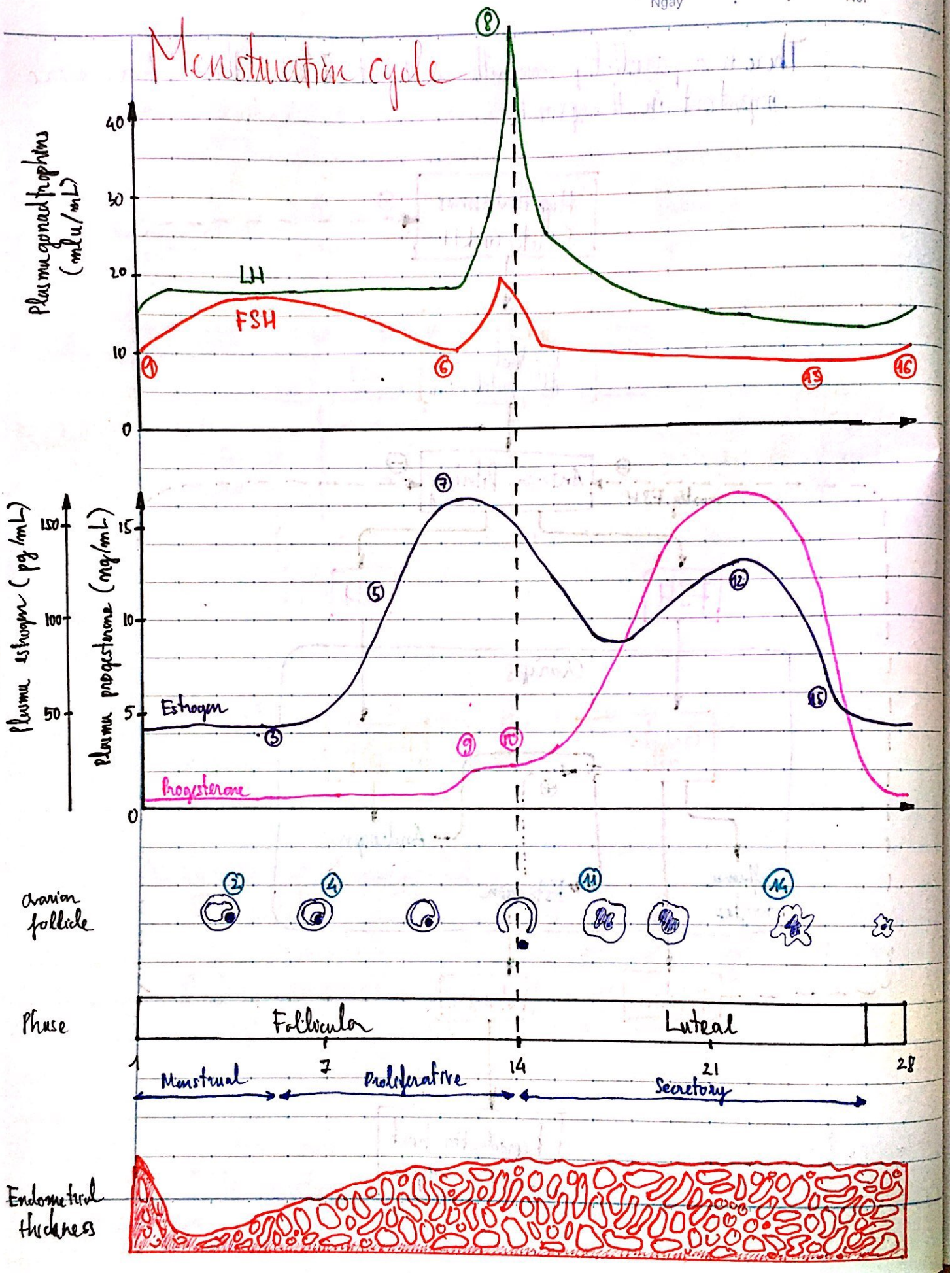
Menstruation cycle



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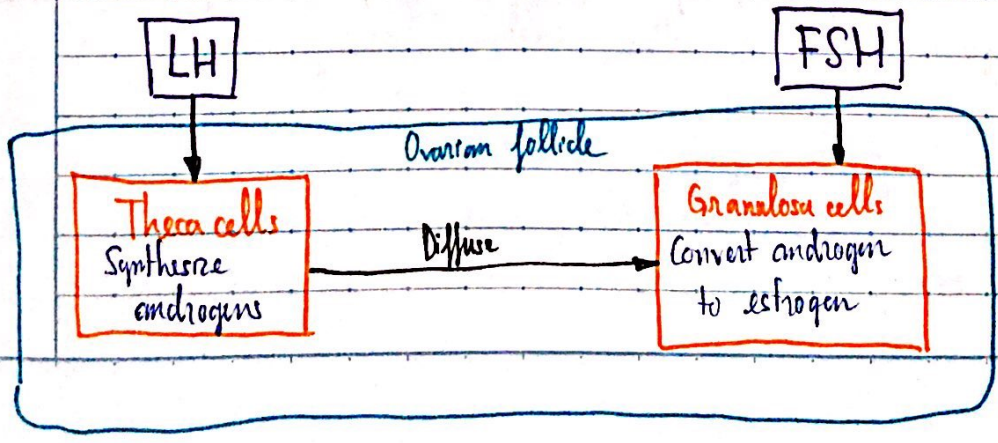
1. FSH & LH secretion ↗ (low plasma conc. → little negative feedback)
2. Multiple antral follicles enlarge & begin to secrete estrogen
3. Estrogen levels ↗
4. 1 Dominant follicle is selected & secretes very large amount of estrogen
5. Estrogen levels keep increasing
6. First, FSH level decrease to cause atresia of non dominant follicle
7. Bat then, increasing estrogen cause a "positive" feedback on GnRH secretion
8. An LH surge is triggered.
9. The egg completes its first meiotic division & maturation while the follicle secretes less estrogen & a bit of progesterone
10. Ovulation occurs
11. The corpus luteum forms & secretes large amount of estrogen & progesterone
12. Plasma estrogen & progesterone ↗
13. FSH & LH secretions are inhibited → plasma concentration ↓
14. The corpus luteum starts to degenerate → less secretion
15. Plasma estrogen & progesterone ↘
16. FSH & LH start to ↗ → new cycle

- During mid-to-late follicular phase, the granulosa cell require help to produce estrogen because they are deficient in enzymes that are needed to produce the androgen precursors of estrogen.
  → Aided by theca cells.



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~ Uterine changes in menstrual cycle

- Can be divided into 3 phases: menstrual, proliferation & secretory.

Menstrual phase:

- Characterized by the degeneration of endometrium.
  → menstrual flow
- The decrease of estrogen & progesterone levels causes a constriction of uterine blood vessels, leading to diminished supply of O_2 & nutrients to endometrial cells.
  → Disintegration of endometrial lining (except the basal lining)
- The uterine smooth muscle undergoes rhythmical contractions to help expel the disintegrated cell
- After initial constriction, endometrial arterioles dilate.
  → Hemorrhage

Proliferative phase:

- The endometrium regenerates under the influence of estrogen. The smooth muscle of the uterus also grows

Secretory phase

- Soon after ovulation, the corpus luteum is formed & secretes estrogen & progesterone under low, but adequate, levels of LH

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Some problem w/ ♀ rep. system

∿ Dysmenorrhea

- Or menstrual cramps, is due to the over production of prostaglandin, leading to excessive uterine contraction.
- Normally { progesterone inhibits the contraction of myometrium
  estrogen & prostaglandin promote contraction
  to prevent the egg from being washed off.
- Prostaglandin could potentially show effect elsewhere
  → cause nausea, headache, vomiting...

∿ Premenstrual tension (PMT, PMS or PMDD)

- These terms are used to describe transient distressing physical & emotional symptoms appearing prior to menstrual flow
- Including: painful, swollen breasts, headache, backache, depression, anxiety ....
  and thought to be mediated by the interplay between sex steroids & brain neurotransmitters

Summary of effects of estrogen & progesterone

∿ Estrogen

- Stimulates growth of ovary & follicles (local effects)
- Stimulates growth of smooth muscle & proliferation of epithelial lining of rep. tract
- Stimulates external genitalia growth, particularly during puberty
- Stimulates breast growth
- Stimulates ♀ body configuration during puberty
- Stimulates fluid secretion of sebaceous glands
- Stimulates bone growth & ultimate cessation of bone growth
- Vascular effects

- Has feed back effect on hypothalamus & anterior pituitary
- Stimulates prolactin secretion but inhibit prolactin's milk-induction effect on breasts
- Protects against atherosclerosis by effects on plasma cholesterol, blood vessels & blood clotting
- Increases myometrial contraction & responsiveness to oxytocin
- Stimulates secretion of cervical fluid
- Increases contraction & ciliary activity in the fallopian tube

∿ Progesterone

- Converts the estrogen-primed endometrium from actively secreting tissue suitable for implantation of embryo
- Induces thick, sticky cervical mucus
- Decreases contraction of fallopian tube & myometrium
- Decreases proliferation of vaginal epithelial cells
- Stimulate breast growth, particularly in glandular tissue
- Inhibits milk-inducing effect of prolactin
- Has feedback effect on hypothalamus & anterior pituitary (inhibit)
- Increase body t°

Androgens in ♀

- Present in blood as a result of production by the adrenal glands & ovaries
- Stimulating growth of pubic hair & axillary hair & skeletal muscle
- Also maintain sex drive

- Excess androgens in ♀ may cause the fat distribution pattern to disappear & the skeletal muscle mass to enlarge

May also cause the appearance of ♂ characteristics.