General Physiology

Cell Membrane

02:00

- Singer Fluid Mosaic Model
- Contents: Proteins >> Lipids
- Lipids include all except triglycerides.

- Main: Phospholipids –
  - Bilayer
  - Polar head [$PO4^{2-}$: Hydrophilic] and non-polar tail [Hydrophobic].

- Proteins: Integral, peripheral and extrinsic proteins.
- Lipids help in integrity, fluidity (unsaturated FA) & solubility (lipid soluble non-polar substances can easily cross cell-membrane).

- Non-polar water-soluble substances use proteins:
  1. Ions → Channels via pumps (ATP)
  2. Aquaporins
  3. Carriers for solutes. Eg: GLUT
  4. Receptors for PPs, NTs etc.
  5. Antigens. Eg: MHC I, II, ABO and Rh system

- 60% of body weight is total body water:
  - ICF: 2/3rd
  - ECF: 1/3rd

- ECF is further divided into:
  - Plasma (25%)
  - Interstitial Fluid (75%):
    - Between cells and vessels
    - All exchange occurs here = internal environment Or Milieu interieur (Claude Bernard)
    - Make lymph
    - Increased fluid → Edema
  - Interstitial fluid is same as plasma except plasma proteins.
  - All plasma proteins are produced by liver except Ig (Gamma globulins) produced by plasma cells.

- **Homeostasis**: Maintenance of internal environment:
  - W.B Cannon: Eg – BP, pH, temperature and regulation.
  - 2 types:
    - Feedback: After value change (Most common)
    - Feed forward: Anticipatory control – Correction occurs before change (Less accurate). Eg:
      - Temperature regulation
      - Motor control
  - Gain = $\frac{Correction}{Error}$
  - Infinite gain, zero error: Eg – Kidney's volume control.
  - Negative feedback: Stimulus and response are in opposite direction. Eg: Increased BP → Baroreceptors decrease BP; Decreased sodium → Aldosterone increase BP.
  - Positive feedback: Stimulus and response are in same direction. Eg: Milk ejection, Clotting pathway.

- **Volume estimation:**
  - Dye dilution method: $Volume = \frac{Amount\ of\ Dye}{Concentration}$ (Minus amount excreted)
    i. Dye leaks out: Decreased concentration → False high volume
  - Total body water = Heavy water (D_2O, T_2O), Amino or antipyrine.
  - ECF: Dye should not enter cell. Eg: Inulin (GFR), Sucrose, Mannitol
  - Plasma: Radiolabelled albumin, Iodine (I125 or I131) or Evan's blue dye.

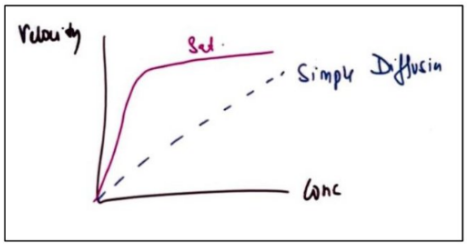
- **Transcellular fluid:**
  - Part of ECF
  - Fluid in body cavities
  - Total: 1 Litre
  - Eg: Pleural fluid, CSF, etc.

- **Transport across cell membrane:**

Active	Passive
Against gradient	Along gradient
Low to high/uphill	High to low/Downhill
Head energy	No energy
Direct use of ATP	Indirect use (Via pumps)
Eg: Pumps	Eg: Osmosis & diffusion ○ Sodium symport/antiport ○ Na^+ glucose symport SGLT ○ Na^+ amino acid symport

- Diffusion: It is of 2 types:

Simple	Facilitated
No carrier	Carriers to increase rate (V_{max})
Eg: O_2, CO_2 diffusion	Eg: GLUT
○ Won't follow	But V_{max} depends on number of carriers → Saturated ○ Follows saturational kinetics

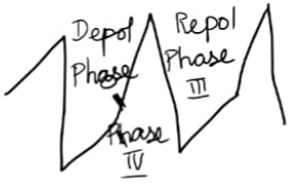


- **Cell junctions:**
  1. Gap junctions: Connexins –
     - Electrical synapses
  2. Tight junctions:
     - Made of Claudin and Occludin
     - In BBB, kidneys
     - Also called zonula occludens
  3. Desmosome & hemidesmosomes:
     - Desmosomes: Cement connecting adjacent cells
     - Hemidesmosomes: Connect basal lamina

CVS - Part 1

PACEMAKER

- Pacemaker is the SA(sinoatrial) node because it has maximum frequency of AP(action potential) genesis
- It has pacemaker or pre-potential phase IV so, pacemaker due to
  - Closure of potassium channels which creates the upward slope
  - Funny/leaky sodium channels
  - Calcium t channels

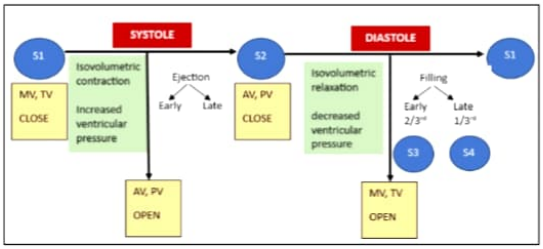


Depol- depolarization
Repol- repolarization

- The slowest conduction is AV node and produce AV delay of 0.1sec

CARDIAC CYCLE - 0.1SEC

04:00



MV- mitral valve TV- tricuspid valve AV- aortic valve PV- pulmonary valve

JUGULAR VENOUS PRESSURE

06:17

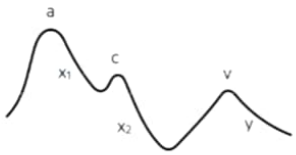
a- Atrial systole

c- Isovolumetric contraction which causes tricuspid bulging into the atria

x- Atrial relaxation

v- Atrial filling

y- Atria empty-when tricuspid valve open



VOLUME CHANGES

08:18

END DIASTOLIC VOLUME (EDV)

- Volume filled during diastole
- Normal value is 120ml
- Depends on venous return (VR)
- Factors that help to maintain VR/Increase VR
  - Inspiration,
  - Supine position,
  - Sympathetic venoconstriction (α1),
  - Calf muscles,
  - Deep fascia
  - Venous valves
- Increase in EDV would increase load on ventricle before contraction. Hence called as preload

STROKE VOLUME (SV)

- It is blood ejected per beat
- Normal is 70-80ml

EJECTION FRACTION (EF)

- Percentage ejected per beat
- Normal is 65%
- Ejection fraction = $\frac{\text{Stroke volume}}{\text{End diastolic volume}} \times 100$

$$EJ = \frac{SV}{EDV} \times 100$$

END SYSTOLIC VOLUME (ESV)

- Blood left after ejection
- End systolic volume = End diastolic volume - stroke volume

ESV = EDV -

CARDIAC OUTPUT (CO)

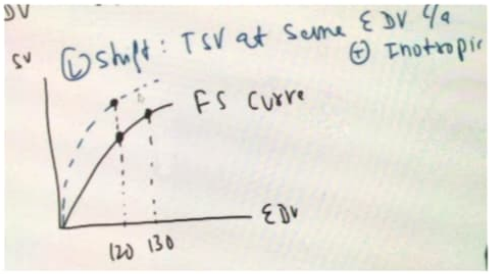
- Blood pumped by each ventricle per minute
- Cardiac output=Stroke volume × heart rate

CO = SV × HR

FRANK STARLING (FS) LAW

13:22

- SV can be increased by Frank Starling (FS) law
- It states that end diastolic volume is proportional to stroke volume



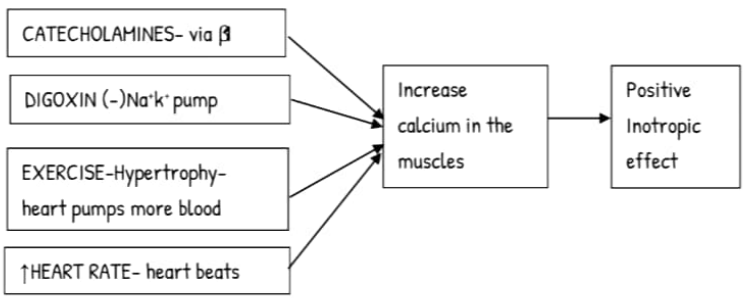
EDV ∝SV

Left shift- increased stroke volume at same EDV. It is called as positive ionotropic effect

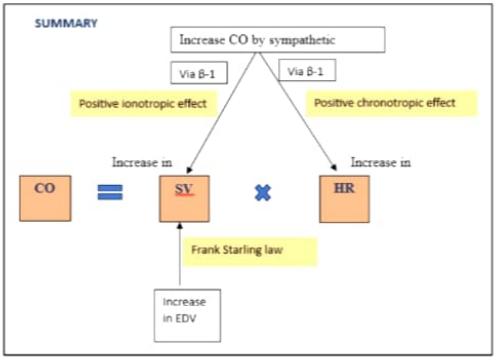
Ionotropic- increase in calcium

Ionotropic agents

- Catecholamines- act through β1 and increase calcium in the muscles- more calcium=> more contraction
- Digoxin- inhibit sodium potassium pump=> increase calcium in the muscles
- Exercise- hypertrophy- enable heart to pump more blood
- Increased heart rate=> calcium accumulation because heart is beating very fast
  - This is called 'treppe' or 'staircase' effect



SUMMARY



BLOOD VESSELS AND THEIR FUNCTIONS

VESSEL	NAME	PROPERTY	FUNCTION
Aorta	Wind Kessel vessel	Elastic recoiling	Creates diastolic pressure and flow
Arteriole	Resistance vessel	Have maximum smooth muscle	Control blood flow
Veins	Capacitance vessels	High stretchability/ compliance	Stretch and store blood (50-60%)c
Capillaries	Exchange vessels	Permeable Minimal velocity Minimal diameter Laminar flow	For exchange Have low resistance due to parallel arrangement

BLOOD FLOW REGULATION

24:05

$$\text{Flow} = \frac{\text{Pressure gradient (P)}}{\text{Resistance (R)}}$$

Any organ can control its own flow with resistance, it is called as autoregulation.

CVS Part 2

- Skeletal muscles have minimum flow at rest. So, offer maximum resistance, main site of peripheral resistance.
- During exercise, the blood flow increases to skeletal muscles to 20-40 times (Maximum flow in body).
- $F = \frac{P\ (increased\ by\ sympathetics: Increased\ SBP, HR, CO, SV)}{R\ (Decreased\ by\ vasodilation\ by\ local\ metabolites)}$

- **Local metabolites:**
  - Lactic acid
  - Substance P
  - Increased Temperature
  - Decreased pH
  - Increased potassium
  - Increased pCO_2
  - Hypoxia
  - Adenosine
  - ADP

  } Metabolic theory of autoregulation

$$R = \frac{8nL}{\pi r^4}$$

- N = viscosity
- L = Length of vessels
- R = Radius – Most important due to 4th power effect. Eg: Double radius/ increased r by 2 times → Resistance is decreased by 16 times (2^4)

Blood Pressure *07:08*

- BP estimation is by Bernoulli's theorem: Potential/Pressure energy + Kinetic energy is constant.
- BP cuff occlude artery and make KE = zero.
- Best method for BP estimation: Intraarterial Catheter BP recording. It is less used as it is invasive.
- Sphygmomanometer: Less accurate but most used as it is non-invasive in nature.

- BP cuff compress brachial artery and produce turbulent flow with Korotkoff sounds:
  - Start: SBP
  - Disappear: DBP

- **Normal SBP**: 120 mmHg
  - Due to ventricular contraction
  - Mainly depends on CO

- **Normal DBP**: 80 mmHg
  - Due to elastic recoil
  - Mainly depends on Peripheral resistance

- BP = CO x PR

- **Pulse pressure**: SBP-DBP
  - Normal: 40mmHg

- **MBP**: Normally 95-98 mmHg
  - It is average pressure during cardiac cycle
  - MBP = DBP + 1/3rd PP OR
  - MBP = 2/3rd DBP + 1/3rd SBP

CVS Regulatory Centre *16:48*

- **It is of two types:**

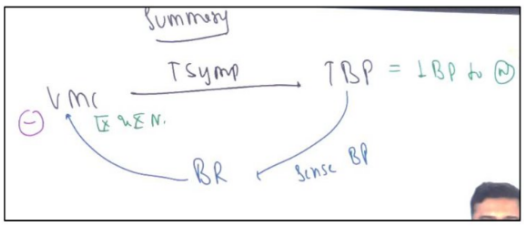
A. VMC (Vasomotor centre)
   - Increases sympathetic outflow: Increases SV, CO, BP, HR

B. CVC (Cardiovagal centre):
   - Increases parasympathetic by vagus
   - It is NTS + NA
   - It inhibits heart via M_2 receptors
   - Decrease SV, CO, BP, Conduction (negative dromotropic effect), excitability (negative bathmotropic effect)

- **Baroreceptors**:
  - Present in aorta (aortic sinus BR) [X nerve] and carotid artery (carotid sinus BR) [IX nerve]
  - Stretch receptors
  - Tonically active
  - Increased BP → Increased BR activity

- They are most sensitive to PP changes but mainly regulate MBP in range of 60-180 mmHg.
- BR mainly act by negative feedback.
- Never increase BP but always decrease BP and HR by stimulating CVC and inhibiting NTS.

- Summary:



CVS reflexes 25:04

1. Bain Bridge reflexes:
   - IV fluids increase heart rate by increased sympathetic flow via atrial stretch receptors.

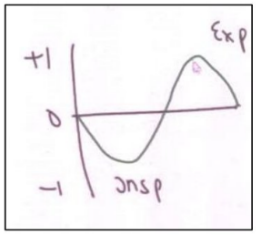
2. Bezold Jarisch reflex:
   - IV irritants (Eg: Capsaicin, Veratridine, 5-HT) act via Ventricular chemoreceptors on Vagus → Decreased HR, BP and cause apnea.

3. Marey's law: BP is inversely proportional to HR.
   - Eg:
     (i) In shock: Decreased BP → Decreased BR and sympathetic stimulation → HR increases.
     (ii) Cushing reflex: Increased ICP: Increased BP → Increased BR and parasympathetic activity → Decreased HR → Reflex bradycardia

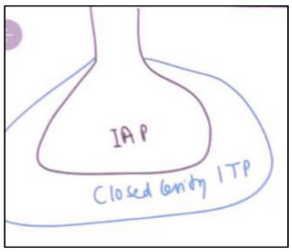
Respiration Part 1

- **Boyle's law:** Pressure is inversely proportional to volume if number of gas molecules are same.
  - Inspiration is active, use muscles: Diaphragm (>5%) and external intercostals (25%): Expand thorax and decrease pressure.
  - Expiration is of two types:
    a. Normal: Passive due to recoil of the lung
    b. Forceful: Active - Use abdominal muscles and internal intercostal muscles → Reduce thorax and increase pressure.

- **Pressure in cavity: Intra-alveolar pressure -**
  - Open pressure
  - IAP at rest: 0/760 mmHg
    - During inspiration: -1/759 mmHg
    - End Inspiration: 0/760 mmHg
    - During expiration: +1/761 mmHg
    - End of expiration: 0/760 mmHg



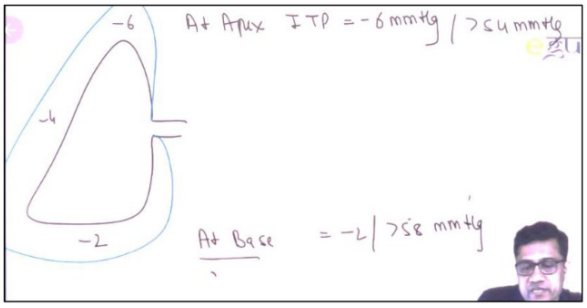
  - Intrapleural pressure:
    - Closed cavity
    - Always negative at rest due to opposite recoil of lungs and thorax. → expand pleural cavity and create negative ITP. And maintained by lymphatic drainage.
    - This negative ITP prevent lung collapse at rest from inward recoil of lungs.



- In open pneumothorax, air enter and ITP is zero as pleural cavity is open cavity.
- Unopposed inward recoil will collapse lung.

- **ITP changes in respiration:**
  1. At rest: -2 mmHg (-3 cmH_2O)
  2. Quiet normal inspiration: - 6 mmHg
  3. Quiet normal expiration: -2 mmHg (return to normal)
  4. Forceful inspiration: - 20 mmHg
  5. Forceful expiration: +30 mmHg

- **Variation of ITP due to gravity:**
  - Due to gravity, maximum ITP is at dependent part of lungs.



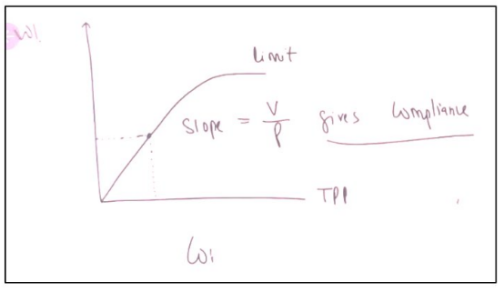
  - Apex: Big but fewer alveoli
  - Base: Small but numerous alveoli → Majority of air shifts to base: Maximum ventilation despite high ITP.

- Trans pulmonary pressure (TPP) = IAP – ITP
  - At rest: 0 – (-2) = 2
  - Inspiration: -1 – (-6) = +5
  - Open pneumothorax: 0 – 0 = 0

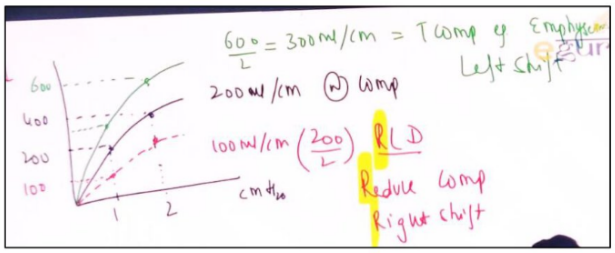
Respiration (Part-1)

Topic Notes: 5

- Lung volume is directly proportional to TPP.
- Volume pressure graph use TPP:



- Compliance = Stretchability
  - Normal elastic lungs = good compliance and recoil.
  - Emphysema: increased compliance due to loss of elastic fibre. Increased compliance → Poor recoil → poor expiration → air trapping
  - Restrictive Lung disease: Poor compliance is hallmark.
  - Compliance = $\frac{\Delta V}{\Delta P}$



  - Normal compliance value:
    - Lungs alone: 220 ml/cmH_2O
    - Lungs and thorax: 130 ml/cmH_2O [Thorax reduces the compliance due to inelastic structures it contains.

- Static compliance: patient holds breath → Just record ΔV & ΔP.
  - It is not affected by airways.
  - Hence static can be normal in obstructive lung disease.

- Dynamic compliance: ΔV & ΔP during inspiration and expiration.
  - Depend on airways also.
  - Hence, dynamic compliance will reduce in obstructive lung disease also.

- Summary:
  - Static:
    - Decreased: RLD
    - Increased: Emphysema
    - Normal → Record dynamic:
      - Normal: Healthy
      - Decreased: Old

Static	Dynamic
Single curve	2 curves: expiration and inspiration → Hysteresis curve → work done by area under curve.
	Expiration has more compliance: Difference due to surface tension. Saline filled lungs: decreased ST → Increased compliance and difference is reduced: Left shift

- **Surface tension**: Inward collapsing force, max at air-fluid interaction. → Surface tension will try to collapse alveoli and pull fluid causing pulmonary edema.

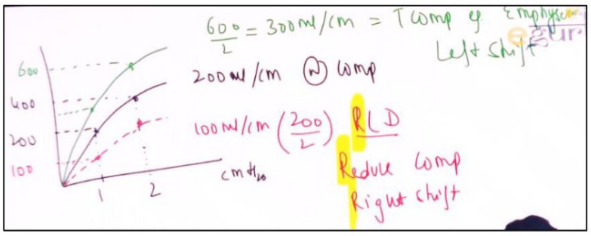
- **Surfactant**: Decrease surface tension by decreasing air-fluid interaction.
  - It is produced by type II pneumocytes and Clara cells.
  - 70% are phospholipids: Main is DPP [Dipalmitoyl Phosphatidyl Choline/ Lecithin]
  - **L/S ratio:**
    - >2: indicate lung maturity and decreased risk of RDS.
  - Production of surfactant: 18-20 weeks of IU life
  - Secretion and action: 28 weeks → <28 weeks: Maximum RDS risk
  - Maximum at 34-35 weeks
  - Mainly by steroids (sex and glucocorticoid [main]), thyroid and prolactin.
  - **Surfactant action:**
    1. Decrease surface tension
    2. Prevent collapse: Atelectasis and pulmonary edema
    3. Increased compliance
    4. Decreased work of breathing
  - Preterm babies: decreased surfactant → RDS/ Hyaline membrane disease

Respiration (Part-1)

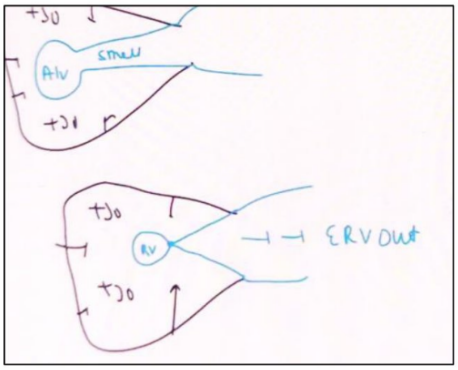
Topic Notes: 5

Spirometry (PFT) *46:57*

- It records air going in and out of lungs.
- It fails to measure air not coming out. Eg: Residual volume
- Capacity: Sum of 2 or more volumes.

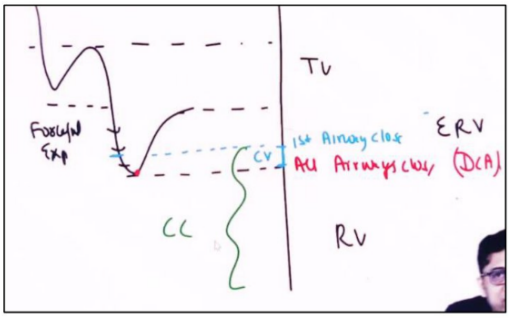


- IC: IRV + TV
- EC: ERV + TV
- RV: air not coming out and left in lungs even after forceful expiration. Normally: 1.2L.
  - Not given by spirometry
  - Also, RV prevent collapse during forceful expiration.
  - RV never comes out due to DCA (Dynamic compression of airways).
  - High ITP during forceful expiration will compress small intra-thoracic airways. So, air gets trapped in alveoli called as RV.



Respiration Part 2

- **Closing volume:**
  - Last part of ERV
  - Start from 1st airway closure in the dependent part of lung
  - When all airway close, CV is over and RV is left
  - CC = Closing Capacity = CV + RV



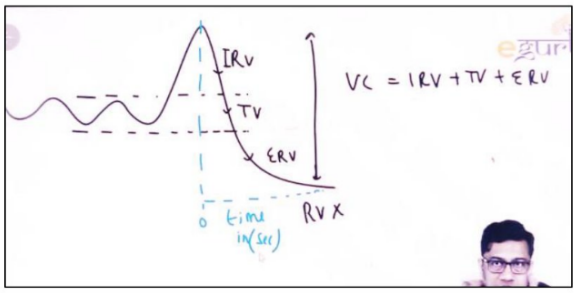
  - CV, RV, CC not given by spirometry
  - We use single breath N_2 washout or Fowler method → Check N2 concentration in expired air. → Best method for dead space calculation. (Earlier: Bohr equation using CO_2 levels)

- **Functional Residual Capacity (FRC):** It is air left in lungs at rest or after normal expiration.
  - FRC = ERV + RV (Normal: 2.5L)
  - Air left after forceful expiration is RV
  - Lung volume at rest: FRC
  - All muscles are relaxed = Relaxation volume
  - TPP pressure at rest = +2mmHg → Relaxation pressure
  - At this pressure and this lung volume (relaxation volume) = FRC → Inward recoil of lungs is equal and opposite to outward recoil of chest wall.
  - Spirometry fails to give FRC. So, we use:
    i. Fowler N2 method
    ii. Helium dilution method

    } Volume = Amount/Concentration

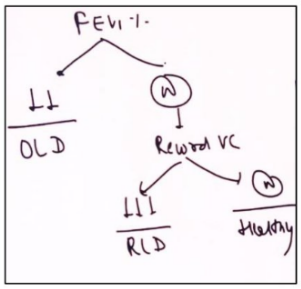
    - Not accurate in old → Prefer plethysmography: P x V is constant

- **Vital capacity**: It is maximum inspiration followed by maximum expiration.
  - It depends on:
    1. Respiratory muscle strength
    2. Compliance of lung



  - Normal VC:
    - Male: 4.8L
    - Female: 3.2 L
  - All values in females are less due to small thorax and less muscle mass.
  - Physiologically Low VC: Old, female children, short, obese, pregnant, supine, etc.
  - VC in diseases:
    - RLD: Decreased VC → due to poor compliance, all volumes are less.
    - OLD: normal VC but increased time/Decreased VC due to air trapping. Eg: Emphysema. Hence for OLD, we use dynamic volume and capacities.

- TVC/FVC = Timed or Forced vital capacity; VC and time taken together.
  - TVC has 2 parts:
    - FEV_1: Air coming out in first second. EG: 3L → FEV1% = ¾ x 100 = 75%
      - Normal FEV1% = 75-80%



- FEV_2
- FEV_3

- **Flow rate:**
  A. PEFR (Peak Expiratory FR): Large airways
     - $FEFR_{0-25\%}$
  B. MEFR (Mid Expiratory FR): Small airways → Gold standard for small airways obstruction.
     - $FEFR_{26-75\%}$
     - Flowrate in middle (26-75%) of forceful expiration

- **Total lung capacity:**
  - Sum of all 4 volumes
  - TLC is directly proportional to lung compliance
  - Eg: Emphysema - Increased TLC, RV, FRC due to air trapping.
  - TLC = IRV + TV + ERV + RV Or IC + FRC Or VC + RV
  - Normal: 6-7 litres
  - Spirometry fails to give CV, RV, CC, FRC, TLC

Ventilation *28:42*

PV (Air going/minute)	AV (Air exchanged per minute)
TV x RR = PV	(TV - Dead space) x RR = AV
Normal: 6L/minute	Normal: 4.2L/minute

- Anatomical dead space: Air not getting exchanged in airways. N: 150ml
- Alveolar dead space = zero
- Total or physiological dead space = anatomical dead space (150ml) + alveolar dead space (0ml)
- Physiological dead space = anatomical dead space

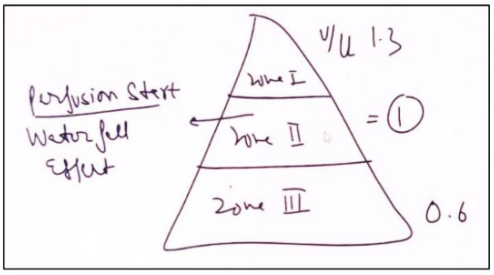
- V/Q ratio → Indicate gas exchange
  - Ventilation: Air/minute
  - Perfusion: Blood/minute
  - If 1 = Ideal V/Q → Best exchange

- If V/Q not equal 1 → V/Q mismatch → Poor exchange, hypoxic hypoxia → Decreased PaO_2 <60mmHg
  - V/Q <1 = Poor ventilation
  - V/Q >1 = Poor perfusion Eg: Pulmonary embolism. Air >> Blood → Air is left unexchanged. → Alveolar/Physiological dead space.
  - Emphysema: High V/Q but still hypoxia persist due to poor gas exchange because of destruction of alveoli and pulmonary capillaries.

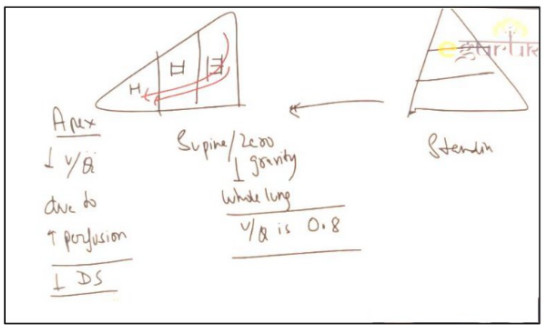
- Normal V/Q of whole lungs = V/Q = AV/ Pulmonary perfusion by RV = $\frac{4.2\ L/min}{5L/min}$ = 0.8

- Apex V/Q = 1.3 (max)
  - Apex: minimum ventilation but V/Q is max due to very poor perfusion

- Base V/Q = 0.6 (min)
  - Maximum perfusion due to gravity
  - Maximum ventilation due to maximum space
  - Despite maximum ventilation, base has least V/Q due to very high perfusion.



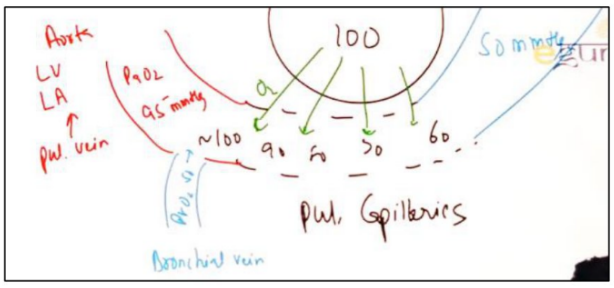
- Apical V/Q >1: Alveolar/Physiological DS present - O_2 left unexchanged → Increased PO_2 in alveoli at apex.
- Hence, TB is most common at apex.



- Pulse pressure: Dalton's law
  - PP = Percentage of gas x Total pressure

Gas	Atm	Alveoli	Venous blood	Arterial blood
pO_2 21%	150-160mmHg	PAO_2: 100%	PVO_2: 40-50	PaO_2 95-98
pCO_2 0.04%	0.2mmHg	$PACO_2$: 40%	$PVCO_2$: 46	$PaCO_2$: 40
PN_2 >8%	590	590	590 (dissolved)	590 (dissolved)

- **Dissolved N_2**: Low pressure = High altitude/Rapid ascent by deep sea diver → N_2 gets precipitated as bubbles → embolism → stroke/MI} → Caisson's disease/decompression sickness.
  - **Treatment**: slow ascent and recompression



  - **PaO_2 <100:** Due to physiological shunt - mixing of pulmonary vein oxygenated blood with bronchial vein deoxygenated blood.
  - PAO_2 - PaO_2 (A-a gradient) = 5-20
    - Increased in membrane defect, R → L shunt and V/Q mismatch

- Diffusion: simple passive diffusion for gas exchange

Respiration (Part-2)

Topic Notes: 6

- **Fick's law:**
  - **Membrane**: Area (A) 70m^2 and thickness (d) 0.5µm → decreased area or increased thickness leads to poor O2 diffusion → Membrane defect: ILD, ARDS
    IOC: DLCO
  - PP → More PP, more diffusion. Eg: O_2 therapy.
  - **Gas**: Molecular weight (MW) and solubility (S) → CO_2 is 20 times faster: more lipid soluble than O_2

- **Fick's law**: rate of diffusion = $k \frac{AS}{d\sqrt{mw}} \; x \; PP \; gradient$

Respiration Part 3

Transport of Gases

00:12

- **CO_2**: 4ml%. It has 3 forms:
  1. Dissolved CO_2: 10% → 0.4ml%
  2. Bicarbonates: 75% → 3ml%
  3. Carbamino form: 15% → 0.6ml%
     - Eg: CO_2Hb

- Bicarbonates get exchanged with Cl^- in RBC of venous blood: Chloride shift/Hamberger → RBC swelling → Increased PCV

- **Oxygen transport**: 5ml% or 250ml/min
  - Arterial blood = 19ml%O_2 (SpO_2 = 100%)
  - Venous (SpO_2 is decreased) = 14ml%O_2

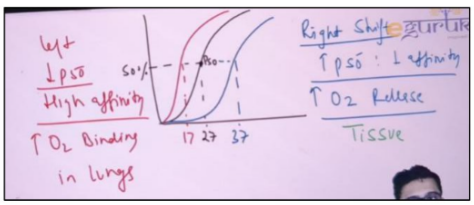
  5ml% Oxygen is taken by tissue
  - Lungs give 5ml% oxygen back.

- 2 forms of transport:

Hb bound oxygen	Dissolved oxygen
1 Hb bind $4O_2$: 98-99%	1-2%
1gm Hb carry 1.33ml O_2 Normal Hb = 14gm% will carry = 14 x 1.33 = 18.7ml% O_2 + Dissolved O_2 = 0.3 ml% O_2 = Total 19ml%	0.3ml%

- **Henry law:** PaO_2 depend only on dissolved oxygen, not Hb bound oxygen.
  - Hence, anemia - decreased Hb; But PaO_2 and dissolved O_2 are normal

- **O_2-Hb Dissociation curve:**
  - **Sigmoidal**: due to relative affinity or cooperative binding
  - Low affinity in start, then it increases as each binding of O_2 increase affinity for next one.



- **Bohr effect**: Right shift release oxygen to tissue. High PCO_2 and H^+ cause loading of CO_2 and unloading of O_2 from Hb.
  - High pCO_2 and decreased pO_2: Hypoxia, exercise, high temperature, high altitude → Increased glycolysis → Increased lactic acid (Acidosis: Decreased pH) and 2-3 BPG

- Haldane effect Left shift binds oxygen in lungs.
  - High pO_2, decreased pCO_2, decreased temperature, increased pH/Alkalosis, decreased 2-3 BPG
  - Stored blood: low temperature causes left shift
  - HbF: 2α and 2γ globin chain (no βchain) → 2-3 BPG bind β-chain of HbA and causes oxygen release. In HbF: No β-chain → No 2-3 BPG binding. → Higher oxygen affinity than HbA. So, HbF can extract O_2 from maternal circulation. Therefore, double Bohr and double Haldane effect occur in placenta.

CO Poisoning *22:44*

- CO has 210 times more affinity for Hb than O_2.
- COHb = Carboxy Hb (Cherry red) → Abnormal Hb form [Anemic hypoxia → It fails to release O2 to tissue (left shift) → Produce death
- CO inhibit Cytochrome P_{450} → Histotoxic hypoxia also. But at 50 times lethal dose.
- Hence, it is mainly anemic hypoxia.

Regulation of respiration *26:37*

A. **Neural**: Respiratory centre
B. **Chemical**: Chemoreceptors

- **Neural control:** Medulla –
  - DRG (Dorsal Respiratory Group of neurons)
    - **I-neurons**: Inspiratory muscles
  - VRG (Ventral Respiratory Group of neurons)
    - Both I and E neurons (Expiratory muscles) → Forceful respiration, exercise, etc
  - **Pacemaker of respiration**: Pre-Botzinger complex [RAMP signal] > DRG Produce automatic involuntary but irregular respiration.
  - Pons make it good volume, smooth and regular respiration → Tuning of respiration

- **Hence**:
  - **Medulla lesion**: respiration stops
  - **Pons lesion**: irregular, shallow

- **Pons**:
  - **Upper**: PC – Pneumotaxic centre: Decreased inspiration and increased expiration by inhibiting apneustic centre.
  - **Lower**: AC – Apneustic centre → Increase inspiration by stimulating I-neurons.
  - If AC is uncontrolled → Too much inspiration and respiration stops in inspiration = Apneusis
  - AC is inhibited by PC and vagus: Prevents apneusis.
  - Midpontine section and bilateral vagotomy = apneusis occurs
  - If either midpoint or bilateral vagotomy = Deep and slow breathing

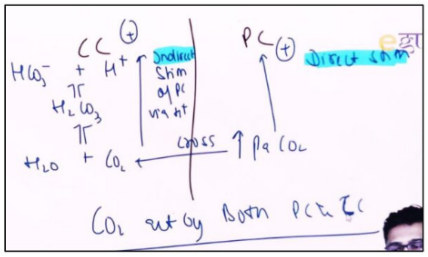
- **2 types of chemoreceptors:**

Central (CC)	BBB	Peripheral (PC)
In ventral medulla: only stimulated by H^+ in CSF		1. Aortic bodies: in Aorta (X nerve) 2. Carotid bodies: in bifurcation of CCA (IX nerve)
		Stimulus: PC sense hypoxia (Decreased paO2 <60mmHg, Increased PaCO2 >37mmHg, Increased H+ – Acidosis) PC contain oxygen sensitive potassium channels in glomus cell-I

- **Hypoxic hypoxia**: Decreased PaO_2 → Less O_2 to PC → Less ATP and K^+ channel close → Depolarization and AP in IX and X nerve → Stimulate respiratory centres: Increased TV & RR → Hyperventilate: Correct hypoxia by increasing PaO_2 and decreasing $PaCO_2$.
- Cyanide poisoning inhibit ETC in PC → Less ATP, K^+ channel close. Cyanide causes histotoxic hypoxia but it stimulates PC directly and maximally despite normal PaO_2.
- PC: Maximum blood flow per 100gm. All O_2 needs are met by dissolved O_2 and not Hb. In anemia as dissolved O_2 is normal, PC are not stimulated.
- All other hypoxia stimulates PC except anemic.
- H+ ion can't cross BBB. H^+ in blood stimulate PC only and H^+ in CSF stimulate CC only.
- O_2 act by PC.

Respiration (Part-3)

Topic Notes: 4



- CC act by both PC & CC. So, CO_2 is main stimulus for regulation of respiration: Hypercapnic drive.

CNS Part 1

- **2 types of cells:**
  A. Neurons:
    - 100 Billion
    - No new neurons except Hippocampus after birth
  B. Glial cells:
    - 1000 Billion
    - Formed new all life.

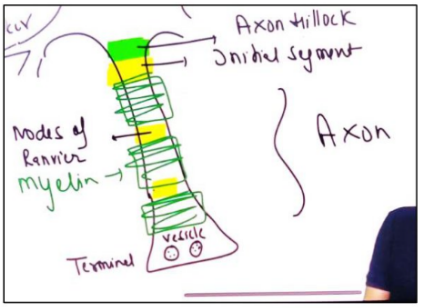
- Glial cells are of 4 types:
  1. Microglia: phagocytosis
  2. Oligodendrocytes: myelin formation in CNS [PNS: myelin formation by Schwann cells]
  3. Ependymal cells: line ventricles
  4. Astrocytes: form BBB along with tight junctions

- CSF is similar to plasma but less concentration of all except Cl^-, Mg^{2+}, HCO_3^-, pCO_2.
- CSF volume: 150ml
- Daily production: 500ml/day or 20ml/hr
- Pressure: 50-130 mmH_2O

- CSF:
  - Secretion: Choroid plexus
  - Absorption: Arachnoid villi

- Nissl Granules: Free Ribosome, make proteins
  - 1st to break (chromatolysis) in neuronal injury, Wallerian degeneration.

- Axon Hillock: AP genesis = Minimum threshold
- Initial segment: Propagation of AP
- Maximum Na^+ channels are present in the nodes.

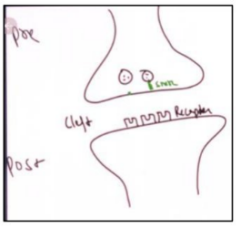


- Axoplasmic transport is of 2 types:
  A. **Rapid**: 200-400mm/day:
     - Molecular motors running on microtubules
     - It is of two types:
       a. Anterograde: Kinesin → Carry neurotransmitter vessels to terminal.
       b. Retrograde: Dynein → Bring empty vesicles back to soma (Virus, toxins)
  B. **Slow**: 20mm/day
     - By microtubules → Polymerization
     - Anterograde

Synapses *13:17*

Electrical	Chemical
Fast	Slow, synaptic delay of 0.5 msec
Gap junction	Neurotransmitters → receptors
Bidirectional	Only anterograde = Orthodromic: Pre to post
<1%	>99% of synapses
Eg: Hippocampus, Retina	Eg: Most places

- Chemical synapses:



- SNARE proteins help in docking of vesicles. Eg: Syntaxin SNAP-25 and Synaptobrevin.
- AP reach terminal Ca^{2+} channel → Ca^{2+} cause exocytosis → Neurotransmitter release → Bind receptor → Open Ion channels → Depolarization (EPSP) or hyperpolarization (IPSP)→ Summation at Hillock:
  - AP: Contraction
  - No AP: Contraction

- Memory formation by increasing synapses, dendrites. Also increased neurotransmitters and receptors. This is called as Synaptic Plasticity. Eg: Long Term Potentiation (LTP)

- Hippocampus (CA, neurons):
  - Convert short term memory into long term memory by increasing NMDA receptors at synapses in Neocortex causing increased response for years to life called as LTP.

- LTD (Long term depression) by GABA receptors in cerebellum. Help in motor memory → Implicit or reflexive memory. Eg: Writing, Walking, Driving

CNS Part 2

Sensory System 00:12

A. **Receptors**: Make APs from stimulus
B. Pathways conduct impulses to cortex
C. **Cortical centres:**
   - Process information
   - Memory
   - Perception

- Properties of receptors (R):
  1. **Threshold**: Minimum stimulus needed
  2. Specificity
  3. **Adaptation**: Reduced sensation on constant stimulation (Decreased Firing rate by receptors)
     - Rapidly adapting like smell, touch
     - Slow adapting: Proprioception
     - Non-adapting: Pain: Felt all the time even at rest
  4. Weber Fechner Law: Intensity discrimination
     - Stimulus (S) is proportional to Intensity (I) of sensation: Due to increased frequencies of impulses by receptor.
     - Steven Power Law: $I = KS^{\wedge}$

I. **Vision**:
   - Rods and Cones
   - Optic Pathway
   - Area 17, 18, 19 in occipital lobe

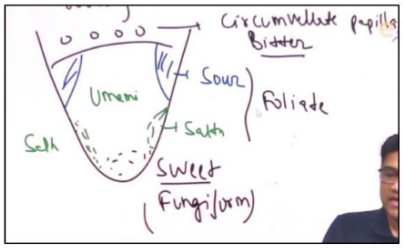
- **Rods**: Rhodopsin - 11-cis-retinal(dehyde) + opsin chain $\underset{Isomerase}{\overset{Light}{\Longleftrightarrow}}$ All-trans-retinal → Closure of Na+ channels via G-protein (Transducin) → Hyperpolarization [Rest all other receptors depolarize]

II. **Hearing**:
   - Inner Hair Cells: Organ of Corti in Cochlia
   - Auditory pathway
   - Area 41, 42; Area 22 (Wernicke) is for comprehension, language

- **IHC**: K^+ channels open → K^+ enter cell from Scala media (K^+ rich endolymph) → Depolarization: CMP (Cochlear Microphonic Potential) → Converted to AP by spiral ganglia → Cochlear nerve

III. **Taste**: Cortical centre – Insula
   - **Taste mechanism:**
     1. Salty: Na^+/K^+ ions
     2. Sour: H^+/Acid
     3. Sweet: G protein receptor → Bind sugar, saccharin, etc
     4. Bitter: G protein receptor → Bind oral drugs, poisons, etc Eg. Quinine
     5. Umami: Mono Sodium Glutamate (MSG) → Azinomoto salt

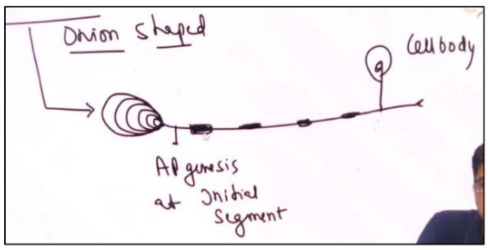
   - Chilly is not taste but pain sensation produced by capsaicin → Bind Vanilloid receptors (TRPV) and produce hot burning sensation.



Somatosensory System [SSS] *17:27*

- Sensations form body like touch, pain, temperature, etc.
- **SSS receptors**: Skin, joints, etc –
  1. **Meissner's corpuscles**: Tip of dermal papillae.
     - Rapidly adapting, low threshold touch receptors.
     - Sense:
       i. Fine/light touch
       ii. 2-point discrimination: Best at finger tips and lips (1-2mm) due to maximum density of receptors.
     - Worst at back

  2. **Pacinian corpuscle**: Onion shaped



- Rapidly acting, high threshold mechanoreceptors
- **Sense**:
  i. Pressure: Deep dermis
  ii. Vibration: Joints

3. **Merkel disks**: In epidermis, rest all in dermis.
   - Slow adapting, low threshold touch receptors
   - Sense sustained touch pressure, 2-point discrimination → Best at finger tips
   - Help blind people read Braille script

4. Krause end bulbs
5. Ruffini endings

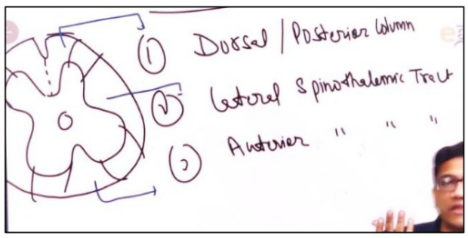
   - Slow adapting
   - Sense position in joints
   - In dermis: Sustained pressure and temperature

   - Ruffini: Warmth
   - Krause: Cold

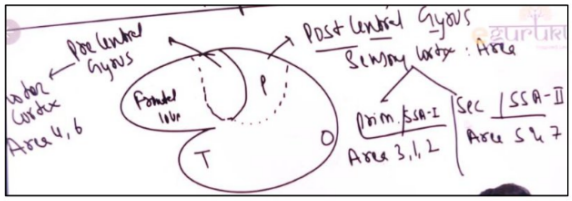
6. **Free nerve endings:**
   - Pain, temperature, sexual sensations and itching (mixed sensation caused by histamine release)
   - Pain receptor absent in brain and viscera → Basically in skin and outer coverings of viscera
   - Pain → Somatic pain
   - Viscera → Visceral pain. Eg: Pleura, duramater

Somatic pain/Superficial	Visceral pain/Dull
Fast pain → Carried Aδ myelinated somatic nerve fibers	C-unmyelinated autonomic fibres
Eg: Skin injury	Angina, Colic pain
Sharp and well localised	Dull and diffuse
Glutamate	Substance P

- **3 sensory ascending tracts in white matter of spinal cord:**
  1. Dorsal: Rest all cortical sensations
  2. Lateral: Pain and temperature
  3. Anterior: Itching and crude sensation



- Dorsal column carries fine touch, pressure, vibration, 2-point discrimination, stereognosis, Graphesthesia, tactile localization



- Area 3, 1, 2 → Perception
- Area 5,4,7 → Learning and memory
- Map of body is called as Sensory Homunculus
  - Body is upside down and distorted
  - Maximum area is for Face (Lips and tongue) and hands

CNS Part 3

EEG & Sleep

EEG Freq ∝ Brain activity

Awake

At rest	Busy
∝ wave	β - wave
Eyes closed	Eye opened
No disturbance	Sensory stimulation
Mind free,	Active thinking
No active thinking	
8-13 Hertz	14-30 Hz.

Sleep

Light (Theta wave)	Deep sleep (Delta wave)
Easy arousal	Difficult
4-7 Hz	0-3 Hz
NREM stage IB(II) ↓ • Longest sleep stage • Sleep spindle k-complexes	NREM stage III & IV • >50% are delta wave • Slow wave sleep. • Dreaming occurs but not remembered. • Sleep walking • Nocturnal enuresis

Adult

- 80% NREM
- 20% REM(newborn 80% REM)
  ↓
- Rapid eye mvmt
  ↓
- Active mind sleep = memory function
- EEG = $\propto_1, \beta$ wave, PGO spikes
- Below neck body paralysis by locus cueruleus.
- Irregular resp.
- Penile erection
- Night mere

- ↑ Co, ↑ BP.

Hypothalamus 13:50

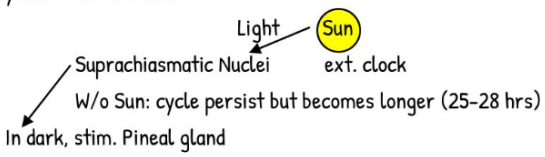
1) Control ANS

Ant HT	Post HT
↑ parasymp.	Symp ↑

2) Sexual behaviour → Pretectal and preoptic nerve
3) Thirst centre → Lateral preoptic N.
   Stimulated by osmoreceptor & ADH
   (Supraoptic nerve) ←

- Located in Ant HT
  ↓
  Sub Fornicular org.
  (Out of BBB)
- Stimulated by ↑ p. osm, ↓ Vol and AT-II

4) Circadian Rhythm → 24 hrs clock



W/o Sun: cycle persist but becomes longer (25-28 hrs)
In dark, stim. Pineal gland

- ↑ Melatonin
- Sleep induction
- Appetite regulation
- ↑ GnRH (arcuate nucleus)

6) Appetite regulation

Hunger centre	Satiety centre
Lateral N. MCH AgRP Neuropeptited Y Ghrelin Orexings "MANGO"	Ventromedial N • ∝-MSH ↑+ve • Leptin (Adipose tissue) • Anti obesity hormones • GIT hormones, Insulin ↓ Post meal satiety

7) Temp. regulation → Feed forward regulation

Ant HT	Post HT
Heat loss	Heat gain, ↑ BMR
Heat adaptation	Cold adaptation
1st change skin, Vasodilation = shunt Vessels	1st skin. • Vasoconstriction • Piloerection • Shivering ↓ Absent in newborn
↑ sweating	Non-shivering Thermogenesis • Brown fat (β_3 receptor) Absent in adult.

Limbic System = Paleocortex *28:46*

Genesis of emotion & memory (involuntary)

Contain:

- Pepez circuit = emotion & memory
  ↓
  Hippocampus → Ant. Thalamic N.
  ↑
  Mamillary body ← Cingulate gyrus

- Amygdala: Fear and Shyness
  - Control sexual behaviour
  - Emotional memory
- Nuc. Accumbens, septum, Medial forebrain bundle
  - Pleasure centre
  - Addiction
  - Reward centre
  - +ve conditioning

Stim, by dopamine and 5 HT

(VT) (DRN)
↓ ↓
↑ in mania ↓↓depression
↓↓depression

Classical conditioning - Pavlov.

- Ring Bell → Saliva
- Skinner = operant conditioning
- Monkey in box → lever A → Banane
  → Lever B → Shock

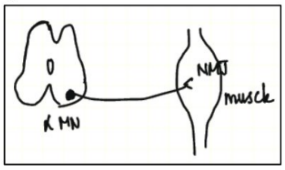
Frontal Lobe *38:00*

- Cognition
- Personality
- Long term memory
- Vol. motor control (Broca's area, 44, 45)
- Control emotion
- Social behaviour

CNS Part 4

Motor System

- Motor unit: Follow all or none law
  ↓
- Single ∝ - motor neuron (in Ant. Horn)
  +
- All muscle fibre if supply



- LMN = control muscle via motor nerve
  Eg: ∝ motor nerve
  LMN lesion:
  - Ant. Horn to muscle any lesion.

- UMN:
  - Control LMN via motor desc. Tracts
    Eg: Betz cells in motor certex.
    (Area 4, 6)
  - Control LMN via CST = PT
    Pyramidal Tract.
  - Tract lesion = UMN lesion
  - All cont. are by αMN (Vol/Invol)

↓

Release Ach at NMJ

↓

Final Nicotinic R

↓

Open Na^+ channel

Depolarised → end plate pot

↓

Act. Potential produced

↓

Excite SR via DHP Ca^{2+} channels.

↓

Release of Ca^{2+} from SR via ryanodine receptor

↓

Ca^{2+} bind Trop - C & displace Tropomyosin

↓

Myosin head binds active chains & form cross bridges

↓

Power stroke

- Stretch Reflex = Myotatic or DTR Deep tendon reflex
  (Regulate length)

Stretch muscle —Reflex arc→ contract (↓ length)

↓ + ↑

Muscle spindle → (+) α MN

↓ ↑

(Inside muscle in II^{el} to muscle fibre) Ia & II afferent fibre

↓ ↘

Annulo spiral spray

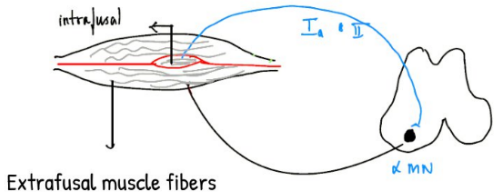
- Muscle spindle = length
- Golgi tendon organ = Tension
  (GTO)
  (near tendon) → Inverse stretch reflex.

↑ Tension → ↓ Tension and permanent rupture

(+) ↑

GTO → ∝ MN

Ib fibre

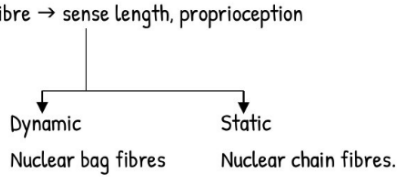


Extrafusal muscle fibers

↓

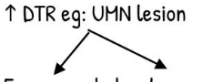
Contract when ∝ MN fibre

- Intrafusal muscle fibre → sense length, proprioception



- γ MN supply intrafusal fibres
- ↑ spindle sensitivity

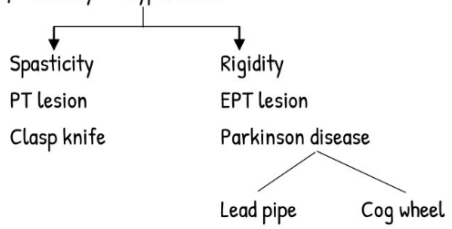
  ↑ DTR eg: UMN lesion



- γ MN $\xrightarrow{(+)}$ Spindle $\xrightarrow{(+)}$ $\propto$ MN → contraction

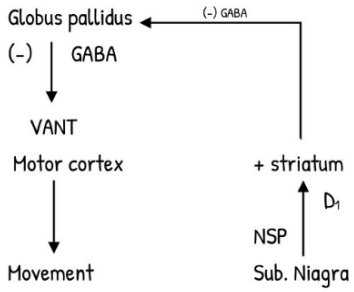
  ↓
- Produce indirect, involuntary contraction
- Called as muscle tone
- Tone help in posture, Gait, Balance.. etc.
- γ MN & Tone controlled by UMN via mainly EPT → extrapyramidal tract. (act on both $\propto$ MN & γ MN)
- EPT → involuntary gross motor control.
- ∴ UMN lesion fail to control γ MN.

  ↑ γ activity → Hypertonia



Basal Ganglia *30:00*

- Planning and programming of motor activity
- Control tone via EPT



- In PKD, Dopamine ↓, ↓ inhibit of GP, leads to ↓↓ movement
- C/f^{-1} Hypokinesia, Rigidity, Resting Tremor, Masked face

Cerebellum *36:08*

2 Aff fibre

Climbing	Mossay
Proprioception from Muscle	Motor plan copy
8° Flexion	Eg: 10° Flexion

2° error → corrected via EPT, γMN
↓
DTR
↓
∝ MN

Cerebellum → ∝ - γ linkay

→Co-ordination
→ ↓ error
→ Motor memory

3 layers & DCN → Deep cerebellar Nuclei

- Dentate
- Emboliform
- Globose
- Fastigial

↓
Brainsterm N
↓
EPT

S cells = Purkinje = GABA

- Only output
- Inhibited by stellate & Basket cell.

Granular cell : Glutamate
Feedback ↓ ↑ Excite all by parallel fibre
Inhibition ↓
Golgi cell

Endocrine System

Hormones → 2 Types

Group – I	Group – II
• Lipid soluble • Thyroid steroid • Cross cell membrane & act directly inside the cell.	Water soluble Polypeptides, Monoamines.

- Thyroid, Vit A, D → Nuclear receptor
- Glucocorticoids, Sex steroids } both N & C receptor.
- Minerelocorticoids → cytoplasmic receptor.

Polypeptides:
Cant cross cell membrane
Act by cell surface receptors
Tyrosine kinase GPCR 7 pass / serpentine receptor

3 Main PPs
Prolactin
Insulin
Glt

Rest all PP.
3 second messenger

cGMP	cAMP	IP_3/DAG
NO	Rest All	TCa^{2+} - SMC
ANP	Regulation,	contraction
	Metabolism	Oxytocin
		Angiotensin
		Vasopressin.
		CCK.

Pancreatic hormones :

Glucagon ↑↑ by hypoglycaemia
↓ GPCR(cAMP))
Cause hyperglycemia

↑ Glycogenolysis
↑ Gluconeogenesis

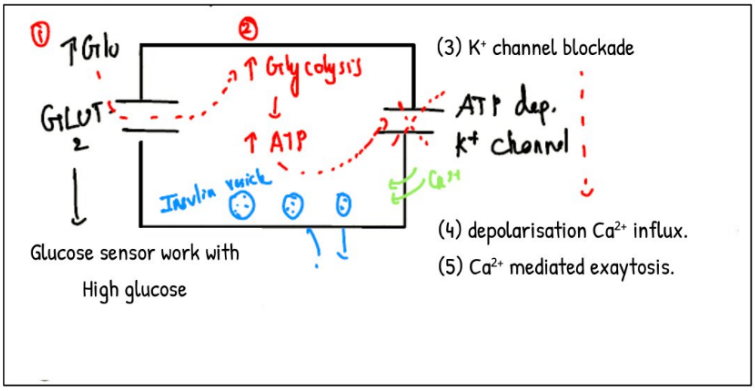
- β - cell: Insulin $\propto \frac{1}{\text{Glucagon}}$

  Only hypoglycemic hormone
- Delta cell → Somatostatin: ↓ GH.

  (-) G. secretion

  (-) G. emptying

Insulin sec: β cell



Insulin sec. with equal conc of c - peptide

Used for estimation of endogenous insulin secretion

Proinsulin → Insulin + C-peptide

Factors

↑ insulin	↓ insulin
→ ↑ ATP: Glu, AA FFA, KA	Insulin itself ↓
→ GIT hormones: GLP-1 GIP	→ Hypoglycemia
→ Parasymp ↑	→ Symp: E, NE ∝ Receptor
→ GH, Glucagon	→ K+ ch. Opener: Diazoxide
→ K+ channel blocker	→ 2 deoxy glucose.

Insulin structure:
2 chains ∝ chain & β chain
(21 AA) (30 AA)
Linked by disulphide bridges
T½ = 2.5 min, daily sec. = 40 units/day
Insulin Receptors (IR): absent in Brain & RBC
↓ (GLUT - 1, 3) (GLUT - 1)
Down reg in obesity

Insulin actions:

Rapid (min)	Slow (hrs. days)
Hypoglycemia By ↑ GLUT-4 on skel muscle adipose tissue, heart Blood glu → cells ↓ BGL.	Glycolysis ↑ Glycogenesis ↑ Lipogenesis ↑ Proteins ↑ (Anabolic) Glycogenolysis (-) Lipolysis (-)

Pituitary Hormones *27:00*

Adenohypophysis (Ant)		Neurohypophysis (post)
Acidophilic	**Basophilic**	Secretes 2 PPs made by Hypothalamus SON → ADH PVN → Oxytocin → Love & aff, Bonding Harmone → Uterine contraction → Milk ejection
GH Prolactin ↓ Milk prod ↑ Glands of breast Dopamine (-)	TSH, MSH ACTH, LH, FSH	

GH regulation

↑ GH	↓ GH
Deep NREM sleep Hypoglycemia Ghrelin	REM sleep Hyperglycemia Somatostatin

Excercise, Starvation, Illness	GCs

GH is 191 aa. PP

T ½ = 10-20 min

Act by Tyrosine kinase receptor

↓

JAK STAT pathway

↓

↑ mRNA

↓

↑ protein june.

GH actions:

- ↑ Growth and size of all tissue except brain
- Hyperglycemia
- Lipolysis
- ↑ protein production eg: soluble collagen
- ↑ Somatomedin C by liver (IGF - 1)
- IGF - 1 for fetal growth.
- Stimulate osteoblast and chondrocytes.

  ↓ ↓

  ↑ Bone form ↑ epiphyseal growth plate
- ↑ Length of long bones
- ↑ Height till puberty
- Epiphyseal closure by sex steroids → Height won't increase
- ↑ GH (pit. adenoma)
  - Before puberty → Height ↑ = Gigantism
  - After puberty → Height same = Acromegaly

GIT

4 layers

- Mucosa = Villi, Microvilli = Absorption
- Submucosa = Glands, vessels, nerve = secretion
- Muscularis = smooth muscle contraction, motility
- Serosa = Attachment

Enteric Nervous System

- Controlled by ANS
- 1) Meissner's (or) submucosa plexus
  2) Auerbach plexus (or) Myentric

Meissner's	Auerbach
• In submucosa • Secretion • Sympathetic inhibit this • Parasympathetic stimulate	• In muscularis • Motility • Symp. Inhibit this • Parasympathetic stimulate

Pace maker of GIT = Interstitial cells of Caja.

↓

Absent in Oesophagus, proximal stomach

↓

Food causes relaxation

↓

Receptive relaxation

- Pacemaker make Basal electrical rhythm [BER] (or) slow wave rhythm
- BER shows cyclical changes b/w – 40 and –60
- BER alone = No contraction
- BER + stimulus [Food, Distension, = Spike potential vagus, Hormones]

Spike pot.

↓

↑ Ca^{+2}

↓

↑ Ca^{+2} in muscle

↓

Bind Calmodulin

↓

Stimulate myosin light

Chain kinase [MLCK]

↓

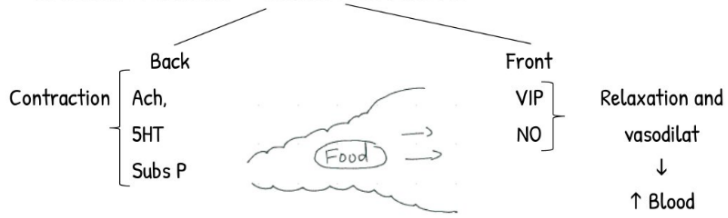
Contraction in power stroke

GIT Movement 9:00

1) Food = Peristalsis

↓

Distension + Pacemaker → Release of Ca^{+}, NTS etc.



- Reverse peristalsis = Vomiting

2) MMC = Migratory motor complex
   - Produced by empty stomach, travel till distal ileum.
   - Hunger pangs
   - Duration = 90 to 100 min
   - Clear GIT, prepare for next meal = "Broomstick, Housekeeping of GIT"
   - Motilin [stomach, Duo M_0 cells] increase all movements including MMC
   - Food inhibits MMC

3) Mass peristalsis
   - Defecation = 3 times a day
   - Ganglion cells of colon
   - Averbach plexus
   - Need ↑ bulk of feces by fibres

     ↓

     Cellulose, Hemicellulose, Lignin, Pectin, Inulin, chitin
   - Rectum = has pressure sensors = urge produced

Gastrocolic reflex:

Food ⟶ Defecation ↑

[↑ Gastrin, ↑ Mass movement of colon]

Site	Freq of BER
Stomach	4/min
Duodenum	12/min
Ileum	9/min
Cecum	2/min
Rectum and sigmoid	4-6/min

Phases of digestion *19:50*

Name	Stimuli	Mediator	Response
Cephalic	Smell, sight, thought of food	Parasym	↑ saliva 10% of Hcl secre
Gastric	Food in stomach	Vague, Gastrin	Max Hcl secretion
Intestinal	Hcl in Duo, Food, Distension, Vagus	GLP, VIP, GIP, Amylin, Secretin	(-) Hcl (+) HCO_3^- rich alkaline secr

Enterogastric reflex

Hcl in Duo ⟶ (Secretin) ↓ Hcl secretion

1) CEPHALIC PHASE

= Saliva secretion [Max = Submandibular gland]

↓

Lubrication, Taste, Mastication

Swallowing, Anti-bac [IgA, Zn]

= Digestive role by S. Amylase (Ptylin)

↓

Activated by Cl^-, pH = 6, 7

>30% of starch digestion

= Sali. Lipase, peptidase

Saliva at Rest ⟶ (on stimulation) pH = 8.0

pH = 6.8

(↑ volume, ↑ Na^+, K^+, HCO_3^-)

Note:

- Max K^+ con = colon
- Max K^+ secretion = Saliva

GIT secretions

GIT sec	Vol/day	PH
Saliva	1-15 L/day	68-8
Gastric	15-2 L/day	1.5-2
Intestinal	2-2.5 L/day	8-8.2
Dencreetic	1-1.5 L/day	8.5
Bile	0.5-0.8 L/day	8.2-8.3
Total = 6-7 L/day		

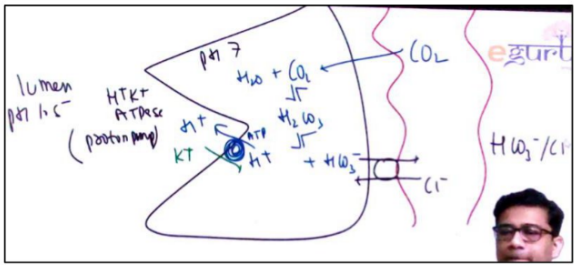
Oral fluid = 1-2 L/day
↓
Total vol = 7-9 L/day (8L/day)
↓
>800 ml/d = Absorption
200 ml/d = lost in feces

- Duod = Brunner gland → sec. Alk mucus
  ↓
  pH = 10-11 (max)

2) GASTRIC PHASE
   Cells of gastric gland
   1) Pareital / oxyntic cells
      = sec Hcl, Ghrelin (↑ GH, appetite)
      = Max at fundus
      = Sec. Intrinsic fact
      ↓
      Bind vit B_{12} and absorption

   2) Chief / Zymogen cells (Enz)
      → Pepsinogen $\xrightarrow{HCl}$ Pepsin
      = Also secretes G.lipase, Amylase, Elastase etc

HCl secretion:



HCO_3^- increases in blood aft food = post prandial alkaline tide

Regulation of Hcl secretion

1) Vagus → Ach = M_3 [M_1]
2) ECL → Histamine = H_2 receptor
3) G - cells → Gastrin = Gastrin receptor (Antrum)

↑ Hcl by proton pumb

↓

Also ↑ Hcl sec
↑ Bile sec
↑ GIT motility
(+) G. emptying = Also stimulated by vagus, liquid, low osm food.

3) INTESTINAL PHASE

- All enz except gastrin
- CCk - P_2, secretin, GLP, GIP, VIP, Enterogastrone, Amylin, Somatostatin
- Common actions

1) (-) Hcl
2) (-) G. emptying
3) ↑ satiety
4) ↑ Insulin = Best by GLP-1, GIP [Incretins]
5) ↑ HCO_3^- rich alkaline secretion. Eg: Pancreatic, bile

[* S cells of Duo release secretin]

↓

Stimulated by Food, vagus, Hcl, protein, AA

6) Secretin = (-) Gastrin, ↑ Bile
[* I cells of Duo = CCK-PZ]

7) CCK = On I.V causes anxiety
= ↑ Bile secretion = choleretic
= Gall bladder contr = cholegogue

Digestion, Absorption *46:00*

1) Proteins —(Pepsin / Trypsin)→ Amino acids
Enterokinase
↓
Absorbed by sodium - AA symport
Trypsinogen (+) Chymotrypsin

2) Fat —(G. lipase, Colipase / P. lipase)→ LCFA + Bile salts
↓ Emulsification
H_2O soluble micelles, absorbed

3) Polysaccharides —(S. amylase)→ oligo
Pancreatic
$\propto$ - Amylase
Di → Mono

Maltose —(Maltase)→ 2 Glucose
Sucrose —(Sucrase)→ Glu + Fructose
Lectose —(Lactase)→ Glu + Golectose

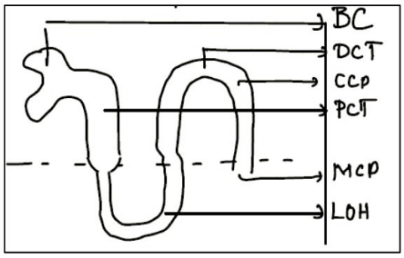
- Absorbed by * secondary active SGLT - 1 (luminal border)
  - Facilitated diffusion
    ↓
    GLUT - 5 = Fructose
    Other GLUT = Glucose, Galactose
  - Hexose faster than pentose
  - In hexose, galactose absorbed faster

- Max abs. in proximal int, jejunum (then ileum, colon)
  ↓
  Exception i) Vit B_{12}, bile salts in terminal ileum
  ii) Fe in Duo
  Diet = Fe^{+3} $\xrightarrow{HCL}$ Fe^{+2} → Enters cell by Luminal DMT-1
  ↓
  Ferroportin ← Leave cells to enter blood by ferroportin
  Inhibited by
  Hepcidin (from liver)

- ↑ Fe abs = Vit C, Amino acids
- ↓ Fe abs = Tannins, phytates

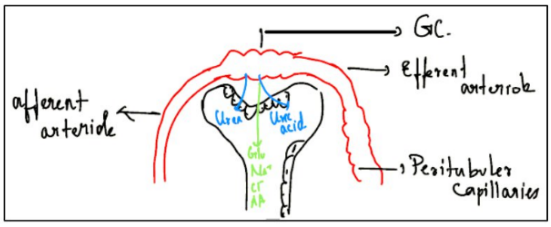
Kidney Part 1

1 - 1.3 million nephrone



- CD is last part of nephron
- All final urine changes occur in CD
- Eg: pH, volume, Osm etc.
- Most hormones act at CD

Blood supply:



G.C (Glomerular capillaries)

Most permeable (after liver) due to fenestrations (opening)

↓

Plasma filtration both good and bad.

Stages in urine formation:

- Filtration → Glomerular func
- Reabsorption } Tubular function
- Secretion }

The branch of PC supplying LDH in medulla is vasa - recta.

Interstitial cells of PC make erythropoietin.

In CKD: ↓ EPO → Anemia

Kidney (Part-1)

Topic Notes: 3

Glomerular filtrate membrane

- Epithelial cells of B.C or Podocytes→ filt. Slits → 10-20 nm
  - Make & deposit - vely charged Sialoproteins & Heparin sulphate in Basement membrane.
- Basement membrane → made up of proteins

Effective pore size:

- 4-8 nm
  Freely filtered
  Eg: Water, Na^+, Glu, Insulin

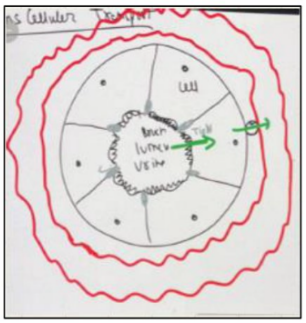
- >8 nm
  Not filtered
  Eg: RBC, WBC, platelets, $\propto$ - macroglobulins, β globulins.

- Substance between 4-8 nm are filterable but depend on charge.

Eg: Albumin ~ 7 cm
Filterable by size but not filtered due to -ve charge
Nephrotic syndrome: Albuminuria loss of -ve charge.

PCT:

- Simple cuboidal epithelial cells with brush border lining (luminal surface)
- ↑↑ Area for absorption.
- Tight junc. b/w PCT cells
- Transport only via cells
- Transcellular transport



- Max ATP, O_2, Blood supply & consumption = PCT
- Because its having max transport.
- Max reabsorb. of all substances in PCT.
- Except Mg^{2+} in Asc. Loop.
- Max secretion of all subs. In PCT
- Except urea in thin loop, K^+ in CD & DCT.
- Kidney removed non-volatile fluids & lungs remove volatile acids. Eg: CO_2 as carbonic acid.
- PCT sec. max acid by Na^+ / H^+ exchange but urine pH is not acidic as sec H^+ get neutralized by urinary buffers.

  1) HCO_3^-: mainly in ECF / plasma to kidney

- $H^+ + HCO_3^-$ (CA) $\rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2$

  ↓

  Filtered from plasma.

  So, Kidneys can't ↑/↓ HCO_3^- buffer → Non inducible

2) NH_3: Can be formed by Kidney

   Only inducible buffer, ↑ NH_3 produced in acidosis

   Mech: Glutamine $\xrightarrow{\text{Glutaminase}}$ Glutamate + NH_3

   $NH_3 + H^+$

   ↓

   NH_4^+

3) PO_4^{3-}: Minor in Kidney, ECF, Plasma but main in ICF/cells and bone

   Non inducible

   Titrable buffer

Distal Tubule = DCT + CD

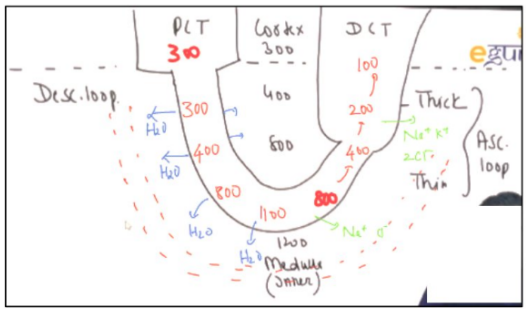
- Acid sec. occur but less than PCT
- Few buffers available, urine pH becomes acidic
- Acidification of urine occurs in PCT only
- Min urine pH → 4.5

Kidney Part 2

Loop of Henle

- Loc. In medulla
- Hypertonic
- Plasma. Osm = 285 - 295 mosm / L (~ 300)
  = 2 Na^+ + B. Glucose (mg%) + B. Urea (2.8)
  (18)
- If same osm as plasma = Isotonic
  Eg: NS, RL, Dextrose (5%)
- Medulla osm = 1200 mosm/L (Hypertonic)
  When urine passes through medulla in LOH & CD, (need ADH also)
  ↓
  High med. Osm will reabsorb water
  ↓
  Conc Hypertonic urine = 1200 mosm/L
  Long loop → more urine conc. Ability
  Eg: Juxta medullary nephrons (15% of total)
  Short loop → ↓ urine conc ability
  Eg: Cortical nephron. (85% of total)

Vasa Recta:



- Vasa recta reabsorb and remove water from medulla to prevent loss of medulla osmolarity
- Ascending loop = Solute permeable
  Most water impermeable.
  Make urine hypotonic in TAL & DCT
  100-200 mosm / L
  Make medulla Hypertonic.

Counter current system (C.C): *13:00*

1) C.C multiplier: Ascending loop of Henle
   It creates high osm. In medulla by accumulating solutes.

2) C.C exchanger: Vasa recta
   It maintains the osm. Of medulla, by re absorption of water

Ascending loop:

Thin	Thick
Simple passive diffusion of Na^+ & CT.	Active transport Na^+ K^+ $2Cl^-$ symport Blocked by loop diuretics Defect in Bartler's syndrome

DCT *17:30*

Main transport:

- Na^+ Cl^- Reabsorption by Na^+ Cl^- symport.
  Blocked by Thiazide
  Defect in Gietelmen syndrome.

- Acid secretion by Na^+ / H^+ exchanges
- K^+ secretion by principal cells (mainly in CD)

↓

Na^+ Re absorption
K^+ secretion
Stimulated by Aldosterone
($TENaC\&Na^+ - K^+$ pump)

↑ Aldo	↓ Aldo
Conn. Syndrome	Addison's disease

Collecting duct *21:27*

- Two types of cells
  P - cell
  I - cell
  } in DCT also.

- ∝ - Intercalated cells: Acid secretion by H^+ pump
  Min. urine pH
  Urine acidification
- CD need ADH for reabs. Of
  - Water (Aquaporin - 2)
  - Urea (UT - 3)
    ↳ Enters medulla & ↑ osmol
    ↳ Help in counter current system.

ADH receptors

V_1	V_2
IP3 / DAG Vasoconstriction	↑ C AMP ↑ AQ-2 & UT-3 ↑ H_2O Reabsorb

RBF = 1250 ml/min
RPF = 625 - 695 ml/min (Renal plasma Flow)
↓
20% filtered by GFR
GFR = 125 ml/min Normal
↓
80% goes unfiltered to PC.

Transport *27:50*

1) Glucose = 100% Reabs in PCT
   Enter cells by SGLT - 2
   Enter blood via GLUT - 2

   Tmax for glucose = Max amt of Glu that can be reabsorbed per minute
   Normal = 375 mg/min

   Filtered load = GFRx Plasma conc.

In Normal person, FL < TMG 100% Reabsorption No Glycosuria.	Expected RT = 300 mg Actual RT = 180-200 mg This is called ß play Not all tubules have same reabs. Valves. (THG)

Renal Threshold:

- It is conc. above which TMG > FL.
- All the filtered Glucose can't be reabsorbed
- Glycosuria.

Amino acids similar to glucose

Na^+ & Cl^- are same in term of reabsorption

>99% of filtered Na^+ is Reabsorption = Glomerulo - Tubular Balance.

<1% is excreted in urine

= Fractional exc. of Na^+ <1%

% Na^+ Reabsorption	Site	Main mechanism
60-70%	PCT	Na^+ / H^+ exchange
20-25%	LOH	Na^+ K^+ $2Cl^-$ symp.
10-12%	DCT	Na^+ Cl^- symp.
3-4%	CD	ENac.

Kidney Part 3

3) Water:

Follow solutes

180 l/day is filtered (GFR)

> 99% - 99.5%	< 0.5 - 1%
reabsorption	excreted in urine.
	1-2 L/day - (N) urine vol.

Site → % Water reabsorption

PCT → 60-70%

LOH → 20-25%

DCT → 5-8%

- Obligatory → 88-90% Reabs. w/o ADH
- 10-12% reabs. Under control of ADh
  ↓
- Facultative water reabsorb 2200 + 2200 + 250
- CD get hypotonic urine from DCT passing through medulla.

If ADH +ve	If ADH -ve
CD water permeable	(-)
↑ Water reabsorption	↓↓
Conc urine (1200)	Dilute urine
Low urine vol	↑ urine polydipsia
High specific gravity	↓↓

Clearance:

- Amt. of plasma cleared off a substance per min.
- If only filtered, No secretion, No reabsorption → CL = GFR.
  Eg: Inulin used for GFR estimation
- If secretion +ve:
  CL ↑
  CL > GFR
  (Filt & sec) (filtr.)
- Eg: Creatinine = 150 - 150 ml/min
- Mainly filtered with little secretion
- CL is close to GFR.

- Used for GFR estimation clinically.
- If 100% sec & 100% CL, All the plasma coming / min is cleared (RPF)
  CL = RPF eg: PAH.

- If reabsorbed: ↓ CL
  CL < GFR.
  Eg: Urea CL = 70-90 ml/min
  Filtered and reabsorbed. (counter current system)
- If 100% reabsorbed, 0% clearance in urine from plasma
  Eg: Glucose, AA_3
  ↓
  Zero clearance
  If Glycosuria: Non zero urine conc.
  Clearance = $\frac{\text{Urine flow rate / min x urine con}}{\text{Plasma conc.}}$

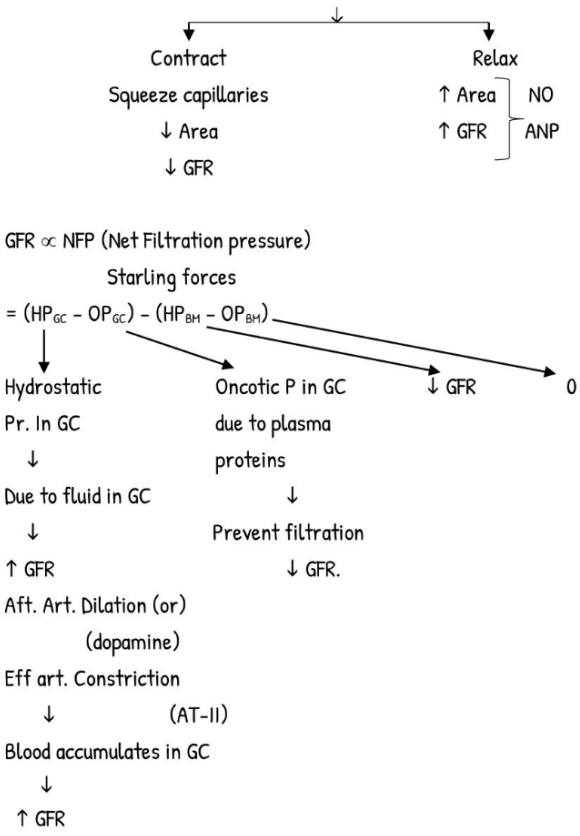
JG Apparatus 15:29

JG cells:
Act as baroreceptors
Sense RBF & pressure in aff. Arteriole
Release Renin when ↓ Blood flow
Eg: Shock, ↓ BT, ↓ Na^+, ↓ Vol, Renal Artery Stenosis.

Liver
↓
Angiotensinogen —Renin→ AT - 1
ACE ↓ lungs
(active) AT-II

Vasoconstriction	↑ GFR
↑ Aldosterone	↑ Na+
↑ ADH	↑ Vol
↑ Thirst	↑ BP

Lacis cells: macrophages
Macula Densa cells: DCT, Asc, loop
GFR regulation called as Tubulo - Glomerular feedback
1st sense GFK mainly by Na^+, Cl^- level.
It correct GFR by mesangial cells (contractile cells)
↓

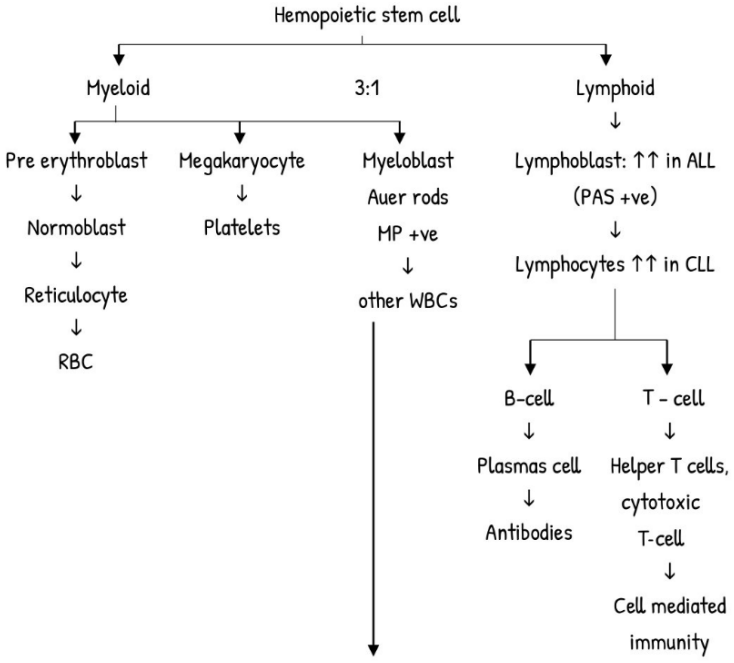

Contract
Squeeze capillaries
↓ Area
↓ GFR
Relax
↑ Area
↑ GFR
NO
ANP
GFR ∝ NFP (Net Filtration pressure)
Starling forces
= (HPGC – OPGC) – (HPBM – OPBM)
Hydrostatic
Pr. In GC
↓
Due to fluid in GC
↓
↑ GFR
Aft. Art. Dilation (or)
(dopamine)
Eff art. Constriction
↓
(AT-II)
Blood accumulates in GC
↓
↑ GFR
Oncotic P in GC
due to plasma
proteins
↓
Prevent filtration
↓ GFR.
↓ GFR
0

Blood

Hematopoiesis

Start at 3rd week in yolk sac — 1st trimester
12th week in liver — 2nd trimester
20th week in BM — 3rd trimester

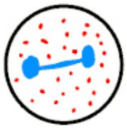
New born: All BM
Adult: Long bone & flat BM.



Monocytes → Largest WBC
Kidney shaped Nuclei
Becomes macrophages
in interstitium.

Granulocytes (-phils)

Neutrophils: 40-60% of WBC
Multilobed Nucleus 2-6 lobe



Cause phagocytosis

↑↑ in acute pyogenic infection

Eosinophils: ↑↑ in allergic condition

& in parasitic infestation

Bilobed nucleus with brick red coarse granular containing histamine

Basophils: Bibbed nucleus with blue colour

Coarse granular containing histamine

Help in allergic condition.

RBC:

Normal count

Male 6-7 million /mm^3

Female 4.5-5.5 million / mm^3

Newborn 7-8 million / mm^3

Hb

Normal count

Male 14-18 gm%

Female 12.5-15.5 gm%

Newborn 18-23 gm%

Anemia ↓ Hb < 12 gm%

Pregnant < 11 gm%

Blood indices used for Wintrobe's morphological classification of Anemia

MCV → Mean Corpuscular volume

Normal → 1 80-90 μm^3

$\frac{PCV}{RBC\ count} \times 10 = \frac{45}{5} \times 10 = 90$

< 80 c/a microcytic anemia

> 100 c/a macrocytic anemia

Megaloblastic Anemia:

Folic acid — Vit B_{12} (Veg. diet)

(-) ← Neurological manifestation (+)

Normal ← ↑ mmA

Colour or chromicity: MCH & MCHC

Mean corpuscular Hb & Hb conc.

↓ ↓

→ $\frac{Hb}{RBC}$ x 10 $\frac{Hb}{PCV}$ x 100

→ Normal → 28-32 pg Normal → 32-38%

If low MCH/MCHC: Hypochromic

If normal then c/a Normochromic

Hypochromic microcytic Anemia

- Sideroblastic
- Fe def → low ferritin, low III BC.
- Thalassemia
- Anemia of chronic inflammation: low Fc