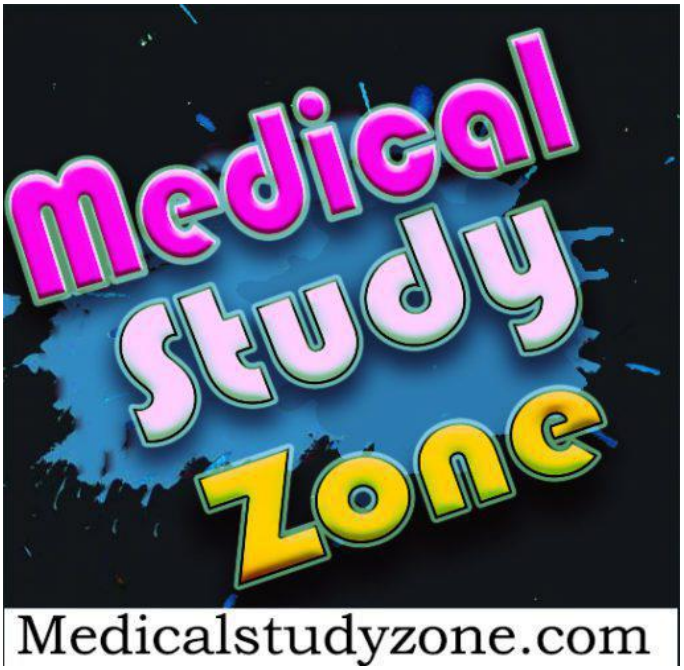
Structured Notes According to

PHYSIOLOGY

Revision friendly **Fully Colored Book/Structured Notes**

For Best results, watch the video lectures along with reading notes

© Dr. Vivek Nalgirkar (Author)



CONTENTS

PHYSIOLOGY

LIST OF IMPORTANT TOPICS

- **General Physiology** - Body fluid compartments, cell membrane composition, trans-port processes
- **Nerve Muscle** - Classification of nerve fibers, injury to nerve fibers, sarcomere, changes during contraction, energy systems in muscle
- **CVS** - Conducting system, cardiac cycle (events, JVP, PV loops), ECG, Cardiac output, blood pressure (Measurement, regulation including Baroreceptors), regional circulations (esp coronary, capillary), cardiorespiratory changes in exercise
- **Respiratory system** - Mechanics of breathing (surfactant, compliance, lung volumes & capacities, dead space), V/Q ratio, Gas transport (oxygen), Regulation of breathing (respiratory center, chemoreceptors), Hypoxia.
- **Kidney** - JG apparatus, GFR (Starling's forces), tubular functions , concentrated urine formation, micturition reflex, types of bladd,er, Acid-base physiology (buffer systems in the body)
- **GIT** - Structure (ENS, BER, reflexes), motility, secretions (saliva, gastric juice, pancreatic juice, bile), GI hormones
- **Endocrine and reproduction** - Pituitary, thyroid, adrenal cortex, pancreas (hormones and their disorders); Estrogen, testosterone, ovulation
- **CNS** - Introduction (synapse, NTs) Sensory system (receptors, ascending tracts, pain) Motor system (descending tracts, cerebellum , basal ganglia, LMN, muscle spindle), higher functions (hypothalamus, sleep & EEG, hemispheres, learning and memory)
- **Special senses** - Visual pathway, visual processes, organ of corti
- **Environmental Physiology** - Temperature (exposure to heat and cold), high and low barometric pressures, energy balance.

LEARNING OBJECTIVES

UNIT 1 GENERAL PHYSIOLOGY

GENERAL PHYSILOGY

- Body Fluid Compartments and its Various Volumes
- Measurement of Body Fluid Compartments
- Various Indicators used
- Disturbances in Body Fluid Compartment
- Dehydration and its Types
- Overhydration and its Types
- Syndrome of inappropriate Antidiuretic Hormone Secretion

CONCEPTS IN PHYS[illegible]

- Body Fluids
- Important concepts- Endolymph
- Donnan Equilibrium
- Concentration Gradient
- Equilibrium VS Steady State Conditions
- Homeostatic Principles
- Homeostatic Regulatory Mechanism
- Feedforward Mechanism
- Feedback Mechanism
- Negative Feedback
- Positive Feedback

CELL MEMBRANE AND TRANSPORT PROTEINS

- Composition of Cell Membrane and Lipids in Cell Membrane
- Proteins in Cell Membrane
- Protein Turnover Rate
- Types of Membrane Proteins
- Membrane proteins & Junctional Complexes
- Transport Proteins in Cell Membrane & Pores
- Gated Channels
- Studying Ion Channels & Blockers of Membrane
- Carriers
- ATP Dependent Transport Proteins
- Structural characteristics of Proteins

TRANSPORT PROCESS

- Transport Across Cell Membrane: Endocytosis
- Exocytosis
- Osmosis
- Diffusion
- Characteristics of Diffusion
- Diffusion Trapping
- Active Transport
- Sodium-Potassium Pump
- Function of Sodium-Potassium Pump
- Stimulators and Inhibitors

1 GENERAL PHYSIOLOGY

Introduction 00:00:13

- Body Fluid compartments
- Concepts
- Cells Membrane
- Transport Processes

BODY FLUID COMPARTMENTS 00:01:03

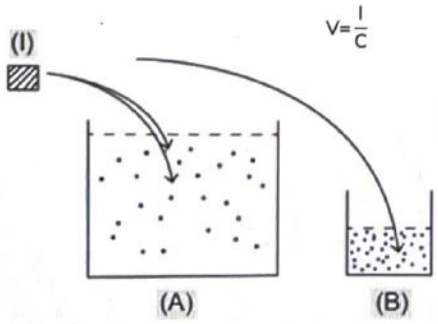
- Total Body water (TBW) = 60% of body weight = (0.6%) x Body wt.
- TBW
  - 2/3rd ICF
  - 1/3rd ECF
- ICF: (0.4) x Body wt.
- ECF: (0.2) x Body wt.
- 72 kg Adult
  - TBW - 42 L
  - ICF - 28 L
  - ECF - 14 L
- ECF
  - 3/4th interstitial fluid (11 L)
  - 1/4th Plasma (3L)

Important Information

- Blood: 8% of body weight
- Plasma: 5% of body wt.

MEASUREMENT OF BODY FLUID COMPARTMENTS 00:10:15

- **Dye Dilution/ indicator Method – based on Stuart Hamilton Principle.**
  - **I:** Initial amount of dye injected
  - **C:** Concentration of dye after it got uniformly dispersed



  - **V = Volume of compartment**
  - **A =** Amount of dye that left the compartment and enter cells/ excreted

$$V = \frac{I - A}{C}$$

Previous Year's Questions

Q. 10gm of mannitol was injected to measure the volume of ECF after distribution in ECF.when the sample was collected for the concentration of mannitol found to be 50mg% and 10% of mannitol excreted out from the body.what is the volume of the ECF?

A. 18L
B. 5L
C. [illegible]
D. 15L

Ans. $V = \frac{10 - 1}{50} = \frac{9}{50} = 18\ L$

- volume of ECF = 18L
  - 14 L-ICF
  - 4 L-ECF

VARIOUS INDICATORS USED FOR MEASUREMENT 00:21:10

- **Total** Body Water (Dueterium space)
  - Dueterium [D_2O]
  - Tritium [$3H_2O$]
  - Antipyrine
  - Aminopyrine
- ECF VOLUME (Sucrose space)
  - Non metabolizable saccharides are used
- INULIN [Best]
  - Fructopolysaccharide
  - Its not metabolized
  - Not lost outside cell
    - → Sucrose
    - → Mannitol
- 1L-transcellular fluid (aqueous humor, synovial fluid)
- ICF VOLUME [TBW] - [ECF]
- Plasma Volume- Radio Labelled Iodine(I 131), radio labeled albumin
- RED CELL VOLUME -51CR - TAGGING

Disturbances [with respect to ECF] 00:29:31

- DEHYDATION (Water lost from ECF)
- OVERHYDRATION (volume gained in ECF)
- Children **more** prone to dehydration due to higher SA: volume ratio

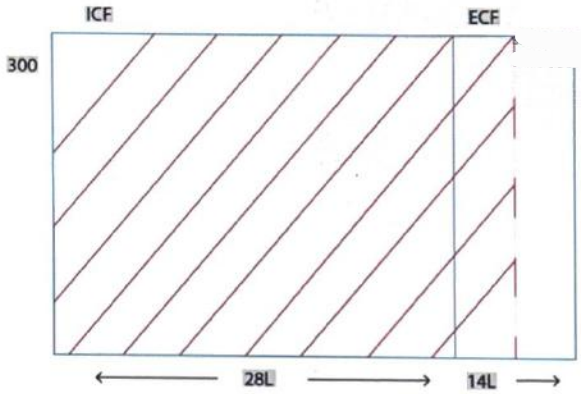
DEHYDRATION 00:32:17

A. ISOTONIC DEHYDRATION

- Water & Na+ lost in equal proportions
- No shift of H2O d/t Isotonicity of ECF

Conditions

- GI Fluids loss
- Burns
- Haemorrhage

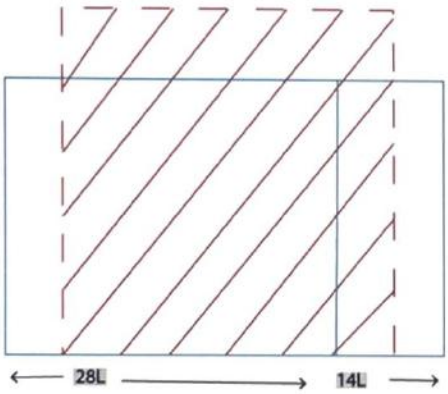


B. HYPERTONIC DEHYDRATION

- Only H2O lost from ECF
- ECF becomes hypertonic
- H2O moves from ICF to ECF
- ICF volume shrunken secondarily

Conditions

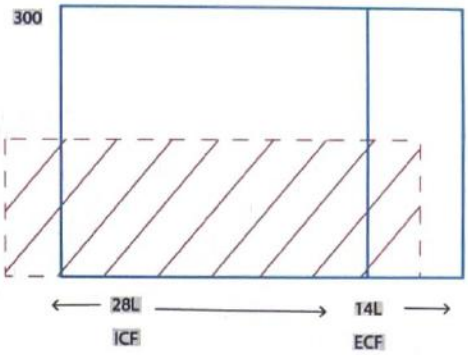
- Diabetes Mellitus
- Diabetes insipidus
- Alcoholism
- Lithium salts



- ICF 2° Shrunk
- ECF:
  - ↑Tonicity
  - ↑Vol.

C. HYPOTONIC

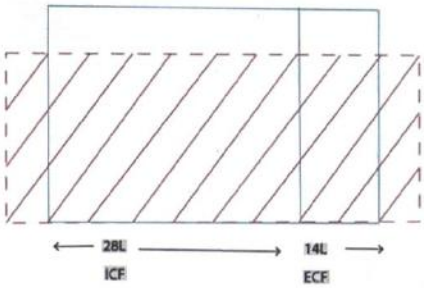
- Na+ loss >>> water loss
- Seen in
  - Primary Hypoaldosteronism
  - Primary Hypoadrenocorticolism
- ECF water shifts into ICF



Overhydration (volume gained in ECF) 00:43:38

a. Isotonic

- Oral / IV Isotonic NaCl



b. Hypertonic

- administration of oral / IV hypertonic saline

c. Hypotonic

- Only water gained to ECF
- Seen in SIADH (Syndrome of inappropriate ADH secretion)
- occurs in surgery & stress

Increase volume
↓
Increase Atrial filling pressure
↓
ANP [Natriuretic peptide]
↓
Natriuresis
Diuresis[EUVOLEMIC HYPONATREMIA]

00:57:03

Previous Year's Questions

Q. By mistake a person drank 1 Ltr of Sea water

A. Hypertonic over hydration
B. Hypotonic over hydration
C. Hypertonic dehydration
D. Hypotonic dehydration

- Sea water osmolarity 2400 mosm / L
- Max. Concentrating ability of kidney 1200 mosm / L
- 2 Ltr of urine to be produced, resulting in Hypertonic Dehydration

- If the osmolarity of consumed fluid is < 1200 mosm /L→ Hypertonic overhydration
- If the osmolarity of consumed fluid is >1200 mosm /L →Hypertonic overhydration

Important Information

Atrial natriuretic peptider(ANP)-heart
Brain natriuretic peptide(BNP)-heart
C type natriuretic peptide(CNP)-heart

2 CONCEPTS IN PHYSIOLOGY

INTRACELLULAR FLUIDS AND EXTRA CELLULAR FLUIDS

00:00:14

- **Homeostasis** mechanism

BODY FLUIDS

00:02:35

- ECF has high concentration of Na+
- K+ is high concentration ICF

ENDOLYPH

00:04:55

- ECF which resembles ICF in body has increase K^+ concentration

Impermeant anions in ICF

- Intracellular Proteins
- Phosphates
- Responsible for relative anions in ICF
- Increase anion inside the cell
- Na^+ Leaking into the cell to maintain equilibrium

DIFFUSION

00:07:45

- Donnan Equilibrium / Gibbs- Donnan
- Concentration gradient by specific ion
- Electric gradient caused by all ions

NA^+

00:13:54

- Moves outside to inside due to oncentration gradient
  - Na+ 141mEq/l out side
  - Na+ 14 mEq/l inside
- moves outside to inside due to Electric gradient
- Always diffuse in

K^+

- Moves inside to outside due to concentration gradient
- ECF K^+ concentration → 4 mEq/L
- ICF K^+ concentration → 145 mEq/L
- Moves outside to inside due to Electric gradient

DEPENDS ON PREDOMINANT GRADIENT

00:26:20

Refer Table 2.1

Milieu interieur[ECF]

- coined by Claude Bernard
- Internal Environment of body

HOMEOSTASIS

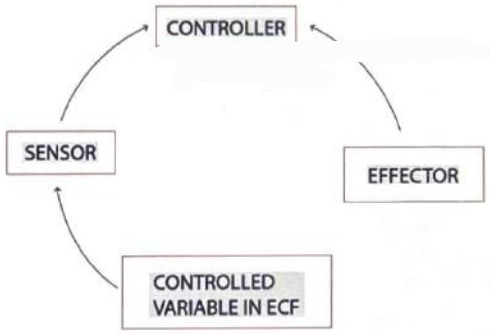
00:31:48

- Coined by water F. Cannon
- maintaining the constancy and stability in the Milieu interior.
- Goal for all the system is homeostasis

Eg:digestive system maintain nutrients level

SCHEMATIC MODEL

00:34:24



FEED FORWARD MECHANISM

00:41:55

- Controller anticipates changes & takes a desired action
- no time lag present
  - Ex: Cephalic phase of gastric acid secretion
  - increase respiratory drive in exercise

FEED BACK MECHANISM

00:44:20

- Change occur in controlled variable & that change is feedback to controller & then the controller taken action
- Time lag is present
- 2 types of feed back

NEGATIVE FEED BACK

00:45:47

- Controller does the opposite
- Change is negated or error is minimized
- Measure of efficiency is GAIN
- Higher the gain, more is the efficiency of system correction will be large, residual error will be less

Ex: a. Kidney Body Fluid mechanism in regulation of blood press has infinite gain-0 error

b. Temperature Regulation 34-36

c. Baroreceptor mechanism 2-4

POSITIVE FEED BACK MECHANISM/ CYCLE

00:55:11

- Controller does the same in direction of error & error is amplified

Ex:

a. Circulatory shock (2nd stage)
b. Oxytocin in parturition
c. Platelet plug / clot formation
d. Action potential from RMP to threshold
e. LH surge leading to Ovulation
f. Bladder filling → MICTURITION
g. HEAD's PARADOXICAL REFLEX-distention of lungs leads to more distension, occur at birth
h. Vomiting

- All these positive feedback will end with negative feedback
- Positive feedback are part of larger scheme of negative feedback process

  Ex a. Oxytocin in partirution
  b. Platelet plug & clot formation

Previous Year's Questions

Q. Most efficient feedback mechanism
A. Baroreflex in BP regulation
B. Temp. regulation by hypothalamus
C. Osmo regulation by hypothalamus
D. Kidney body fluids mechanism in regulation ~~of~~ BP

Table 2.1

EQUILIBRIUM	STEADY STATE CONDITIONS
Ion Equilibrium [K^+]	Blood Glucose 100 mg%
	BP-120mm / Hg
Involves 2 adjacent compartments	Not necessary
Involves 2 equal & opposite forces	Not necessary
ATP not needed	ATP breakdown necessary
Short lived	Long lived

3 CELL MEMBRANE & TRANSPORT PROTEINS

COMPOSITION

00:01:16

- Lipids → Occupy 42% surface area
- Proteins → Occupy 50-55% surface area
- Carbohydrates → Occupy 3% surface area
- By weight, Lipids: Proteins → 1:1

Carbohydrates

- Provide asymmetry
- Responsible for immune reactions

LIPIDS

A. Phospholipids

- Maximum concentration & main constituent of Lipids
- At low concentrations → form mono layer
  → Eg. Surfactant
- At moderate concentrations → form circular aggregates
  → Eg. Micelles
- At high concentrations → form bilayers
  → Eg. Lipid Bilayer

B. Cholesterols

- Fluidity Buffer of membrane -responsible for membrane fluidity

Previous Year's Questions

Q. Micro needle inserted to injury to cell membraine what is occur the healing process
A. Lateral movement of lipid
B. Lateral movement of proteins
C. Enzyme interaction
D. Hydrophobic interaction

PROTEINS

00:12:30

- Concentration varies from cell to cell
- Concentration varies from time to time even in the same membrane

Previous Year's Questions

Q. High protein lipid concentration
A. Presynaptic membrane
B. Oligodendrocytes
C. Schwann cell membrane
D. Hepatocytes

- Eg: N2 narcosis high pressure, Gases dissolve, N2 has ↑affinity for lipids
- Oligodendrocytes - 76%

Oligodendrocytes & Schwann cell membrane

- Have high lipid content
- Forms myelin
- associated with Nitrogen narcosis

High protein : Lipid concentration

- Inner Mitochondrial Membranes 76% Proteins
- Pre Synaptic membranes 70% Proteins

High lipid : Protein concentration

- Shwann cell membrane 76% Lipids
- Oligodendrocytes
- Protein concentration varies from time to time even in the same cell
- Protein Content depends on Protein turnover rate of cell

Protein turnover rate of cell 00:21:46

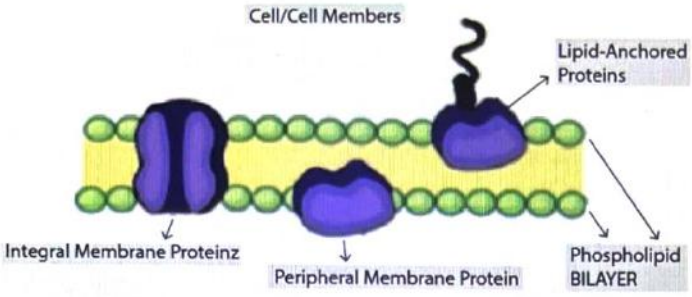
- during removal, it first TAGGED by UBIQUITIN
- degradation takes place in 26 s Proteosome
- Mechanism of increase NA^+ Reabsorption by aldosterone
- Na^+ Reabsorption Mechanism
  - ENac is Tagged by Ubiquitin NEDD / NEDD - 4 like
  - Aldosterone inhibits NEDD / NEDD - 4 like & promotes Na+ reabsorption
  - Aldosterone also increases the number of Na+ - K+ Pumps on baso - Lateral membrane
    → Aldosterone deubiquinates ENaC increases Na^+ reabsorption increases the number of Na^+ k^+ pumps

TYPES OF PROTEINS

00:31:10

1. Integral proteins

- Span the membrane
- Located within the membrane
- Eg: GPCR [G Protein coupled Receptor]
- 7 trans membrane segments present
- aka SERPENTINE RECEPTORS
- SONS OF SEVEN (spans membrane 7 times)
- Cyclic AMP
- Cyclic GMP



2. Peripheral proteins
- attached on one side of membrane either inside or outside

3. Glycosyl Phosphotidyl Inositol - GPI Linked proteins
- DAF [Decay Accelerating Factor]
- Present on RBC membranes
- Prevent Complement attack on RBC
- Defect Leads to Paroxysmal Nocturnal Hemoglobinuria induced of Complement lysis Eg: CD55 or CD59

Previous Year's Questions

Q. Paroxysmal nocturnal hemoglobinuria occur from which of the following defect ?
A. Integral proteins
B. Peripheral proteins
C. GPI Linked proteins

Previous Year's Questions

Q. Which of the following ligated ion channels
A. GABA A receptor
B. GABA B receptor
C. muscarinic acetylcholine receptor
D. NMDA receptor for glutamate

JUCTIONAL COMPLEXES

00:38:54

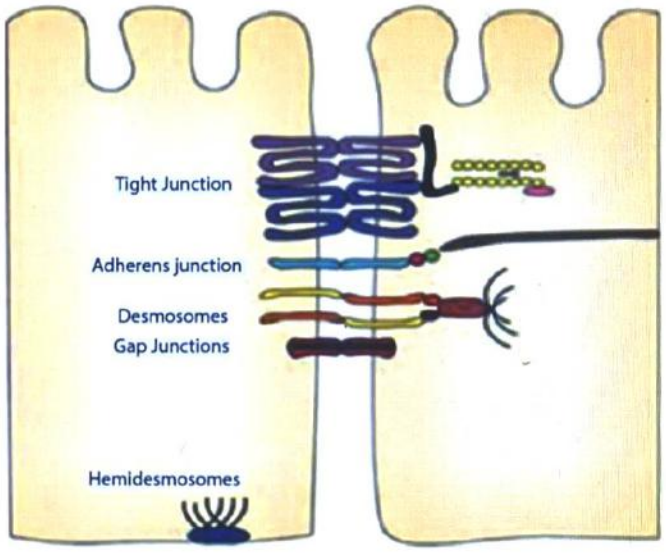
1. Desmosomes/macula adherence
- Epithelial cells are connected to each other with Desmosomes
- Protein involved → DESMOPLAKINS
  - Fibrillar proteins extends into them
- Provides Tensile strength to the tissue
- Found at places where
  - increase Tensile strength required - skin
  - High Wear & Tear of the tissue present - Gums, Cervix

2. Gap junctional
- Low resistance passages
- Free passage of ions from one cell to others
- Found is Heart, Smooth muscles in wall of the gut
- Protein made up of Made of 6 CONNEXON

Charcot marie tooth disease
- Peripheral neuropathy
- Defective myelination
- Defective connexin 32→ Defective gap junction b/w Schwann cells

Idiopathic atrial fibrillation
- defective Connexin 40

Tight juctions (zonula occludens)
- Selectively permeable
- Found at Blood Brain Barrier, Lining of Gut
- Proteins involved
  - Claudins
  - Occludins
  - Junctional Adhesive Molecules(JAMS)



TRANSPORT PROTEINS IN THE CELL MEMBRANE

00:51:20
- Pores
- Channels
- Careeiers
- Pumps

Pores
- Always open
- Ex: Aquaporins, Perforins
  Responsible for H_2O movement

Channels

- Carryout simple Diffusion of water soluable substance
  - 2 types of channels
    - → Leaky channels - Na+ Leaky channel present on all cells
    - → Gated channels

GATED CHANNELS

00:59:19

1. Voltage gated ion channels

- Na+ channels in nerve membranes

2. Ligand gated ion channels /Inotropic receptor Associated channel

- GABAA
- Nicotinic Acetyl Choline Receptor

3. Cyclic nucleotide gate channel [CAMP, CGMP] or Metebotropic recepyor associated channel

- G protein coupled Receptor involved (HCN) Hyperpolarization activated cyclic nucleotide gated channel
  - Funny Na Channel
  - More the hyperpolarization, more is activation of channel
  - Ex: GABAB , Muscarinic Ach Receptor

4. Time gated channels

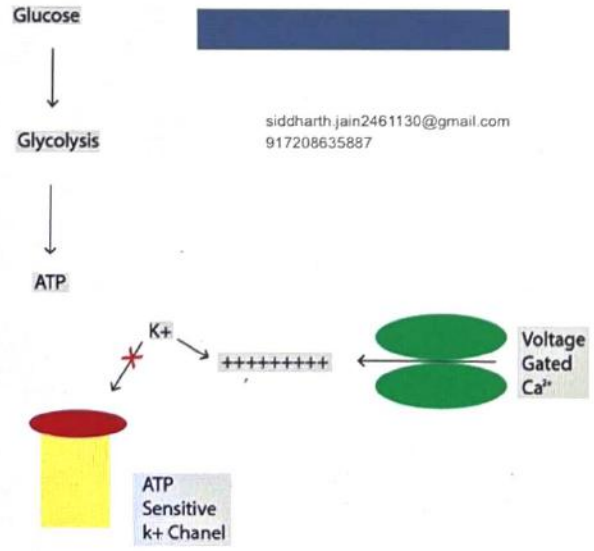
- K^+ channels in nerve membrane
  - Ex: Slow Ca^{2+} channels in heart

1. Echanically gated channels

- Ex: Touch Receptors in the Skin

2. Chemical gating channels

- Intracellular chemicals
- Hypoxia causes vasodilation everywhere, but vasoconstriction in LUNGS



- Ex:O2 hypoxia sensitive K+ channel in lungs Vascular SM cell at sensitive K+ will accumulate near membrane occur Depolarization cause Vasoconstriction
- In other organs (systemic circulation)O2 hypoxia sensitive K+ channel Vascular SM cell have lack of ATP so channel remains open Hyper polarization cause Vasodilatation
- O2 SENSITIVE K+ CHANNELS Found at - lungs,Carotid Body
- Erythropoietin synthesizing cells in kidney

ATP SENSITIVE K+ CHANNELS

- Found in PANCREATIC β CELLS
- Glucose undergoes glycolysis & releases ATP
- ATP Sensitive K+ Channels causes intracellular K+ accumulation & causes opening of voltage gated Ca2+ channels
- Ca2+ enters which results in synthesis of Insulin by exocytosis
- study of single ion channels done by PATCH CLAMP TECHNIQUE

POISONS / BLOCKERS OF CHANNELS

01:24:59

- 1. Na+ Channel Blockers → Tetrodotoxin Nerve gas toxin found in puffer fish Saxitoxin
- 2. K+ Channel Blocker→ Tetra Ethyl Ammonium(TEA) - Component of Mamba snake venom
- Patch clam method used for -study of single ion channel

CARRIERS

01:28:56

- Involved in facilitated diffusion (uniport)
- 2° Active transport (symport/ antiport)
- GLUCOSE TRANSPORTS INTO ALL CELLS by facilitated diffusion by GLUT
- EXCEPT in GIT & KIDNEY occurs by 2°active transport by SGLT
- GLUCOSE TRANSPORT IN GIT & KIDNEY

Glucose crosses 2 membranes

- Transport occurring for absorption or reabsorption

PUMPS / ATPases

01:38:36

- Carries 1° Active transport
- They bind & breakdown ATP & Utilize ATP directly
- Ex: Na^+ - K^+ Pump in all membranes SERCA

ATP UTILIZING TRANSPORTERS

a. ATP ases (pumps)
  - Have single domain
  - 3 TYPES

1. P - TYPE [E1-E2]
   - Na^+ - K^+ pump
2. V - TYPE
   - present in membranes of vesicles
   - H^+ ATPases
3. F - TYPE
   - F_0 - F_1 pump
   - Works like a ATP Synthase

Previous Year's Questions

Q. Which of the following ligagated ion chennels?
A. GABA a
B. GABA b
C. Muscarinic acetylcoli receptor
D. NMDA receptor for glutamete

(ABC) ATP Binding Cassette Transporter

- have one domain, where ATP will be bound
- Other part of protein will act as a channel or carrier
- Ex: Multidrug Resistance transporter (MDR)transporter
- P-glycoprotein
- Found in cancer Cells & XDR (extremely drug resistant)
- Critical concentration not achieved → resistance
  - SUR (Sulfonyl Urea transporter
  - CFTR → chloride channel
- Voltage clamp technique - voltage across membranes
- Cathode Ray Oscilloscope – Action potential

STRUCTURAL CONFIGURATION OF TRANS PORT PROTEINS

01:44:33

7	GPCR (pans 7 times)
6	Connexon (6 subunits)
5	Ligand gated channels (5 subunits) CYS loop receptors
4	Voltage gated channels (tetramers)
3	ENaC – Trimeric G-Protein Na^+ - K^+ pump (,,) subunits
2	Integrins (dimers)

CLINICAL QUESTIONS

Q. Your professor is giving a lecture on Charcot Marie Tooth Disease, He conducts a pre-test before the start of the lecture. One of the questions mentioned in the paper is "Which among the following defective connexin causes the disease?" Choose the right answer among the following option.

A. Connexin 30
B. Connexin 32
C. Connexin 36
D. Connexin 40

Answer: B

Solution:

- Charcot Marie Tooth disease is a peripheral neuropathy.
- It results from defective **connexin-32** that forms **gap junctions between adjacent Schwann cells.**
- Defect in connexin 40 – Idiopathic atrial fibrillation.

Reference: Ganong's Review of Medical Physiology 26th Edition, Page No. 44

4 TRANSPORT PROCESSES

2 TYPES 00:00:22

1. ACROSS MEMBRANE /cytopemsis
- Endocytosis
- Exocytosis

2. THROUGH MEMBRANE
- Osmosis
- Diffusion
- Active transport

00:03:33

A red cell with initial volume 100u3 intracellular tonicity 300 omsol pre liter was suspented in a solution having a osmolarity of 100miligram pre liter how much the final cell volume?

ACROSS MEMBRANE 00:06:17

- Vesicular transport/ CYTOPEMPSIS/ TRANSCYTOSIS/ ENDOCYTOSIS
  - Occur for Large molecules Particles
  - Foreign Substances

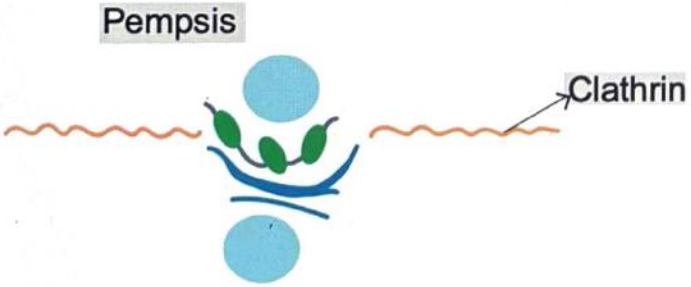
2 TYPES

a. Phagocytosis (cell eating)
Ex: Bacteria entry into neutrophil

b. Pinocytosis (cell drinking)
Ex: Soluble proteins enters the cell

- **MECHANISMS**

1. CONSTITUTIVE → vitamin entry
2. RECEPTOR MEDIATED / CLATHRIN MEDIATED ENDOCYTODSIS
→ In the fig
There is a pit with Receptor in the membrane
CLATHRIN (Fibrillar Protien) present in the pit
Ex: IDL Entry into steroidogenic cells



3. CAVEOLIN MEDIATED ENDOCYTOSIS (POTO/ PODO CYTOSIS)
- Ex: Folate entry into cells

2. EXOCYTOSIS/ CELL VOMITING 00:17:44
- Reversed pinocytosis (if liquid)
- 2 types

a. CONSTITUTIVE EXOCYTOSIS
- Ex: Mucus Secretion
Ig Secretion by plasma Cell

b. REGULATED EXOCYTOSIS
- Ex: I) Neurotransmitter Secretion at Synapse
ii) Hormone Secretion

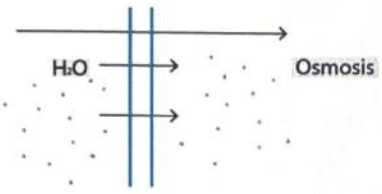
All types of Exocytosis need increased intracytoplasmic Ca^{2+}
Except
1. PTH Secretion
2. Renin Secretion by JG CELLS

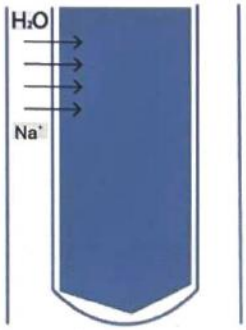
Ca^{2+} creates the bridge between both the membranes, which otherwise repels each other.

TRANSPORT THROUGH THE MEMBRANE

1. OSMOSIS 00:27:26
- H_2O moves from low solute to high Solute Concentration
→ Bulk flow or solvent drag protein
- water moves in bulk & it drags Na^+ along with it
- Occurs in

1. CSF absorption
2. Capillary filtration
3. Descending limb of LH





OSMOSIS

OSMOLARITY → Number of solute /solution in liter
OSMOLALITY → Mass of Solute / kg of water

Temperature will influence osmolority NOT OSMOLALITY

Q. Na^+ - 145, glucose – 720 mg%, BUN – 28 What is serum osmolality?
SERUM OSMOLALITY (mOsm/ kg of water

$$[2.1 \times Na^+] + \left[\frac{Glucose}{18}\right] + \left[\frac{BUN}{2.8}\right]$$

- Osmolality includes all solutes

TONICITY→NON PENETRATING SOLUTES ARE CONSIDERED, because
→ They do not cross membrane easily & remains unequal on either side of the membrane & cause movement of H_2O resulting in change of Cell Size
→ UREA → INEFFECTIVE OSMOLE, NOT CONSIDERED FOR TONICITY
→ Urea permeates the membrane very easily & very rapidly it reaches equilibrium. It will not cause movement of water

Q. Red Cell Volume → 100 μ^3 , IC tonicity → 300 mosm/L, placed in a solution with osmolarity of 100 mosm/L. Final red cell volume?

$\Pi_i V_i = \Pi_F V_F$
300 x 100= 100 x V_F
30000 = 100 V_F
V_F = 300 μ^3

Π_i → Initial osmolarity
V_i → Initial volume
Π_F → Final osmolarity
V_F → Final volume

2. DIFFUSION

- Passive transport (no ATP needed)
- Net effect - down-hill transport (high to low)

TYPES

a. SIMPLE DIFFUSION

- Kinetic energy drives the diffusion
- Ex: Lipid soluble substances diffusion by Lipid Bilayer

Water soluble Substances through channels

FICK's LAW (J) = $\ominus$ DA x $\frac{\Delta C}{d}$

(FLUX)
D = Diffusion co-efficient
A = Surface area
C = Concentration gradient
d = Thickness of membrane or Diffusion Distance

FACTORS

1. LIPID SOLUBILITY

- CO_2 is 20 times as lipid soluble as compared to O_2
- CO_2 diffusion > O_2 diffusion

2. No. of Channels

- K^+ channels > Na^+ channels

3. TEMPERATURE (directly proportional)
4. SURFACE AREA (directly proportional)

- Ex: Emphysema
- destruction of alveolar Septa (↓ SA) → ↓ diffusion

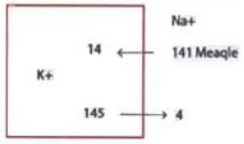
5. THICKNESS OF MEMBRANE (Diffusion Distance) → Inversely proportional
6. SIZE / RADIUS / MOLECULAR WEIGHT OF SUBSTANCE → Inversely proportional

- Ex : Hydrated Na^+ (2.2 nm) > Hydrated K^+ (2.0 nm)
- Hence, hydrated K^+ moves faster

7. CONCENTRATION GRADIENT → Directly proportional

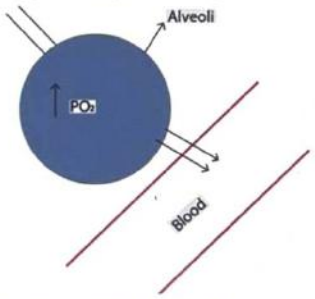
- Ex: K^+ diffusion is 50 - 100 times Faster than Na^+ diffusion

Most diffusible ion	K^+
Most diffusible ion for excitable cell	K^+
Most diffusible ion for exciting membrane	Na^+



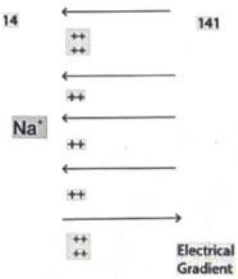
8. PRESSURE GRADIENT

- For gases transport
- Ex: Hyper boric O_2 in CO poisoning



9. ELECTROCHEMICAL GRADIENT

- Cation, diffuses from high no. of positive charges to low no. of positive charges by Electrical gradient (Wider gradient, greater the diffusion)



a. FACILITATED DIFFUSION

- Carrier mediated transport

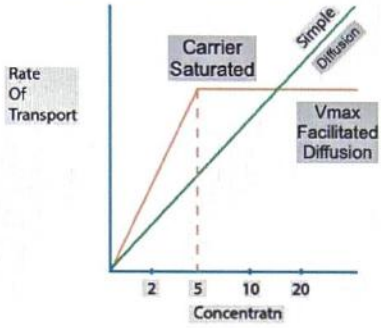
- no ATP needed
- net - down-hill transport

CHARACTERISTICS OF FACILITATED DIFFUSION

01:19:03

1. SATURABILITY [MICHAELIS - MENTON KINETICS]
2. SPECIFICITY
3. INHIBITION
   - Glucose transport by GLUT inhibited by PHLORETIN [PHLORIZIN]

GLUT
[Glucose Transporter] TYPES



1. GLUT 1 → Constitutively expressed, Ubiquitous
2. GLUT 2 → Pancreatic ß cell
   → Glucose exit the cell by GLUT 2
3. GLUT 3 → constitutively expressed, predominant in Brain
4. GLUT 4 → Insulin dependent glucose transporter present in muscle & Fat
5. GLUT 5 → fructose transporter

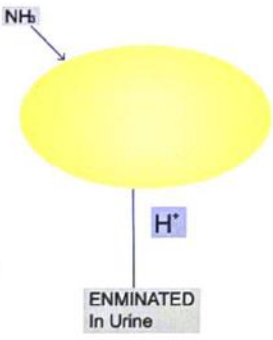
→ Carries are based on principle of concentration gradient
High concentration → High affinity
Low concentration → Low affinity

NON IONIC DIFFUSION [DIFFUSION TRAPPING]

01:34:48

- Seen in weak acids & weak bases
- PRINCIPLE → NON IONIC FORMS ARE MORE DIFFUSIBLE THAN IONI FORMS

1. EX: Aspirin entry into parietal cells
   NH_3 buffering in kidney



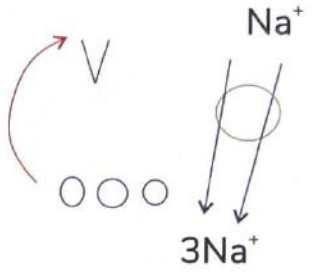
2. ACTIVE TRANPORT

1.01:39:29

- Uphill transport (low to high)
- Needs ATP

A. 1° ACTIVE TRANSPORT

- Carried by pumps
- ATP used directly
- creates & widens the concentration gradient for Na+
- potential energy stored in this concentration gradient is utilized by carrier to carry 2 substances
- Ex: $Na^+ K^+$ Pump
  SERCA Pump



1. Na^+ → high to low
2. Other Substance → Low to high

B. 2° ACTIVE TRANSPORT

- Achieved by carrier
- ATP used indirectly

A. SYMPORT / CO - TRANSPORT → 2nd substance goes in the same direction

Ex: 1. SGLT

- For Glucose entry into cells of GIT & KIDNEY
- 3 types

$SGLT_1$	→	Carries 2 Na^+, 1 glucose
$SGLT_2$, $SGLT_3$	→	Carries 1 Na^+, 1 glucose
Na^+	→	High to Low
Glucose	→	Low to High

2. TRANSPORT OF AMINO ACIDS

ANTIPORT OR COUNTER TRANSPORT OR EXCHANGE

2nd substance goes opposite to Na^+

Ex: 1 (NCX) sodium -calcium Exchanger 3 Na^+; 1 Ca^{2+} Inside outside

2. Cl^- - HCO_3^- Exchanger in Red cell membrane
→ Band 3 protein
→ Anion Exchanger type 1

- All the 2° active transports are absolutely dependent on 1° active transport
- Na+ -k+ pump creates and windens concentration gradient for Na+. Drive high to low and potential energy stored in concentration gradient will be used by the carrier 2nd substance simultaneously from low to high

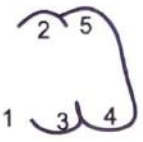
NA^+ - K^+ PUMP

01:48:16

- 1° active transport
- has 3 sub units & 5 binding sites α, β, (γ - FXYD)
- discovered by JENS SKOV

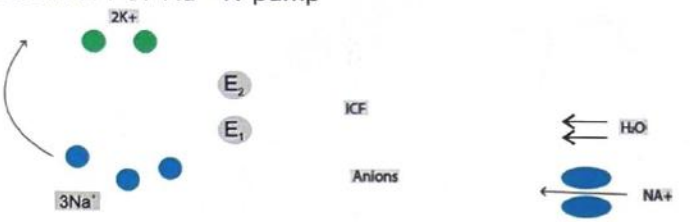
- Present in all the membranes & active all the times

3 SUB UNITS →α→ Catalytic, β & γ→ supportive

2 = K^+ binding site 5 = Ovabain biding site		1 = Na^+ binding site 3 = ATP binding site 4 = Phosphorylat^n site

→Hypokalemia potentiates Digitalis toxicity

ACTIVITY OF Na^+ - K^+ pump



- FUNCTIONS

02:06:02

1. Opposes the Donnan Equilibrium d/t excess of impermeant anions
2. Regulates the cell volume
3. Involved in recharging of excitable cells

↑Na^+ in cells
↓
Draws in H_2O
↓
Cell will enlarge & burst
Prevented by Na^+ K^+ Pump

4. Involved in process of basal metabolic rate or basal energy

Expenditure

BMR/BEE

→40% [for entire body]

70% [FOR NEURON]

B. Electrogenic

→Contribute to negative charge on membrane (-4mV directly contributed by Na^+ - K^+ Pump)

02:17:08

STIMULATOR	INHIBITORS
• Aldosterone → ↑ No. of Na+ K+ pump • Thyroid → ↑ Activity of Na+ K+ pump • Insulin → ↑ pump activity • Catecholamines → ↑ Pump activity	• Digitalis • Diuretics • Dopamine in the kidney • DNP

Digitalis inhibits Na^+ - K^+ Pump
↓
NCX can't function
↓
↑Ca^{2+} in myocardial cells
↓
Strong contractions

Hypokalemia → digitalis toxicity
↓
Rx – Add K^+
↓
K^+ Binds to oubain binding site)

CLINICAL QUESTIONS

Q. Solution A and solution B are separated by a membrane, which is permeable to K+ and impermeable to Cl-. Solution B is at 1 mM KCl and solution A is at 100 mM KCl. Which among the following statements is best related to the Solution A and solution B?

A. K+ ions will diffuse from solution A to solution B until the [K+] of both solutions is 50.5 mM
B. K+ ions will diffuse from solution B to solution A until the [K+] of both solutions is 50.5 mM
C. KCl will diffuse from solution A to solution B until the [KCl] of both solutions is 50.5 mM
D. K+ will diffuse from solution A to solution B until a membrane potential develops with solution A negative with respect to solution B

Answer: D

Solution:

- The membrane is permeable only to K+ ions.
- K+ will diffuse down its concentration gradient from solution A to solution B, leaving some Cl^- ions behind in solution A.
- A **diffusion potential will be created, with solution A negative with respect to solution B.**
- Generation of a diffusion potential involves movement of only a few ions and therefore, does not cause a change in the bulk concentration.

Reference: Ganong's Review of Medical Physiology 26th Edition, Page No. 8

LEARNING OBJECTIVES

UNIT 2 NERVE MUSCLE PHYSIOLOGY

MEMBRANE POTENTIAL

- Origin of RMP
- Nernst Equation
- Goldman's Constant Field Equation
- RMP of Nerve

EXCITATION AND ACTION POTENTIAL

- Membrane Excitation
- Stimulus
- Rheobase
- Chronaxie
- Membrane Excitaion and Impulse Transmission
- Electrotonic Conduction
- Action Potential Conduction Myelinated
- Unmyelinated Nerve Conduction
- Action Potential and its Properties
- Phases of Action Potential
- Other ways of Depolarisation
- Gating behaviour of Na+ Channels
- Refractory Period significance
- Effects of Ions (Changes in ECF Concentration)

NERVE

- Neuron
- Classification
- Nerve Fibres
- Nerve Injury & Grading
- Wallerian Degree

MUSCLE PART 1

- Types of Muscles
- Neuromuscular Junction
- Events occurring at Neuromuscular Junction
- End Plate Potential
- Difference Between End Plate Potential and Action Potential
- Excitation Contraction Coupling
- Difference between Excitation Contraction Coupling in cardiac muscle and skeletal muscle

MUSCLE PART 2

- Neuromuscular Junction
- Autoimmune disease of Neuromuscular Junction
- Excitation Contraction Coupling in Skeletal muscle
- Diseases associated with EC coupling
- Excitation Coupling in Cardiac Muscle
- Types of Skeletal Muscle Fibres

SARCOMERE

- Definition
- Length of Sarcomere
- Starling's Law
- Ratio of Thin & Thick Filaments
- Muscle Proteins
- Various Bands & Zones
- Changes with Contraction & Shortening

SMOOTH MUSCLE

- Types of Smooth Muscles
- Electrical Activity of Smooth Muscles
- Ratio of Thick to Thin Filaments
- Latch Bridge Phenomenon

5 MEMBRANE POTENTIAL

- Resting membrane potential RMP 00:00:45
- Action potential
- Nerve & muscle physiology

MP

- Each cell has increase negative charge inside the membraine potential
- Every cell has the negative charge the charge varies cell to cell.

- Red cell, epithelial cell – 8 to – 20 mV
- Smoth muscle cell – 38 to – 45 mV
- SA Node – 55 to - 65 mV
- Nerve – 70 mV
- Skeletal muscle & purkenj Fiber in heart – 90mV

Previous Year's Questions

Q. Which of the following cells transmembraine electrical gradient is highest?
a. RBC
b. Skeletal muscle
c. Rod in Retina
d. Hair cell in cochlea

- All the cell surround by ECF (outside)
- Hair cell surround by Fluid endolymph
- Endolymph has high K^+ concentration so its resemble ICF
- Endolymph potential is +80mV endoiochlear potential
- Hair cell – 150 mV

RESTING MEMBRAINE POTENTIAL (RMP)

- Nerve, muscle existable tissues
- Nerve – 70mV
- Skeletal muscle – 90 mV

ORGIN OF RMP 00:11:30

- Equilibrium potential for anion
- Highest equilibrium – Ca^+

Na^+

- Concentration gradient narrow
- Electrical gradient created across the membrain
- At one point concentration gradient equal to electrical gradient
- Equilibrium potential for Na^+ +61mV

NERNST EQUATION 00:15:35

$$EMF(mV) = \pm 61 \times \log \left[\frac{C_1}{C_2}\right] \frac{141}{14}$$

$$\text{Log}10 = 1$$

$$\pm 61 \times 1 = \cdot 61\,mV$$

K^+

- In concentration gradient potassium moves out from call (mEq/L)
- Electrical gradient created a cross the membrain

Equilibirum potential For K^+ - 94mV

- Na^+ & K^+ both moves the potential – 90 mV
- K^+ diffusion inside to outside
- $Na^+ < K^+$, incontribution of RMP

Equilibrium potential For Cl^- = - 89 mV 00:27:18

Previous Year's Questions

Q. Which ion close st to RMP of muscle?
a. Na^+
b. k^+
c. Cl^-
d. Ca^+

- When all 3ions moves & reach equilibrium we use Goldman's constant Fild (GHK)
  - Concentration gradients
  - Relative membraine permiability

EMF (mV) = 61 x Log [3 ions]

$$\frac{\left[C_{Nai^+} \times P_{Na^+}\right] + \left[C_{Ko^+_i} \times P_{K^+}\right] + \left[C_{Nl^-_i} \times P_{Cl^-}\right]}{\left[C_{Na^+_o} \times P_{Na^+}\right] + \left[C_{K^+_i} \times P_{K^+}\right] + \left[C_{Nl^-_o} \times P_{Cl^-}\right]} = -86mV$$

$= I\zeta 0 - \text{inside}\ \zeta\ \text{outside}$

00:33:18

- -86 mV K^+ diffusion
- -4 mV Na^+ - K^+ pump
- -90 mV RMP
- RMP of Nerve -70mV

EP for Na^+ +60mV
EP for K^+ - 90 mV

EP for Cl^- - 70mV
EP for Ca^{++} + 129 mV
EP for H^+ - 23mV
EP for HCO_3 – 25 mV

Previous Year's Questions

Q. Which in Equlibirum is closed to nerve RMP?
a. Na^+
b. k^+
c. Cl^-
d. +129mV

- K^+ is closed Cl^- is same value

6 EXCITATION & ACTION POTENTIAL

Stimulus:
- Intensity
  - Rapidly rising
  - If slow rising result in membrane accommodation
- Duration should be optimum
- Retrangular pulse, exponential pulse –best

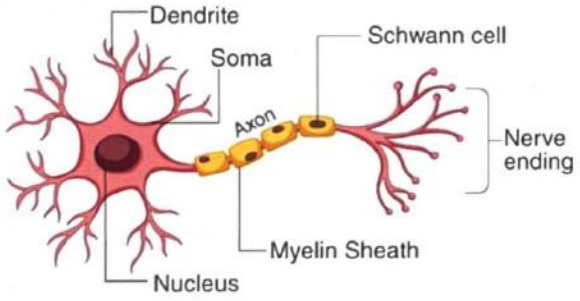
Rheobase
- Minimum strength of stimulus that can excite a tissue

Chronaxie
- Measure of exitability
- E.g.:
  - Myelinated nerve
  - Unmyelinated nerve
  - Skeletal muscle
  - Cardiac muscle
  - Smooth muscle

↓ least

Membrane excitation & impulse transmission:
1. Action potential propagation
2. Electrotonic conduction

Impulse transmitted by combination of this actions.



Impulse transmitted via:
- Dentried to axon hillock – next neurons

Electro toxic conduction:
- Direct, passive spread of charges
- Charge leakage by membrane capacities
- Decremental conduction
- Dendrite to axon hillocks the charges pass in electronically
- Action potential develops in axon hillock
- In axon hillock enough number of Na^+ channel in low threshold

Salutatory	Local circuits
• Less decremental because of myeli sheath • Faster • Less ATP e.g.: Retina Rod to ganglion	• Unmyelinated nerve convert the Ap o Slower o More energy need

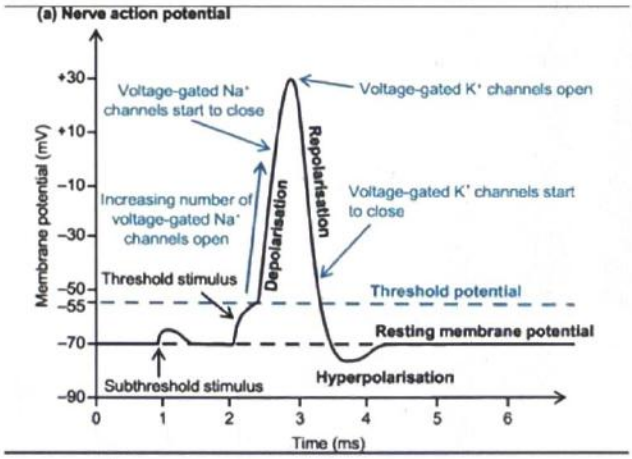
- Inter nodule 1-3 mm
- In demyelination disease nodule 10 mm
- If patient demyelination disease taken not bath membrane capacities increase

Action potential
- Self-regenerative process
- Self-propagated process
- Non- decremnetal conduction
- All or none law

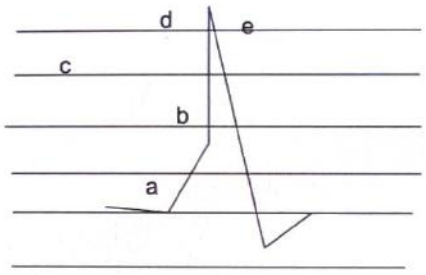
Phase of Ap
- Cathode Ray oscilloscope [CRO]
- Patch – clamp
- Voltage – camp

- Depolarization – Na^+ entry
- Repolarization – K^+ entry

Other way of depolarization
1. Heart SA node – Ca^{++} entry
2. Hair cell in endolymph – K^+ entry
3. Pancreatic beta cell – accumulation of K^+



Q. Na+ channel closed which point?



Ans. c

Phase 1 – local potential change
- Due to Na+ influx
  Threshold – massive, instantaneous surge of Na^+ immediately followed by closure of Na^+ channels

Phase 2 – Depolarization
- Due to rapid Na^+ influx
- During action potential, can go to + 35 mv

Phase 3 – repolarization
- Due to k+ efflux

Phase 4 – hyperpolarization phase
- RMP is = 90 mv
- GABA causes inhibition by hyperpolarization
- Hyperpolarization by cl^- influx & K+ efflux.
- EP for IC^+ = 90 mv

Gating behavior
- Na+ channels
  - 2 gates
    → M activation
    → H inactivation gate
  - 3 possible states
    → Resting state
    → Open state [depolarization]
    → Inactivation state [repolarization]
  - Resting – m gated closed, H gate open
  - Open – both gates open, Na^+ freely comes inside
  - Inactivation – m gate – open, H gate closed

Refractory period:
- Determit frequency of stimulation of tissue
- e.g.:
  - RF 1 sec = 60/mins
  - RP 5 sec = 12/mins

Effect of ions:
- Changes in EOF concentration

1. Na^+
   - AP
   - Hyponatremia
   - Amplitude of AP decrease
   - Severe hyponatremia – conduction may stop

2. K^+
   - RMP
   - Hypokalemia – Hyperpolarization

3. Ca^{++}
   - ECF ca^{++} is necessary for stability of Na^+ channel gating
   - Hypocalcemia (Tetani)
     i. Trouseen's sign
     ii. Chortek's sign

7 NERVE

00:01:22

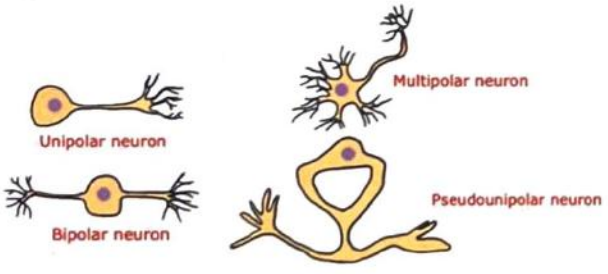
Q. Post ganglionic parasympathetic neuron is?
a. Multipolar
b. Bipolar.
c. Anaxonal.
d. Pseudounipolar

Q. A person sustains a sharp injury to nerve in a road traffic accident. Complete transection of the nerve is seen. What is the first change post injury?
a. Chromatolysis
b. Axonal degeneration
c. Myelin degeneration
d. Schwann cell proliferation

- No new neurons formed after birth EXCEPT for OLFACTORY NEURONS. It is a terminally 00:02:40 differentiated cell. Olfactory neurons are superficial and prone to injury. Hence, it is frequently replaced.

CLASSIFICATION OF NEURON 00:12:02

1. MULTI POLAR - Brain & cerebral cortex (majority)
2. BIPOLAR - Retina, Olfactory neuron
3. PSEUDO UNIPOLAR - Nerve cell in dorsal root ganglion

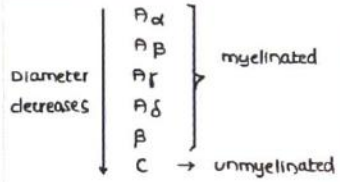


ANAXONAL NEURON - Post ganglionic parasympathetic neuron

Ex: Anacrine cell in Retina

CLASSIFICATION OF NERVE FIBRES

- In Myelinated nerve fibres, conductiona 00:18:20 proportional to 6 times the diameter
  - Eg. A α – 20 μ - 120 m/s
- In unmyelinated fibres, conductional velocity* $\sqrt{\text{Diameter}}$

6TYPES	CONDUCTION VELOCITY
	1. DIAMETER • Smaller the diameter more axoplasmic resistance Lesser 18the conduction velocity 2. MYELINATION • Conduct velocity is faster in myelinated nerve fibres

MYELINATION IS BY

- In PNS (20:1) - Schwann cells
- In CNS (1:20) - Oligodendrocytes
- A α - Proprioception & α - motor neurons fastest conduction for voluntory movements
- A β - Touch & pressure
- A γ - γ motor Neuron to muscle spindle. Maintains excitability of muscle spindle
  - Ex: JENDRASSIK'S MANEUVER
- A δ - Fast pain & temperature
- B - Preganglionic Autonomic nerve Fibres
- C - Somatic → Slow Pain
- Autonomic → Post ganglionic Sympathetic

NUMERICAL CLASSIFICATION

A α	I a	Primary afferents – proprioception from annulo – spiral endings of muscle spindle→length of muscle to spinal cord.
A β	I b	From golgi tendon (to detect – muscle tension)
A γ	II	Proprioception (from flower spray endings of intrafusal fibres)

A δ	III
C	IV

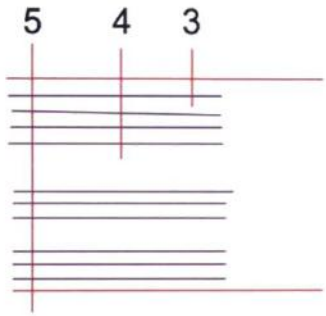
Opioids acts on type C fibers, relieves slow pain

INJURY TO NERVE FIBRES

00:35:16

	most susceptible
Pressure	A
Hypoxia	B
Local anesthesia	C

SUNDER LAND'S		SEDAN'S
1° →	Mild pressure, hypoxia	NEUROPRAXIA
2° →	Severe & sustained pressure	
3° →	Single axonal transect^{n}	→ AXONOTMESIS
4° →	Never Fascicles are disrupted	NEUROTMESIS
5° →	Nerve trunk transection	



Q. What is the Ist change seen in Wallerian degeneration?
a. Chromatolysis
b. Axonal degeneration
c. Schwann cell proliferation
d. Myelin degeneration

WALLERIAN DEGENERATION

00:42:36

- Named after Augustus Waller
- Repair of nerve fibers after Injury
- Seen after 5th degree injury when entire nerve trunk is damaged
- Changes seen in distal stump or proximal stump near the nodes of Ranvier

Within 24 - 48 hrs	-	Chromatolysis
Upto 3 days	-	distal stump still functional
6th day	-	Axonal degeneration
10th day	-	Myelin degeneration
15th day	-	Repair
		o Sprouting
		o Schwann cell proliferation
80th day	-	Repair Completed

- If the question is about 1st change seen post nerve injury, it is CHROMATOLYSIS
- If the question is specifically about WALLERIAN DEGENERATION, 1st change seen is AXONAL DEGENERATION (Chromatolysis is seen in the nerve cell body)
- Chromatolysis – Nissel cells are grounded and they disappear
  - Cell imbibes H_2O & swells.
- Nucleus pushed to the periphery.

CLINICAL QUESTIONS

Q. A gradual increase in threshold caused by prolonged slowly rising sub-threshold stimulus resulting from the inactivation of sodium channels, i.e., the normal threshold may be passed without the firing of an action potential, when the nerve is depolarized very slowly. Which one of the following is being described here?

A. Adaptation
B. Accommodation
C. Refractoriness
D. Electrotonus

Answer: B

Solution:

- **Accommodation**: refers to a gradual increase in threshold caused by **prolonged slowly rising sub-threshold** stimulus resulting from the inactivation of sodium channels, i.e., When a nerve is depolarized very slowly, the normal threshold may be passed without the firing of an action potential (option-2).
- **Adaptation**: When a continuous sensory stimulus is applied, the receptor responds at a high impulse rate at first and then at a progressively slower rate until finally, the rate of action potentials decreases to very few or often to none at all (option-1).
- **Refractoriness:** If the second stimulus applied during the refractory period of the first stimulus, the second stimulus fails to excite the tissue for one more time (option-3). While, in accommodation, the tissue fails to respond even for the first time.
- **Electrotonus**: Dendrites fail to transmit action potentials because their membranes have relatively few voltage-gated sodium channels, and their thresholds for excitation are too high for action potentials to occur; refers to a passive spread of charge inside a neuron (option-4).

Reference:

- Berne & Levy Physiology.CHAPTER 5 Generation and Conduction of Action Potentials, 6th edition, Pg. 72.
- Guyton and Hall Textbook of Medical Physiology, Unit IX The Nervous System: A. General Principles and Sensory Physiology, Chapter 45 Organization of the Nervous System, Basic Functions of Synapses, and Neurotransmitters. Pg. 555,556.

8 MUSCLE -1

SKELETAL MUSCLE –VOLUNTARY, STRIATED

00:02:12

- Cardiac muscle – involuntary, striated
- Smooth muscle –involuntary (visceral), non-striated

Previous Year's Questions

Q. Correct statement about Ach synthesis?
A. Ach & its vesicles are synthesized in nerve cell body.
B. Ach & its vesicles are synthesized in nerve terminal.
C. Ach in cell body but vesicles is formed locally.
D. Ach is formed locally & its vesicles in the nerve cell body.

Previous Year's Questions

Q. Choose the correct statement about contraction.
A. Deplarization → muscle contraction
B. Repolarization → muscle contraction
C. Both Depolarization & Repolarization → muscle contraction
D. Both Depolarization & Repolarization → muscle contraction & relaxation

NEUROMUSCULAR JUNCTION

00:03:05

- Ach vesicles will be synthesized in Nerve cell body
- Ach Synthesized locally in nerve terminal
- Nerve to nerve junction called synapse
- Nerve to muscle junction called neuro muscular junction
- In the nerve terminal – ach receptor,ca++ channels,ATPs are main contribution
- In muscle ligant gated ion channels pentamer, non specific cations
- Nicotine Acetylcholine receptor
  - Ligand gated channel and Nonspecific cation channel
  - Acetylcholine Binds to Receptor the Channel opens and the Same channel allows Na+ influx, K+ efflux but at -9[illegible] Na+ influx predominantly Results in EPP (End Plate Potential)

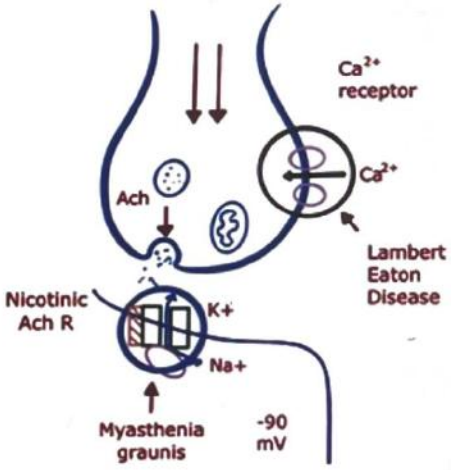
DEPOLARIZATION

00:16:39

- It is a travelling impulse, resulting in muscle contraction.
- Relaxation occurs if one more depolarization does not come in
  - Ca^{2+} pumped back resulting in relaxation.

REPOLARIZATION

- Do not travel, occurs point by point
- Recovery from excitation
  - 1 Impulse = 60 vesicles released Each vesicle = 10,000 molecules
- Ach released by exocytosis.while channel opens Na+ influx predominate then k+ that will result in net enter of -90mV
- End Plate Potential EPP = 40mV trigger Action potential result in Muscle contraction

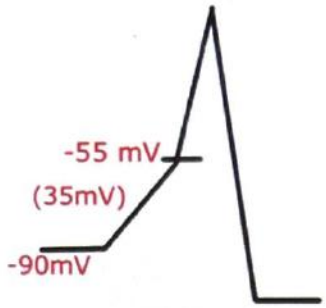


- Why net(+)?
- Na+ - (+61) mV
- K+ - (-96) mV
- The closer the membrane potential to the electric potential of the ion → ion movement is lesser

END PLATE POTENTIAL (EPP)

00:26:18

- Amplitude is 40 mv,
- Depolarization reach threshold trigger AP then muscle Contraction
- Graded Potential, Forerunner of action potential (AP)



EXCITATORY POST SYNAPTIC POTENTIAL (EPSP)

- Developed in CNS synapses
- Amplitude is 2, 3, 4 or 5 mV
- Multi EPSP will summate to create Action Potential

00:33:13

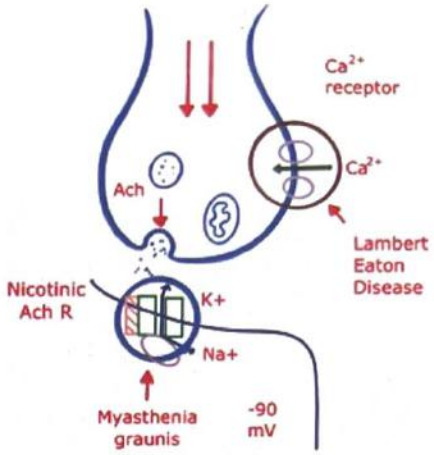
EPP	AP
• Localized (passive spread)	• Propagated
• Monophasic	• Biphasic
• Graded	• All or None

MINIATURE END PLATE POTENTIAL (MEPP) 00:38:54

- Even in resting conditions, small pockets of ACH released asynchronously, in minute quantities, creating MEPP
- Amplitude in microvolts

AUTOIMMUNE DISEASES RELATED TO NM JUNCTION

- Ca^{2+} channels -LAMBERT EATON
  - Presynaptic disease
- Nicotinic Receptor channel defect MYASTHENIA GRAVIS DIFFERENCE,
- With repeated contractions, with a continuous voluntary activity
- Strength will worsen in Myasthenia gravis due to Ach exhaustion
- Strength will increase in Lambert Eaton disease due to Ca^{2+} accumulation



EXCITATION CONTRACTION (EC) COUPLING 00:45:18

Previous Year's Questions

Q. DHPR is?
A. t-type Calcium channel (CC) in t-tubule.
B. l-type CC in l-tubule.
C. t-type CC in l-tubule.
D. l-type CC in t-tubule.

Previous Year's Questions

Q. Succinyl choline is administered to a 12 year old boy prior to a surgery. He starts shivering. Where is the defect?
A. DHPR
B. RyR
C. Dystrophin
D. Titin

- Binds with DHP-Calcium Channel Blocker
- Has voltage sensor in muscle tissue
- l - type voltage sensitive Ca2+ channel in t-tubule

SARCOTUBULAR SYSTEM OF MUSCLE 01:06:12

- EC coupling occurs in the sarcotubular system of muscle
- In skeletal muscle - 2 t tubules / sarcomere +nt
  - T–tubules are at the junction between I & A bands
  - Deep in structure
- In cardiac muscle- 1 t tubule / sarcomere +nt
  - In front of z– lines
  - Shallow &wide

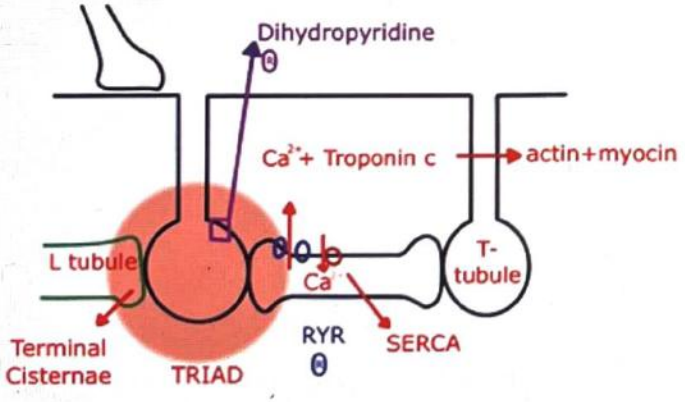
- In smooth muscle - Rudimentary
- Coupling occurs in the TRIAD
- TRIAD → One end of t-tubule with 2 ends of l-tubule on either side
- Expanded end of l-tubule are Terminal cisternae

RYANODINE RECEPTOR(RYR)

01:11:45

- In l-tubule
- When depolarization arrives via t-Tubule into muscle, it is sensed by DHPR
- DHPR interacts with RyR → Ca2+ will be released into sarcoplasm upto this is electrical
- Ca2+ combines with Troponin C, resulting in actin & myosin interaction
- Muscle contraction (this is mechanical).
- During Relaxation, Ca2+ will be pumped out by SERCA PUMP (vs. Repolarization – point by point recovery)
- Genetic defects of RyR result in
  - Malignant hyperthermia
  - Central core disease
  - Brody's disease

Depolarization arrives
↓
Travels into muscle via t-tubules
↓
Sensed by DHPR
↓
DHPR+RyR
↓
Ca^{2+} released into sarcoplasm
↓
Ca^{2+} + Troponin C
↓
Muscle contraction



MALIGNANT HYPERTHERMIA

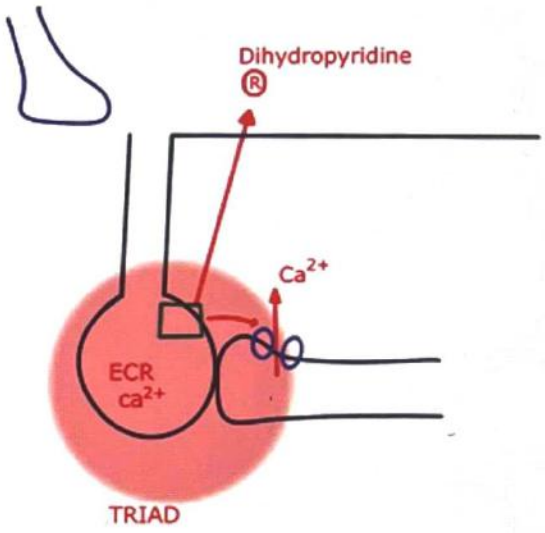
- It's a disorder of genes that cord for RyR
- Before Surgery, d/t administration of Sch/ Halothane / Ether →
- Sudden massive release of Ca2+ occurs-results in excessive rhythmic contraction of muscle (shivering)-increase muscle metabolism produce Generation of Heat in the body causing HYPERTHERMIA
- Rx by DANTROLENE Na (Uncoupler of Excitation & Contraction)

CENTRAL CORE DISEASE

- Excess Ca^{2+} release, mitochondria studded with Ca^{2+} & they will disappear leaving a core in the cell

EC COUPLING IN CARDIAC MUSCLE

- Shallow & wide t-tubules.
- Invagination of muscle membrane
- Store house of ECF Ca2+
- Depolarization sensed by DHPR →DHPR itself opens
- ECF Ca2+ enters muscle→Causes further
- Ca2+ release from RyR→Ca2+ Induced Ca2+ Release (CICR)
- ECF Ca2+influences cardiac contractility (vs. Skeletal muscle – Depolarization Induced Ca2+Release)



- Due to difference in the DHPR Receptor structure,
- NIFEDIPINE, Acts only on cardiac muscle contractility. It won't act on skeletal muscle contractility.

9 MUSCLE - 2

SARCOMERE

00:00:13

Previous Year's Questions

Q. How many thick filaments surround each thin filament?

A. 3
B. 4
C. 6
D. 2

Previous Year's Questions

Q. What is the optimal length that will generate maximum tension in the muscle?

A. 2 μ
B. 2.2 μ
C. 3.7 μ
D. 3 μ

00:04:28

- Basic structural unit of muscle is – sarcomere (the smallest unit where changes in muscle structure is taking place)
- Basic functional unit of muscle – motor unit
- The distance b/w the (2) Z - lines- SARCOMERE
- Normal resting length - 2 μ [L_o or L_{rest} = 2 μ]

STARLING LAW

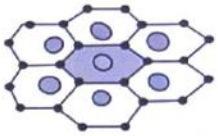
00:11:43

- Greater the initial length of muscle, stronger is the contraction, within physiological limits
- Length optimum(Lo)-2.2 μ Produce strongest contraction
- Length maximum(L max)-3.7 μ inter digitations is lost i.e.physiological limit

Previous Year's Questions

Q. Limb girdle muscular dystrophy is defect of?

A. Lamininopathy
B. Dystropinopathy
C. Titinopathy
D. Myosinopathy



Previous Year's Questions

Q. Which is the largest known human protein?
Ans: Titin

- Largest gene – Dystrophin gene

TITIN

00:14:46

- Anchored to Z- lines & it enters thick filament
- Largest human protein
- Aids in alignment of thick filament to sarcomere
- Genetic defects causes LIMB GIRDLE MUSCULAR DYSTROPHY
- The thin filament is attached to Z line by α-actinin & cap-2-protein

DYSTROPHIN

00:24:15

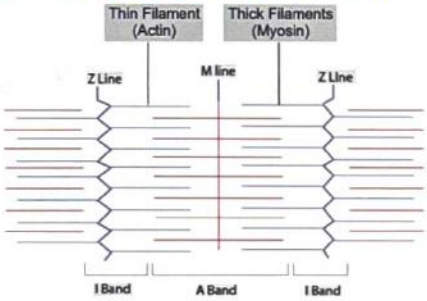
- Linked to thin filament & reaches sarcolemma
- Dystrophin linked to β-dystroglycan, which is intern linked to α-dystroglycan
  2 Dystroglycans linked to 4 sarcoglycans → Total : 6
  - α-dystroglycans are linked to laminin (ECM PROTEIN)
  - Tension generated by actin - myosin interaction is transported exterior to the tendon by Dystrophin
  - Defect causes DUCHENNE MUSCULAR DYSTROPPHY
- All sarcomeres will shorten when the muscle contracts

Previous Year's Questions

Q. Which band / zone or line will become prominent with muscle contraction?
A. A band
B. I band
C. H zone
D. M line

- I - Band -Thin filament on either side of Z line 00:26:17
  - Isotropic to polarized light
- A - Band -Remaining Part
  - An isotropic to polarized light
  - Contains thin & thick filaments
- H – Zone → Present at the centre of A Band
  - Have thick filament
  - In centre of H zone, M - Line is present (dark – myomesin)
  - On either side of M-Line, light areas are present
  - PSEUDO H – ZONE → Dark M Line& adjoining light areas on either side

DURING MUSCLE CONTRACTION



- Sarcomere Shortening
  - A-Band Remain unchanged
  - I-Band Shortens
  - H-Zone: Disappears
  - M-Line Become prominent
- At 1.5μ contracted length of sarcomere: Cm band appears
- At 1.25μ contracted length of sarcomere: Cz band appears
- Thick Filament
  - 1 thick filament = 500 myosin molecule
  - Each Myosin: 2 heavy chains + 4 light chains
  - Head Of Myosin: ATPase enzyme
- In the skeletal muscle- 2 T tubules pre sarcomere located in front of I band to A band
- In cardiac muscle -1 T tubules

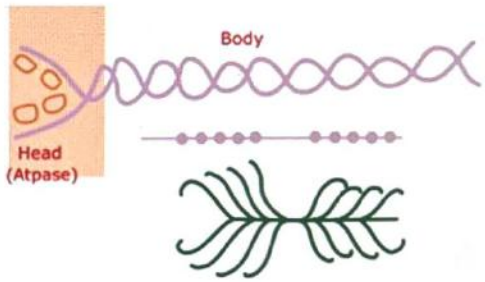
MOLECULAR BASIS

00:42:14

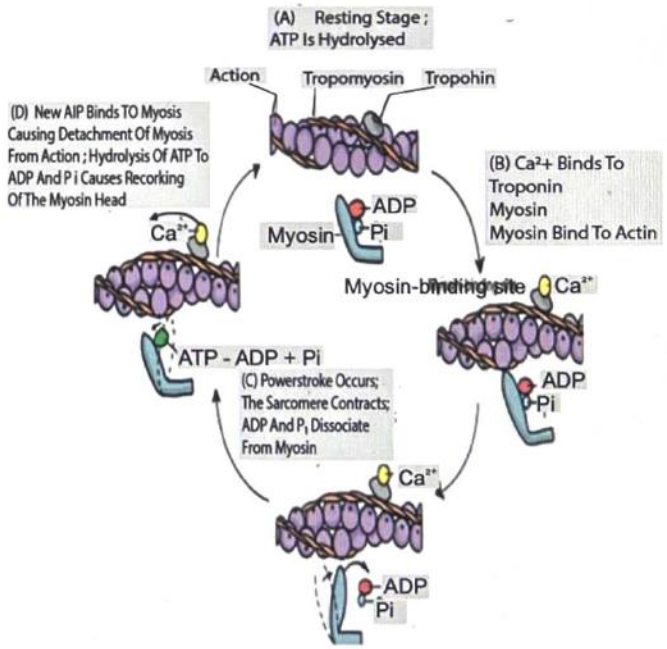
Previous Year's Questions

Q. What is the ratio of actin, troponin & tropomyosin in thin filament?
A. 1:1:1
B. 1:3:1
C. 7:1:1
D. 1:1:7

- THICK **FILAMENT** → made up of 500-1000 myosin molecule
  - 2 heavy meromyosin
  - 4 light meromyosin
  - Responsible for Rigor Mortis
  - Myosin head has ATPs → after

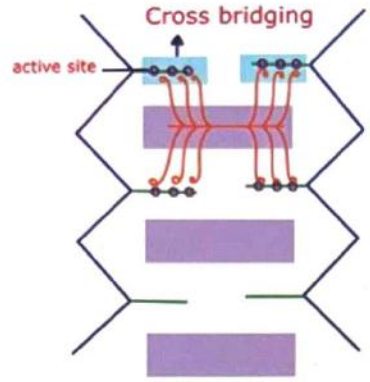


- Thin Filament: Made up of 3 molecules
  - Actin 7 : Troponin 1 : Tropomyosin1
- Have active sites and active sites covered by troponin-tropomyosin complex
- Ca^{2+} binds troponin - site is uncovered and actin - myosin interaction occurring stage:



CROSS BRIDGE CYCLING

00:53:11



- Each myocine heads contact with active sites called cross bridge
- During this z line pulled invade,mucsle shortening occur
- Tension α No. of active cross bridges
- Shortening α speed of cross bridge cycling
- Due to cross bridge cycling 5-30 per sec.
- Each thin filament active site interacts with myosin head

ISOMETRIC CONTRACTION

00:59:42

- Only tension developed in muscle
- No shortening, length remains same
- No work is done / no load is displaced
- More heat liberated

ISOTONIC CONTRACTION

- Tension remains same
- Muscle shortening occurs
- Work is done only during isotonic contraction

How to remember

Isotonic -shortening
Isometric- tension

Previous Year's Questions

Q. A man is lifting a heavy load with his biceps. What is the exact nature of muscle contraction?

A. Purely isometric
B. Isotonic →Isometric
C. Isometric →Isotonic→Isometric
D. Axotonic→ Myotonic

FACTORS AFFECTING STRENGTH OF CONTRACTION

01:11:19

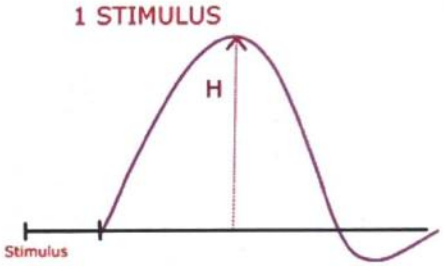
1. **Length tension relationship** - Based on Starlings Law

01:13:08

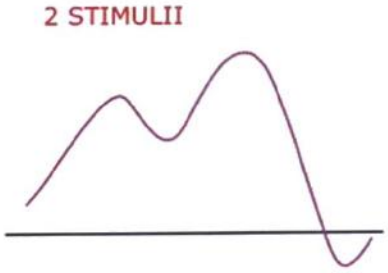
- Greater the initial length (of muscle / muscle fiber / sarcomere) - greater the contraction
- Strongest L_o - 2.2 μ
- L_{Max} – 3.7 μ

2. **Frequency-tension relationship**

01:16:02

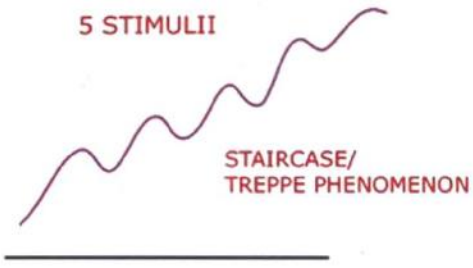


- Greater 'H'
- Stronger the contraction



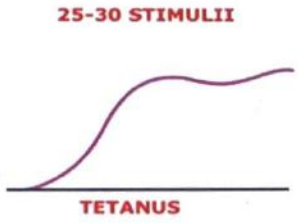
- ↓ viscosity in muscle
- ↑ temp. in muscle

} Beneficial effect



- Eg. Warm-up exercises
- Strength of contraction α Sarcoplasmic Ca^{2+}

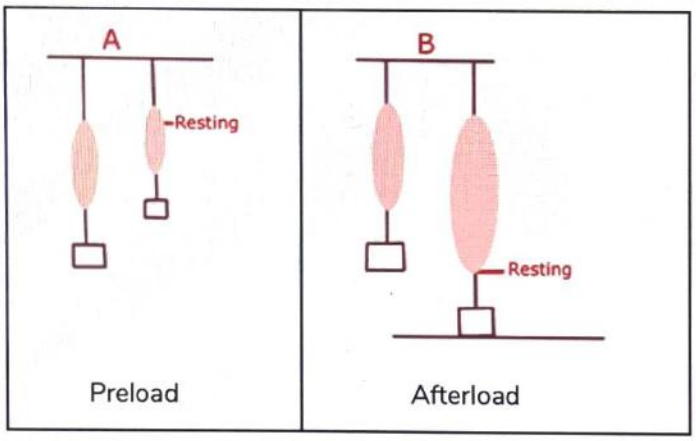
01:26:04



- Tetanus- sustained state of contraction
  - Failed relaxation
  - From high frequency stimulation

- Tetanizing frequency 01:29:03
  - Reciprocal of contraction period 25-30sec
  - No time for Ca^{2+} to be pumped out → Ca^{2+} accumulation

3. **Load** - opposes contraction 01:35:46



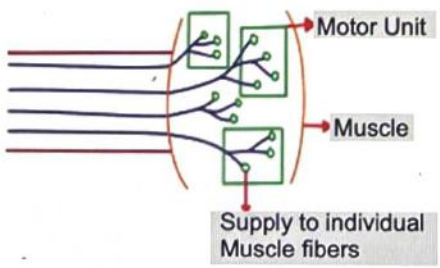
- Preload – load starts acting on the muscle before start of contraction
  - Even at rest
  - Eg. Holding a dumbbell without lifting it
- Afterload – load starts acting on muscle after contraction by opposing it → work is done.
  - Eg. Lifting the weight with biceps

4. Fatigue 01:48:03
- Repeated stimulation → ↓Contraction strength
- Inability to respond normally
- Depletion of Ach of NMJ

5. Motor unit 01:49:07
- Consists of – single motor neuron + all its branches + all the muscles fibers supplied by it.

Factors Influencing the Strength of Contraction 01:52:05

a. No. of motor units in a muscle
b. No. of fibers in a motor unit



- A single motor unit obeys All or None law
- Entire muscle doesn't obey All or None
- It depends on recruitment

ENERGETICS IN MUSCLE 01:56:30

- During continuous muscle activity,

1. STORED ATP
- 1st Utilized
- Energize the muscle for 2-3 sec

2. CREATINE PHOSPHATE (PHOSPHAGEN SYSTEM / Cr~P)
- LOHMANN REACTION
- CREATINE PHOSPHATE →ADP → ATP → Utilized
- Used for immediate synthesis & Utilization of ATP
- For only 10 - 12 sec.

3. GLYCOGEN LACTIC ACID SYSTEM
- Next source of energy
- Anaerobic glycolysis for next 1-2 min

4. OXIDATIVE PHOSPHORYLATION
- Next source of energy
- Longest serving energy Source of ATP
- For many hours
- Slow and sustain supply – Eg. Marathons

Previous Year's Questions

Q. 800 metes running event which energy system in muscle utilized maximally ?
A. Stored ATP
B. Oxidative phosphorylation
C. Glycogen lactic acid system
D. Creatine phosphate

RED (Aerobic)	WHITE (Pale)
• Slow oxidative	• Fast glycolytic
• High myoglobin content	• Low myoglobin content
• High mitochondria	• Low mitochondria
• High vascularity, capillary density	• Low vascularity, capillary density
• Slow sustained	• Lesser duration
• Fatigue resistant	• Fast fatigeable

CLINICAL QUESTIONS

Q A tetanic contraction is a sustained muscle contraction evoked when the motor nerve that innervates a skeletal muscle emits action potentials at a very high rate. During this state, a motor unit has been maximally stimulated by its motor neuron and remains that way for some time. Tetanizing stimulation of the muscle causes a sustained forceful contraction due to?

A. Recruitment phenomenon
B. Failure of Ca^{++} removal from the sarcoplasm
C. Summation of the stimuli
D. "Beneficial effect"

Answer: B

Solution:

- If the frequency of stimulation is increased, the individual twitches occur together (fuse) and cause the muscle tension to remain at a steady plateau state, in which the individual twitches are no longer distinguishable from each other is referred to as **tetanus**.
- **Tetanizing stimulus** (high-frequency stimulation) - stimuli are applied in quick succession; there is a release of Ca^{++}, with each stimulus, from the SR into the sarcoplasm.
- **For the muscle to relax**, this **Ca^{++} should be pumped back into the SR**, which **fails to happen due to the rapid succession of stimuli**. The muscle remains in a sustained state of contraction, called **"tetanus"** (option-2).
- **Recruitment** (option-1) - A simple means of increasing the force of contraction of a muscle is to recruit more muscle fibers. Because all the muscle fibers within a motor unit are activated simultaneously, a muscle recruits more muscle fibers by recruiting more motor units.
- **Summation** means adding together the individual twitch contractions to increase the intensity of overall muscle contraction (option-3).
- **Beneficial effect**: The amount of tension is increasing due to an increase in the amount of Ca^{++} as the Ca^{++}released by the previous stimulus itself is not cleared and still, Ca^{++}continues to release due to subsequent stimuli (option-4).

Reference:

- Textbook of Medical Physiology. Guyton & Hall. 2nd South Asia edition, Pg.102
  Medical Physiology, A Cellular and Molecular Approach, UPDATED SECOND EDITION. Walter F. Boron, Emile L. Boulpaep. Section-II, Physiology of Cells and Molecules, Chapter 9, Cellular Physiology of Skeletal, Cardiac, and Smooth Muscle. Pg. 251.

10 SARCOMERE

SARCOMERE

00:00:13

Previous Year's Questions

Q. How many thin filaments surround each thin filament?
A. 3
B. 4
C. 6
D. 2

Previous Year's Questions

Q. What is the optimal length that will generate maximum tension in the muscle?
A. 2 μ
B. 2.2 μ
C. 3.7 μ
D. 3 μ

00:00:39

- Sarcomere is a Basic structural unit of muscle the smallest unit where changes in muscle structure is taking place

Vs. Basic functional unit of muscle – motor unit

00:02:13

The distance b/w the (2) Z - lines- SARCOMERE
Normal resting length - 2 μ [L_o or L_{rest} = 2 μ]

STARLING LA[illegible]

00:03:08

- Greater the initial length of muscle, stronger is the contraction, within physiological limits
- Length optimum(Lo)-2.2 μ Produce strongest contraction
- Length maximum(L max)-3.7 μ inter digitations is lost physiological limit

00:05:32

Previous Year's Questions

Q. Limb girdle muscular dystrophy is defect of?
A. Lamininopathy
B. Dystropinopathy
C. Titinopathy
D. Myosinopathy

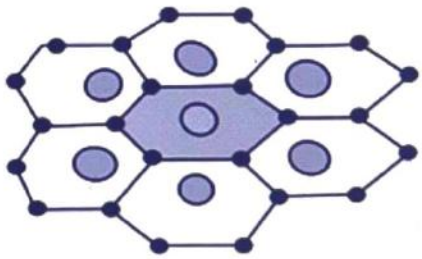
Previous Year's Questions

Q. Which is the largest known human protein?
Ans: Titin

LARGEST GENE – DYSTROPHIN GENE

TITIN

00:07:47



- Anchored to Z- lines & it enters thick filament
- Largest human protein
- Aids in alignment of thick filament to sarcomere
- Genetic defects causes LIMB GIRDLE MUSCULAR DYSTROPHY

The thin filament is attached to Z line by α-actinin & cap-2-protein

DYSTROPHIN

00:24:15

- Linked to thin filament & reaches sarcolemma
- Dystrophin linked to β-dystroglycan, which is intern linked to α-dystroglycan
  2 Dystroglycans linked to 4 sarcoglycans →Total : 6
  - α-dystroglycans are linked to laminin (ECM PROTEIN)
  - Tension generated by actin - myosin interaction is transported exterior to the tendon by Dystrophin
  - Defect causes DUCHENNE MUSCULAR DYSTROPPHY

All sarcomeres will shorten when the muscle contracts

Previous Year's Questions

Q. Which band / zone or line will become prominent with muscle contraction?

A. A band
B. I band
C. H zone
D. M line

Various Bands & Zones

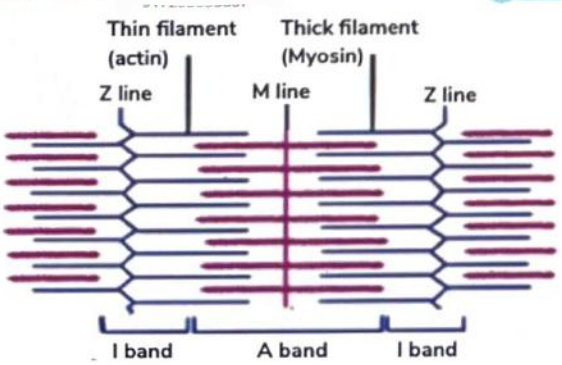
- I - Band-Thin filament on either side of Z line

00:12:46

  - Isotropic to polarized light
- A - Band-Remaining Part
  - An isotropic to polarized light
  - Contains thin & thick filaments
- H – Zone→ Present at the centre of A Band
  - Have thick filament
  - In centre of H zone, M - Line is present (dark – myomesin)
  - On either side of M-Line, light areas are present
  - PSEUDO H – ZONE→ Dark M Line& adjoining light areas on either side

DURING MUSCLE CONTRACTION

00:16:58

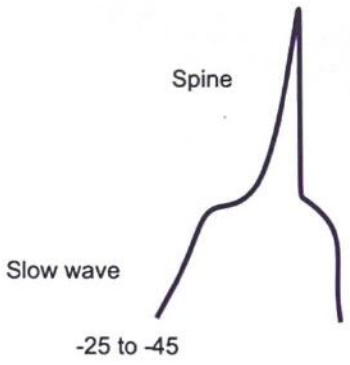


- Sarcomere Shortening
  - A-Band Remain unchanged
  - I-Band Shortens
  - H-Zone: Disappears
    M-Line Become prominent
- **At 1.5μ contracted length of sarcomere**: Cm band appears
- **At 1.25μ contracted length of sarcomere**: Cz band appears

11 SMOOTH MUSCLE

00:00:22

1. SINGLE UNIT- Bundle of fibers work together as simple Unit
   - Ex: Viscera
2. MULTI UNIT-Individual Fibers, behave independently as separate units
   - Ex: Iris, Arrector pili muscles of skin



00:02:18

RMP

- -35 to -45 mV
- An oscillatory potential
- There is electro mechanical coupling in addition to pharmaco mechanical coupling

00:03:53

Previous Year's Questions

Q. What is the ratio of thin : thick filaments in smooth muscle?

A. 2:1
B. 1:1
C. 1:2
D. 15:1

Vs Skeletel muscles – 2:1

- TUBULAR SYSTEM IS RUDIMENTORY
  - CAVEOLAE - Membrane depressions
  - CAVEOLIN - Protein a/w caveolae
- Instead of Z lines, DENSE BODIES are present in regular intervals
- Thin : Thick filaments ratio - 15:1

SMOOTH MUSCLE CONTRACTION

00:09:20

1 Calmodulin binds with 4 (Ca^{2+}) ions

↓

Ca^{2+} +

↓

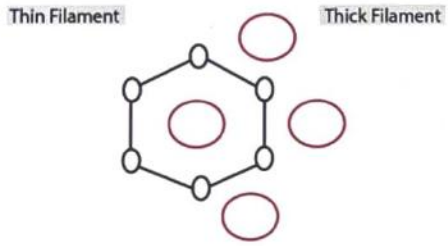
Activation of MLCK

↓

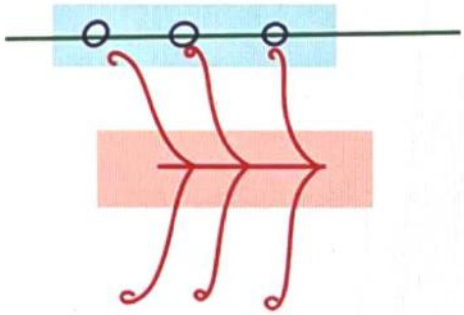
Actin, Myocin interaction

↓

Contraction



- Thick filaments regulates the contraction. Hence, called THICK FILAMENT REGULATED CONTRACTION
- LATCH - BRIDGE PHENOMENON shown
- After a certain time of cross bridge cycling, cross bridges remain latched
- No further cross bridge cycling &
- No further ATP breakdown (sustained tension with lesser ATP consumption)



LEARNING OBJECTIVES

UNIT 3 BLOOD PHYSIOLOGY

BLOOD PHYSIOLOGY PART 1

- Blood Composition
- Plasma Proteins
- RBC's
- Stages of Erythropoiesis
- Factors that Influences Erythropoiesis
- WBC's
- Neutrophil
- Monocyte
- Lymphocyte
- Eosinophils
- Basophils
- Platelets
- Clot Formation
- Clotting Factors
- Anti Coagulant Mechanisms
- Blood Groups
- Bombay Blood Group
- Rh Blood Group
- Blood Indices

BLOOD PHYSIOLOGY PART 2

- WBCs and their charecteristics
- Immunity and role of lymphocytes
- Hemostasis and events of hemostasis
- Clotting factors in plasma
- Anticoagulants

BLOOD PHYSIOLOGY PART 3

- ABO blood group system
- Concepts of donor and recipient
- Rh system
- Blood transfusion
- Matching

12 BLOOD PHYSIOLOGY PART - 1

Introduction 00:00:58

- Blood is a liquid connective tissue. It is a component of the extracellular fluid.
- It circulates throughout the body within blood vessels. It is red in colour due to presence of hemoglobin inside red blood cells.
- pH of blood 7.4 & plasma 1.030
- specific gravity 1.060 & cells 1.090
- blood is 8% of body weight
  - 35% cell
  - 55% plasma (3 liter)
- Viscosity
  - Relative viscosities of water, plasma and whole blood are 1,3,5 respectively
  - Absolute viscosity is measured in poise

Blood cells: 00:05:20

1. Red blood cells (RBCs or erythrocytes)
   - 4.5 to 6 million /mm^3 of
   - Their main function is O2 & CO2 in blood.
   - A part from that, they also play a role in body's acid-base balance.
2. White blood cells (WBCs or Leucocytes)
   - 4000 to 11000/mm^3 of blood
   - They are concerned with body defence mechanisms and immunity
3. Platelets (or thrombocytes)
   - 1.5 to 4 lacs /mm^3 of blood
   - They perform a function of stoppage of bleeding after a blood vessel is ruptured.

- The plasma component of blood is mainly composed of water (91%)
- Other substances in plasma
  - Inorganic substances – Na+,k+,ca++,cl-, iron, copper, etc.
  - Organic substances – proteins, lipids, glucose, other nutrients, hormones, etc.

Plasma proteins 00:06:30

- Proteins present in plasma
- Normal level 6 to 8 gm%

How to remember

- Plasma & haemoglobins in 'gm' else all were in 'mm'

3 major plasma proteins are

- Albumin (4.5 to 5.5 gm%)
- Globulins (1.5 to 2.5 gm%)
- Ribrinogens (0.2 to 0.4 gm%)
  - **Albumin: Globulin ratio (A:G) = 1.7: 1 (upto 2:1)**

Albumin:

- Synthesized in the liver
- Performs 2 important functions:
  - Exerts colloid osmotic pressure of the plasma
  - Transports various substances [bilirubin, hormones, etc]

Globulins:

- 3 types =
- Alpha & beta globulins transport various substances in plasma
- Gamma globulins are immunoglobulin formed by white cell called beta immunoglobulin (lymphocyte)

Fibrinogen:

- Synthesized in the liver
- It converts into fibrin to forma a blood clot. This happens when a blood vessel is ruptured

Functions of plasma proteins 00:13:28

- Colloid osmotic pressure
  - Plasma proteins (mainly albumin) exert this pressure
  - It is about 25-27 mmHg
  - It is a pressure that pulls water into the blood capillaries by osmosis
- Transport of substances
  - Albumin transports various endogenous & exogenous substances. E.g. hormones, bilirubuin drugs.
  - Globulins also perform the function of transport.
  - Example
    i. Haptoglobin (Hb) when Hb is outside RBCs in the plasma.
    ii. Ceruloplasmin transports copper.
    iii. Transferring transports iron in plasma.
- Defence mechanisms
  - globulins are immnoglobulins or antibodies.
  - These antibodies are formed by beta-lymphocytes when an antigen body, antibodies react with it. It is an important part of our defence reactions.

- Blood coagulation
  - When a blood vessel is ruptured some reaction or sequential steps at that site form "prothrombin activator".
  - It convert prothrombin into thrombin
  - Thrombin then acts on fibrinogen present in plasma & forms fibrin
  - This results in clot formation (or) coagulation of blood it allows for healing of the vessel.

Clinical significance: 00:15:48

- Edema in liver & kidney disease

In liver

- Plasma protein levels in disease of kidney & liver. Since liver synthesizes these proteins, in severe liver diseases [cirrhosis, liver failure] level of plasma protein

In kidney

- Normally don't allow proteins to be filtered and excreted in urine.
- Certain disease of kidney e.g. nephrotic syndrome result in loss of protein in urine.
- Decreased plasma proteins decrease in plasma coloid osmotic pressure result in fluid from interstitium will not be pulled into the capillaries in normal amount excess accumulation of fluid in the interstitium cause "edema"

Cells

- Erythrocytes [RBCs or red blood corpuscles]
- Anemia is a very common clinical condition that results from a decreased RBC count for reduced Hb.

Structure & important features of RBCs

- RBCs are biconcave shaped cells
- Mean RBC diameter = 7.2 to 8
- They are non-motile and non nucleated
- RBCs have no mitochondria or ribosomes
- RBC s contains hemoglobin. It performs the function of O_2 transport

How to remember

- RBC – non motile non nucleated
- WBC – motile, nucleated

- Normal RBCs count:
  - In male 5 to 6 million /mm^3
  - In female 4.5 to 5.5 million /mm^3

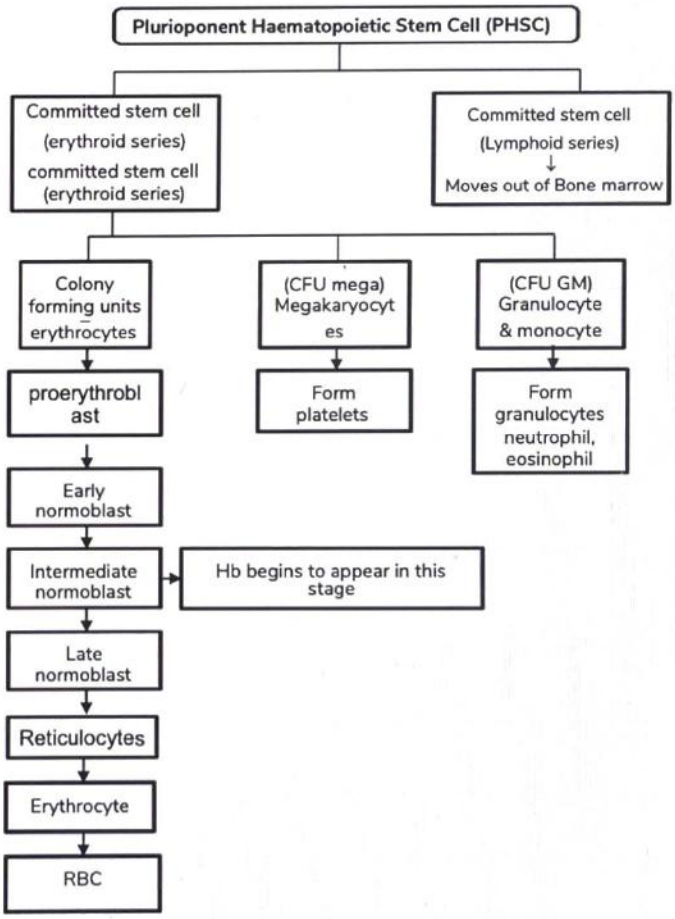
Erythropoiesis 00:21:57

- It is the process of formation of RBCs
- All the blood cells are process is also called hemopoiesis or hematopoiesis

1st trimester [1st 3 months of pregnancy]	Mesoderm of the yolk sac	Mesoblastic stage
[3-6 months of pregnancy]	Fetal liver & spleen	Hepatic stage
3rd trimester [6 month onward]	Fetal bone marrow	Myeloid stage

- At birth, all bones of the child have (RBM)"red bone marrow"
  - After fat infiltration few have RBM
  - Proximal ends of long bones
  - Sternum & some flat bones
  - Vertebral bodies
  - Anterior superior iliac spine

Steps in erythropoiesis:



- In lead poisoning – basophilic stippling in RBC
- Normal reticulocytes count in PB 0.2 – 2%
- Reticulocytes high in new born babies
- In hypoxia – reticulocytes in peripheral blood is increase

1. Cell size
   - Note that pluripotent stem cell, the first precursor of RBC, is 24 in diameter, whereas the last stage has a diameter of T-8
   - Why? – cell division & cell maturation are occurring simultaneously in bone marrow.
   - Daughter cells have little time to grow to the parent cell.
2. Nucleus
   - Pluripotent stem cell is a nucleated the fully matured RBC is non-nucleated
3. Cytoplasm
   - Initially the cytoplasm is basophilic acidic contents hence attacks basic stain finally its acidic

Erythrocyte

- A matured RBC is biconcave shaped, non-motile, non-nucleated cell.
- Diameter = 7-8, lack of mitochondria & ribosomes
- Normal RBC count
  - 5-6 million /mm3 of blood in males
  - 4.5 to 5.5 million /mm^3 of blood in females
- Life span of RBC – 120 days
- Entire process of erythropoiesis occurs in 7 to 9 days.

Factors regulating the rate of erythropoiesis

00:47:47

- Tissue oxygenation: (hypoxia)
  - It is the most important regulator of the rate of RBVC production
  - Hypoxia: any condition that decreases the quantity of oxygen transported to tissues
    i. At high altitudes: air pressure and oxygen pressure are less. Less oxygen is available for the body.
    ii. Heart or lung disease: serious diseases of these two organs result in deficient O_2 supply to tissues.
  - These hypoxic conditions stimulate erythropoiesis by increasing the activity of the hormone erythropoietin.
- Erythropoietin
  - It is a hormone synthesized by kidney.
  - 90% erythropoietin is formed by kidney; 10% by liver.
  - When there are hypoxic conditions, interstitial cells of kidney secrete erythropoietin into blood.
  - It reaches bone marrow. Bone marrow has specific receptors (Ep-1, Ep-2) on which erythropoietin acts. It stimulates the rate of erythropoiesis.
  - Specifically, conversion of hematopoietic stem cell to proerythroblast occurs faster. Subsequent steps also occur at a faster rate. Under the influence of erythropoietin, process of erythropoiesis is completed in 5 to 6 days. {Generally, it occurs in 7 to 9 days}.
- Dietary factors
  - RBCs contain hemoglobin.
  - Hemoglobin = heme + globin
  - Heme contains iron and globin is made up of amino acids.
    → Iron in diet - required for the synthesis of heme.
    → Amino acids (proteins in diet) – necessary for the synthesis of globin.
    → Vitamin B12 and folic acid in diet – RBC is a non-nucleated cell but its precursors are nucleated. Vitamin B12 and folic acid are necessary for synthesis of DNA in the RBC precursors. In deficiency of vitamin. B_{12} or folic acid – results in failure of nuclear maturation in RBC precursors. Deficient nucleus cell division and maturation is hampered. Cells will remain large and immature. The condition is called "megaloblastic anemia". {Mega = large; blast = immature cell}.
    → Other factors – (role in erythropoiesis not proven)
    - Vitamins B_1, B_2, and B_6
    - Minerals – Cu^{++}, cobalt, zinc.
- Hormonal factors
  - Androgens /testosterone – it is the male sex hormone. It stimulates erythropoiesis possiblyt in following ways:
    → It stimulates erythropoietin production from kidney.
    → It potentiates the action of erythropoietin on bone marrow.
    → It may directly stimulate the rate of erythropoiesis.
    It is due to stimulation of erythropoiesis by testosterone, that the RBC count is more in males.
  - Estrogens – Estrogen is a female sex hormone. It has been hypothesized (not proven entirely) that estrogen suppresses erythropoiesis to.

Clinical significance:

- Some drugs (e.g, chloramphenicol) and radiation are known to suppress erythropoiesis. They result in anemia and pancytopenia (formation of all blood cells suppressed).
- Persons residing at high altitudes are chronically exposed to hypoxic environment. As hypoxia is the most important stimulus for erythropoiesis, these people tend to have a very high RBC count – polycythemia.
- Erythropoietin is synthesized in kidneys. Patients of chronic renal failure lack erythropoietin, and hence have a low RBC count.
- RBCs do not have mitochondria and ribosomes. But they do have cytoplasmic enzymes that can metabolize glucose and produce ATP. The enzymes also help in

maintaining flexibility of the red cell membrane and keep the iron in ferrous state. ATP is required to maintain the functioning of Na+-K+- pump in the red cell membrane.

- Toward the end of life span, these systems gest exhausted. The red cell membrane becomes more fragile. Now, the cell will be ruptured while membrane becomes more fragile. Now. The cell will be ruptured while passing through a tight spot in circulation. Majority of the RBCs are destroyed in spleen. (Spleen is RBCs).
- Splenic macrophages swallow the fragment of the red cell. Haemoglobin is now liberated. Hemoglobin is split, by macrophages, into heme & globin.
- Heme is converted into bilirubin by macrophages in spleen.
- Bilirubin then enters portal blood.
- In blood – bilirubin combines with albumin. Bilirubin combined with albumin is then transported to liver.

Jaundice 01:10:53

- It is "yellowish discoloration of mucous membranes and skin" due to increase in bilirubin levels of blood.
- Jaundice becomes clinically apparent when serum bilirubin exceeds 3 mg%.
- Normal serum bilirubin: 0.3 – 1 mg%.
- Jaundice is detected clinically by examination of the sclera.

Reason:

- It can be easily made out when a white sclera turns yellow.
- Sclera contains a protein –elastin –for which bilirubin has high affinity. [this is also the reason why sclera continues to look yellow even after jaundice has been cured.]

Types of jaundice

- The 3 types of jaundice are based on the course of bilirubin after its formation from heme.

1. Pre – hepatic jaundice:
   - The abnormality lies in the process before bilirubin goes to liver
   - Excess breakdown of RBCs – excess liberation of Hb and excessive formation of bilirubin from heme. Hence, it is also called hemolytic jaundice.
2. Hepatic jaundice
   - The abnormality lies in the processing of bilirubin once it has reached liver.
   - Disease of the liver parenchyma and injury to liver cells will cause bilirubin to enter blood directly has reached liver.
   - Diseases of the liver parenchyma and injury to liver cells will cause bilirubin to enter blood directly from liver.
   - Causes: Hepatitis A. hepatitis B, and other types of hepatitis, cirrhosis etc.
   - Post-hepatic jaundice

- Once bilirubin is conjugated in the liver, it is excreted in bile. Then via bile ducts it reaches intestine. If there is obstruction of the bile ducts, bile and bilirubin will not reach intestines.
- Bilirubin will start entering directly into blood. This type is also called 'obstructive jaundice'.
- Since bilirubin is already conjugated by liver, it is the conjugated bilirubin that increases in serum, in this type stools are chalky, pasty

Some investigations related to RBCs

- Erythrocyte sedimentation rate [ESR] –
- It is the rate at which RBCs settle down, when a blood sample is placed in a vertical tube
- The tubes used to measure ESR
  - Wintrobe's tube
  - Westergren's tube
- A blood sample is mixed with an anticoagulant and placed in Wintrobe's (or Westergren's) tube. The tube is held vertically and left undisturbed for 1 hour. The RBCs begin to settle down or sediment slowly. At the end of 1 hour, the height of the column of supernatant plasma is measured (at the top of the blood column).

Normal values:

- 0 to 5 mm at the end of 1 hour (females)
- Physiology:
  - When in circulation, RBCs have a negative potential on their membranes. This potential, also called "zeta potential", prevents coming together of RBCs.
  - When blood is made to stand still outside the body, RBCs form aggregates and pile on each other (like a stack of coins). These aggregates are called "rouleaux". The rouleaux then begin to settle down.
  - Some asymmetric macromolecules in plasma hasten the rouleaux formation and settling down of RBCs. E.g. fibrinogen; gamma globulins in plasma hasten this sedimentation and thus increase the ESR. Conditions in which such proteins are increased in plasma will therefore exhibit an increase in ESR.
  - ESR increases in conditions like TB, malignancy, rheumatoid plasma will therefore exhibit an increase in ESR.
  - ESR increases in conditions like TB, malignancy, rheumatoid arthritis, anemia

Significance

- ESR does not have diagnostic significance as such. It does not help in diagnosis, since there are many conditions in which ESR.

- ESR has a prognostic significance. {Prognosis means progress of a disease}. Once a disease id diagnosed, ESR of the patient is recorded. And then with continued treatment, ESR is measured at regular intervals. If ESR decreases during the course of treatment, it means patient's condition is improving.
- Packed cell volume [PCV]
  - It is expressed as the percentage of RBCs present in a unit quantity of blood. It is also called "hematocrit".
  - In any unit quantity of blood, 45% volume is of cells and 55% is plasma. Major chunk of the cell volume is than of RBCs.
  - PCV values
    → Males 40-45%
    → Females 38-42%
  - Determination of PCV: (Wintrobe's method)
    → Wintrobe's tube is filled with blood sample mixed with an anticoagulant. The tube is then kept in a centrifuge, at 3000 RPM for 30 min. this creates an optimum centrifugal force; RBCs are packed together at the bottom half and plasma separated positioned at the top half of the blood sample. [4 layers of created in the tube from below upwards
      I. Packed RBCs at the bottom half
      II. A this buffy coat layer of WBCs above the RBC layer
      III. A very thin dark line of hemolysis or lysed RBCs above the buffy coat, and layer of supernatant plasma at the top half of the tube].

Significance of PCV:

- Anemia: since the RBC count is decreased in anemia, the PCV will be lower (<38%).
- Polycythemia: increased RBC count; PCV value will be higher (>48%).
- Conditions that cause loss of plasma (Hemocon centration) – diarrhea, vomiting, etc – would have an increase in PCV value. {Note: It is the relative proportion of cells and plasma. If plasma decreases in a unit quantity of blood, cells will be relatively increase in proportion.}
- Jaundice: normal plasma is straw-colored. The plasma bilirubin increases in jaundice. Bilirubin is a yellow –colored pigment; it will turn plasma color into yellow in jaundice. Thus, the separated plasma appearing yellow in the PCV tube is a pointer to jaundice.

Blood indices: 01:33:25

- These are numbers or values related to RBCs, derived from observations and calculations.

1. Packed cell volume (PCV): (described above)
2. Mean corpuscular volume (MCV)
   - It is the average volume of a single red blood corpuscle.
   - A blood sample is collected. RBC count is done. And, packed cell volume (PCV) is measured. If the blood sample has a certain number of RBCs and all those RBCs when packed together have a certain packed cell volume (PCV), we can calculate the average volume of one single RBC in the formula.
   - Normal MCV range: 78 to 93 3
   - When MCV is more than 93 3, the RBC is termed a macrocyte.
   - In megaloblastic anemia, the RBCs will be macrocytes.
   - When MCV is less than 78 ^{3}, the RBC is termed a microcyte.
   - In iron deficiency anemia, the RBCs will be microcytes.

3. Mean corpuscular hemoglobin (MCH)-
   - It is the average amount of hemoglobin (Hb) present in a single RBC.
   - In a blood sample, Hb estimation and RBC count is done. If a certain number of RBCs contain a certain amount of Hb, one RBC will contain how much Hb (average)? The formula would be:
   - MCH = [Hb]/[RBC count] (if these many RBCs have this much total Hb, then on an average, how much is the Hb present in a single RBC?)

- Normal range of MCH – 28 to 32 pilogramme

$$MCH = \frac{Hb}{RBC\ count.(Per\ mm)} \times 10$$

- Its reduced in microcytic anemia

4. Mean corpuscular haemoglobin concentration (MCHC)
   - It is the relative percentage of Hb in a single RBC.
   - Normal value: 32-38%
   - MCH is normal but MCHC is reduced due to megaloblastic or microcytic anemia
5. Colour index
   - It is the ratio between Hb% and RBcs
   - Hb level 15 gm% taken as 100% Hb. So, if a patient has 10 gm% of Hb, it is 66% Hb.
   - RBC count (in millon / mm3) is converted into percentage value. 5 million /mm3 is considered 100%. So if a patient's RBC count is 4 million / mm3, it is 80% color index.
   - Normal value – 0.8 to 1.1
   - If patient <0.8 index – hypo chromic anemia

Anemia 01:45:58

- It is defined as decrease O_2 carrying capacity of blood.
- O_2 is carried by Hb within RBcs, anemia is due to decreased RBC county or decreased Hb level or both.

Classification of anemia

- Etiological classification – according to cause
- Morphological classification – according to morphology
- Clinical classification – according to Hb levels

Example:

- 10-8 gm Hb – mild
- 8-6 gm Hb – moderate
- <6 gm Hb – severe

Treatment

- Mild – oral irons
- Moderate – injection
- Severe – blood transfusion

1. Etiological classification – excessive blood loss there may be loss of RBCs, reduced RBC count
   - Acute blood loss e.g: accident piles, worm surgery in intestine
   - Chronic blood loss e.g: accident piles, worm surgery in intestine
   - Anemic d/t excessive RBC destruction e.g.: hemolytic anemia
     - → Type I – congenital cause e.g: sickle cell anemia
     - → Type II – acquired cause e.g: malaria
   - Anemia d/t decreased RBC production
     - → Nutritional deficiency – it leads to deficient globin formation in hemoglobin
     - → Iron deficiency anemia – iron is required for heme formation. Lead to impaired Hb formation in RBCs. Commonest in India.
     - → Vitamin B12 a folic acid deficiency – This is required for nuclear maturation in RBC precursor. It will hamper the cell division & maturation in erythropoiesis
     - → Aplastic anemia – due to certain drugs, x- rays, toxins suppress bone marrow

- Megaloblastic anemia – B12 & folic acid deficiency this is vital for DNA synthesis.

- B12 deficient food
- Cause – intrinsic factor of castle is not produced in surgical resection of ileum.

- Pernicious anemia – neuronal formation deficiency autoimmune origin

2. Morphological classification: base on appearance
   - Normocytic anemia – RBC size normal, content is normal but count is reduced e.g: blood loss anemia
   - Macrocytic anemia – RBC size is large MCV > 94 ^{3} e.g.: megaloblastic anemia

Based on the color index

- Hypochromic - <0.8 e.g.: microcytic hypochromic anemia
- Normochromic – 0.8 – 1 e.g.: normocytic normochromic anemia

Sign & symptoms of anemia:

- Pallor
- easy tiredness
- Breathlessness
- Palpitation
- anorexia

Hemoglobin: (Hb) 02:05:06

- It is conjugated chromo protein, present inside the RBCs. It contains iron (Fe^{++}). It is due to Hb that the red cells & blood are red in colour
- Its main function is to transport oxygen to tissues. Important role in acid –base buffering in the ECF
- Normal level
  - 14-18 gm% in males
  - 12-16 gm% in females
- O_2 carrying capacity of blood:
  - 1 gram of Hb – carries 1.34 ml of O_2
- Hb made up of heme & globin
  - 2 & 2 in adult Hb

Synthesis of Hb

- 2 succinyl COA + 2 glycine – pyrrolering
- 4 pyrrole – protoporphyrin IX
- Protoporphyrin IX + Fe++ - heme
- Heme + polypeptide – hemoglobin chain (or)
- 2 chains + 2 chains – HBA (adult Hb)

Glycosylated Hb (HbA1C):

- Also called glycated Hb: glucose in plasma gets attached to Hb non-enzymatically & irreversibly.

- Percentage of Hb that is in the glycated from is a good indicator of plasma glucose over a certain period.
- If plasma glucose is consistently high. More of glucose will attach with Hb, thus giving a high value for glycosylated Hb up to 6% is normal.
- Once glucose is attached to Hb the Hb remains glycosylated for the remainder of the life span of the red cell. Hence glycosylate Hb value indicates the average plasma glucose level over a 3 months period

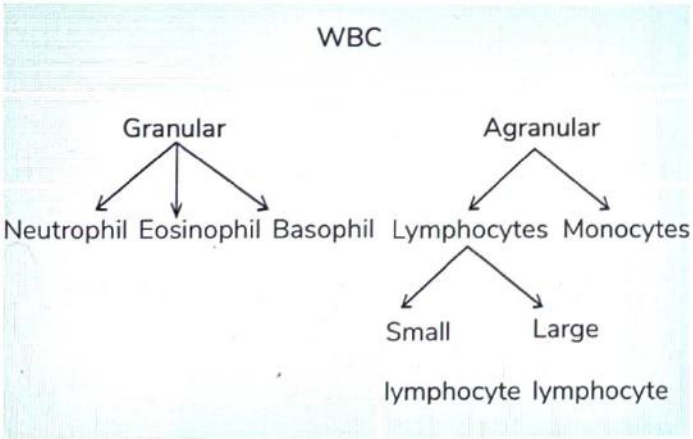
13 BLOOD PHYSIOLOGY PART - 2

Introduction of WBCs 00:01:04

Characteristics of WBCs 00:01:07

- Some characteristics of WBCs
  - There are different types of WBCs with different morphology and functions.
  - WBCs are motile cells. They can move on their own, when they have migrated out of blood vessels. (RBCs and platelets are non-motile)
  - They are **nucleated** cells. (RBCs and platelets are non-nucleated)
  - Most WBCs have short life – span; and they remain in circulation for short periods of time. They are produced in bone marrow and they are required to perform their function in tissues. Thus, they use blood just as a vehicle to reach the tissues.
- Total leucocyte count [TLC]: 4000 to 11,000/mm3
- Increase in leucocyte count is called **leukocytosis**. It occurs in various types of acute and chronic infections.
- Decrease in leucocyte count is called **leucopenia**. It may occur in bone marrow suppression.
- There are different types of leucocytes in the body. Counting each type of leucocyte and giving its number in relative percentage (or per 100 cells) is called differential leucocyte count [DIC].

Types of WBCs 00:10:47



Absolute Counts

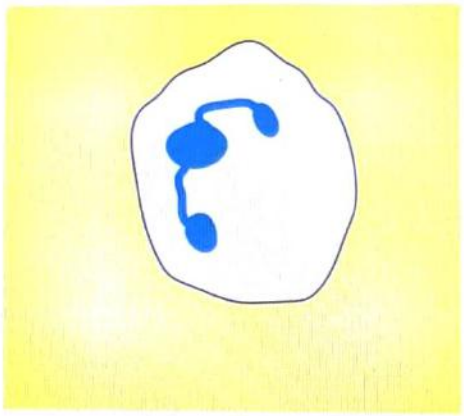
- The percentages of the WBCs are the relative numbers.
- These are per 100 wbcs Only. For instance, there are 60 neutrophils, 25 lymphocytes, and 15 others.
- Eg: If in a patient, 80 neutrophils are found (in 100 WBCs), lymphocytes and other cells will be less as it is a count of 100 cells only. This decrease in lymphocytes and other cells may be only a relative decrease (because neutrophils have counted more), or there may be an actual decrease in the number of those cells.
- To verify these numbers, **absolute** counts of each type of cell can be derived. First find out the total WBC counter per mm^3. Then, find out the differential count of each cell type. The actual count (per mm^3) can then be calculated. E.g. The TLC is 20,000/mm^3, neutrophil count 80% and lymphocyte 18%. The absolute neutrophil count would be (80% of 20,000)= 16,000/mm^3. One can then conclude that WBC count has increased because neutrophils have increased. The lymphocytes (18%) may be relatively low, but absolute count of lymphocytes may fall within the normal range.
- ~ There are two types of WBCs
  - **Granulocytes**: Those having granules in the cytoplasm, and
  - **Agranulocytes**: No granules in the cytoplasm.
- Agranulocytes are two types
  - Lymphocyte (20-30%), and
  - Monocyte (2-8%)
- Granulocytes are classified according to the staining property of their granules:

1. Eosinophil : The granules take up acid stain (as their contents are basic)
2. Basophil : The granules take up basic stain (as their contents are acidic)
3. Neutrophil: The granules take up both acid and basic stains.

Morphology and functions of the individual WBCs: 00:11:10

- Granulocytes:

1. Neutrophil: (50-70%): **["first line defence"]**
   - The most numerous of the WBCs
   - Diameter ≈10-12μ



neutrophil

- It is a granulocyte. Granules in the cytoplasm take both acid and basic stain.
- Nucleus: When a neutrophil is formed in the bone marrow, its nucleus initially has 1 or 2 lobes.
- As the nucleus matures further, the number of lobes increases. Most matured neutrophil will have 5 to 7 lobes.
- **Arneth count:** It is a count of neutrophils, based on the nuclear lobes. In peripheral blood, 100 neutrophils are counted and then classified according to the number of lobes.
  - Grade I-1 lobe ≈ 5%
  - Grade II – 2 lobes ≈ 10-15%
  - Grade III-3 lobes ≈ 35-45%
  - Grade IV -4 lobes ≈ 10-15%
  - Grade V – 5 lobes ≈ 5-10%
- Normally, highest number of neutrophils will have 3 lobes in the nucleus.
- Granules: the cytoplasmic granules are of two types

1. Primary granules
2. Secondary granules

- The primary or lysosomal
- The primary or lysosomal granules contain

a. Various proteolytic and amylolytic granules
b. Myeloperoxidase (MPO) granules and
c. (MPO) granules, and lysozyme enzyme granules.

- These granules cause **bacterial destruction or digestion.**
- The secondary granules contain

a. Lactoferrin, which inhibits bacterial growth
b. Alkaline phosphatase, and
c. Other substances or enzymes

- Life –span: Once neutrophils are formed in the bone marrow, they remain in the bone marrow pool.
- Neutrophils released from bone marrow into circulation become part of the vascular pool of neutrophils.
- Neutrophil has short life – span in blood – 4 to 8 hours.
- It then enters tissues and lives for another 4-5 days
- Thus, the total life span of a neutrophil (bone marrow → blood → tissue) is about 12 to 14 days.

Functions of the neutrophil:

A. Antibacterial role:

- When pathogenic bacteria have entered the body, neutrophils attack and kill the bacteria. The sequence of events, at the site of infection, would be
  - Vasodilatation – Local blood vessel dilate.
  - Margination and
  - Margination and emigration- Neutrophils, normally travelling at the centre of the blood vessel, come near the vessel wall and get adhered to the endothelium of the vessel ('margination'). They then come out blood vessel to enter the connective tissue (emigration)
  - Chemotaxis – The bacteria have released certain chemicals (or chemo attractans). They attract the neutrophils toward them. Neutrophil movement toward the bacteria is called chemotaxis.
  - Phagocytosis- Neutrophils reach the bacteria, engulf and swallow them ('phagocytosis')
  - Finally, the swallowed bacteria are digested / degraded. The enzymes present in the neutrophil granules are responsible for killing or degradation of bacteria.
  - The neutrophil can produce H_2O_2 and superoxide (O_2). In the presence of the myeloperoxidase (of granules), H_2O_2 becomes very lethal for the bacteria.
- Pus formation – dead cells, tissue fluid, and dead WBCs together form

a. Fluid called pus

B. Role in acute infection:

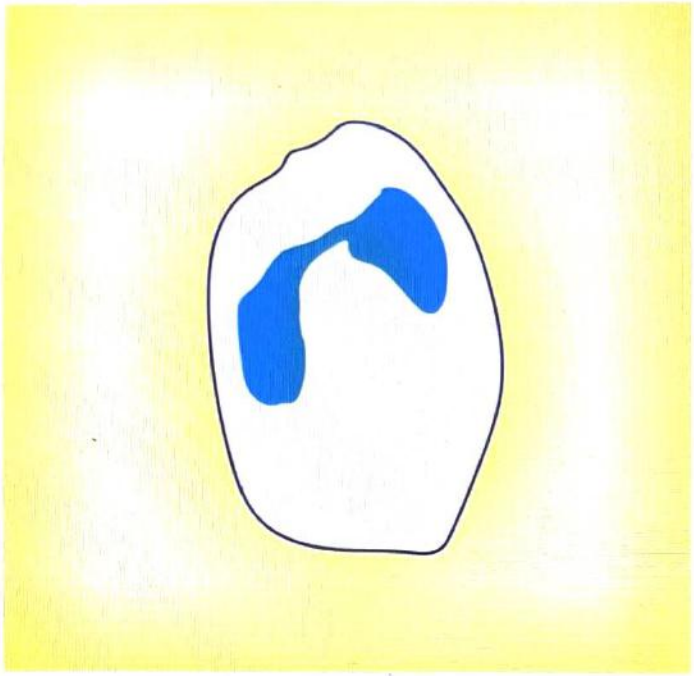
- Neutrophils are the "first line defence" against any acute infection. When a micro – organism enters the body, neutrophils are the first cell to reach the site of infection and attack the micro – organism.

a. Neutrophilia: Increase in the neutrophil count. It may also cause leukocytosis. It occurs
  - Acute infections (bacterial, viral etc)
  - Many types of fevers
  - Infection by pyogenic (pus – producing) bacteria.

b. Neutropenia: Decrease in the neutrophil count. It may occur in typhoid fever, and factors that cause bone marrow depression.

2. Eosinophil: (1-4%)

- 10-14 μ diameter
- Nucleus: Bi-lobed or spectacle shaped
- Cytoplasm: contains granules that take acid stain and hence appear reddish orange



- Granules of the eosinophil
- Granules of the eosinophil contain alkaline material (hence take acidic stain); the granules contain:
  - Eosinophilic peroxidase (EPO) enzyme
  - Major basic protein (MBP)
  - Eosinophil cationic protein
  - Life span: Eosinophils stay in the bone marrow pool for about 5 days. When they enter bloodstream, they remain in the blood for about 8-12 hours; then they migrate to tissues where they die.
  - Functions of eosinophil

a. Major basic protein (MBP) is an important constituent of eosinophil granules. It acts mainly against parasites (hookworm, filarial, etc) that have invaded the body. MBP can kill larva of many parasites.

b. Eosinophils play a role in allergic conditions. They migrate to the site of allergy and assist the mast cells during allergic inflammation.

- Eosinophilia: Increase in eosinophil count. It occurs in

1. Parasitic infestations (hookworm, threadworm, etc)
2. Allergic conditions (like bronchial asthma)
   - Eosinopenia: Decrease in eosinophil count. Steroids
3. Basophil: (0-1%)
   - 10-12μ diameter
   - Nucleus: Irregular, often 'S' shaped
   - Cytoplasm: Covered with coarse basophilic granules; the granules cover even the nuclear zone, nucleus is barely visible

- Basophil granules contain

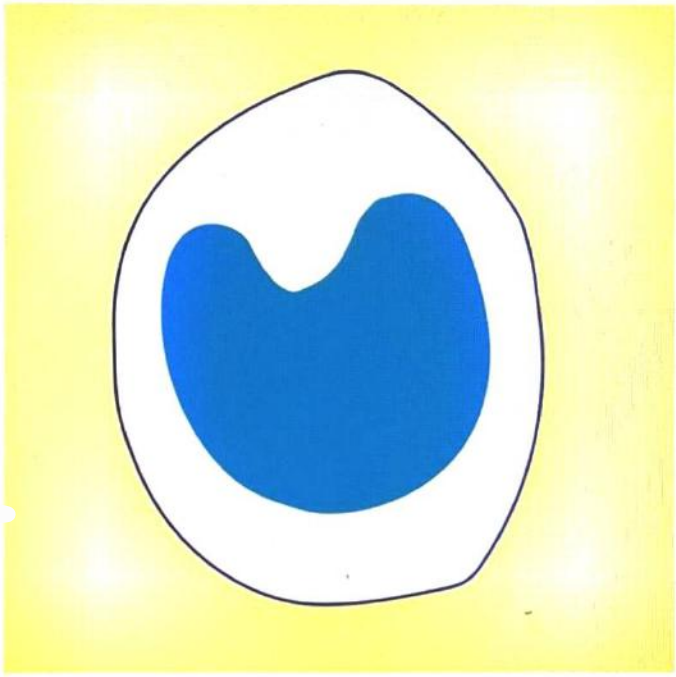
a. Histamine
b. Heparin
c. Acid peptides, acid hydrolases, and other enzymes

- Basophil remains in blood for short period. Then it migrates into the tissues. It was previously believed that after moving out of the blood vessel, basophil remains attached to the tissues; it would be called **"mast cell"**. Recent evidence indicates that basophil and mast cell are two different cell types. However, these two cells are very similar and closely related cells with similar function
- Mast cells have an important role to play in **allergy**.

Agranyulocytes: 00:36:00

1. Monocyte: (2-8%) **["second line defence"]**

- It is the **largest** WBC; 14-18μ diameter.



- Nucleus: Horse –shoe shaped nucleus, with deep indentation. It occupies almost 70% of the cell volume.
- Cytoplasm: About 30%
- Cytoplasm is visible in the cell volume.
- Life span: After its formation in the bone marrow, a monocyte remains there for a while. Later, it is released into circulation. It remains in blood for a short period (upto 8 hours or so), it then enters the tissues.
- In the tissues, monocyte enlarges and becomes a "macrophage". As a macrophage, it remains in the tissues for a long period of time (several years)
- Functions:

A. Monocytes are considered as the **"second line defence"** of the body. Neutrophils, the first line defence, reach the

site of infection immediately. After 24-48 hours, monocytes migrate to the site of infection.

B. Phagocytosis – Monocytes perform the function of attacking and killing / degrading the bacteria, in a manner similar to the neutrophils.

a. Monocytes are much stronger phagocytes compared to neutrophils. The engulf bacteria, tissue debris, organic & inorganic substances, etc. Much greater number of micro – organisms is phagocytosed by monocytes, as compared to neutrophils. Cannot be attacked by neutrophils. E.g malarial parasite.

C. Formation of tissue macrophage – Once they leave the circulation and enter the tissues, monocytes become tissue macrophages. E.g. Kupffer cells in liver, alveolar & splenic macrophages. They remain attached to the tissue for many years. Their main function is to **remove various undesirable substances** (old RBCs bacteria, foreign bodies, etc) by phagocytosis.

D. Role in lymphocyte – mediated immunity
   - The macrophage produces 'monokines' which causes death of the invading antigen.
   - The macrophage takes up an antigen; it presents this antigen to the T- and B lymphocytes for further action.

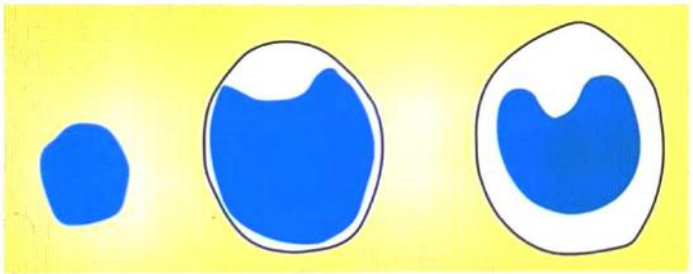
- **Monocytosis**: It is an increase in the number of monocytes. It occurs in acute bacterial infections, malaria, and other such infective conditions.

2. Lymphocyte: (20-30%) ["third line defence"; role in long – term immunity]

- In peripheral blood, two types of lymphocytes are found

a. Small lymphocyte -7 to 10 μ diameter; nucleus occupies the entire cell volume (cytoplasm barely visible).

b. Large lymphocyte- 14-16 diameter; bean shaped or kidney shaped nucleus occupies almost 90% of the cell volume and 10% cytoplasm is volume and 10% cytoplasm is visible.



All other WBC types have short life spans in the circulation (few hours). Each cell type is formed as a colony in bone marrow. Then, all cell of the

Functions of lymphocytes:

- Lymphocytes are considered as "third line defence" of the body.
- They play the important role in chronic infections.
- Lymphocytes form the basis of "specific" immunity (neutrophils & monocytes) form the non-specific immunity; lymphocytes have the central role in the long-term immunity of an individual.
- T-lymphocytes are involved in cell – mediated immunity and B-lymphocytes are the basis of humoral immunity.

Immunity and role of lymphocytes 00:54:36

- In general terminology, immunity means the body's resistance capability or ability to act against foreign harmful substances

"Self and non – self"

- The proteins and other substances or materials which are present in the body right since the conception starts are considered as "self" of the body.
- The material which enter the body from any external source are considered to be "non-self" (or foreign) by the body (e.g. bacteria, viruses, antigens, transplanted organs etc.).
- The body's immune system has the ability to distinguish between " self" and "non-self". The body tries to remove all the "non-self" material.
- The important mechanism for this removal is **lymphocyte – mediated mechanism** and is called **"immunity"**
- The lymphocytes are of two types:
   - T- lymphocytes and
   - B- lymphocyte

Antigen:

- It is a substance (a non-self matter) which, when introduced into the body, can generate an immune response. Bacteria, viruses, etc are non-self. Actually, some of the **proteins** of these substances are the actual antigens

Antibody

- Antibody are immunoglobulins (-globulins). They are formed by the body's immune system in response to an antigen that has entered the body. The antibodies react with the antigen and cause the destruction of antigen.
- Two types of imunity are : **"cell mediated"** immunity and **"humoral"** immunity.

A. Cell mediated immunity and T- lymphocyte
   - Functionally, thre are two major types of

lymphocytes: T- lymphocytes and B-lymphocytes. (Some other types are also present. E.g natural killer[NK] cells)

- In peripheral blood, 70-80% lymphocytes are T-lymphocytes, 10-15% are B – lymphocytes, and remaining are of other types.
- T – lymphocytes are **"Thymus- dependent"** cells {T= Thymus}. Thumus gland is present in the mediastinum at birth. It is present in body for the first decade of life. By the time of puberty, it undergoes involution (disappears completely from the body). It causes processing of lymphocytes; those lymphocytes are called T-lymphocytes.
- After birth, body is exposed to millions of types of antigenic materials. Thymus takes up each antigen, and processes a lymphocyte against it. Thus, the body will have a great number of specific lymphocytes.
- Lymphocyte specifically active against a particular antigen. When the body is exposed to a particular antigen again, the T lymphocyte specific for that antigen replicates itself to form many more lymphocytes of the same type. These lymphocytes then attack and destroy the antigen.

There are various types of T- lymphocytes 01:00:00

- T-helper cells
- T- suppressor cells
- Cytotoxic T-cells
- Delayed type
  - T helper cells are regulatory and play the central role in immune mechanism by helping various other cells involved in immune mechanisms. It is these cells which are attacked by the HIV virus, making the immune system completely deficient.
  - T- suppressor cells limit the immune reactions so that the damage done to the host's innocent cells is contained
  - Cytotoxic T-cells are direct killer cells.

B. Humoral immunity and B- lymphocyte:

- "B" stands for Bursa of Fabricius. It was discovered by Fabricius. It was discovered Fabricius that there are lymphoid structures in birds, chicken, etc;
- In humans, no such bursa was found. Humans have the so-called "bursa equivalents" – the structures that process B- lymphocytes. Bone marrow is the bursa equivalent; gut associated lymphoid tissue (GALT) is another structure which may be similar to the bursa. [Thus, in humans, "B" would also mean bone marrow.] antibodies or immunoglobulins (Ig).
- 5 types of immunoglobulins formed by B-cells are – IgG, IgA, IgM, IgD, IgE.
- Each type of antibodies has specific characteristics. E.g. IgG antibodies can cross the placental barrier (anti – Rh antibodies are of IgG type). IgA antibodies are "secretory" antibodies; they are secreted in milk (thus transferred from mother to fetus). IgE antibodies are involved in allergic conditions.

Clinical Application 01:10:42

- **Allergy and anaphylaxis**: A person may be hypersensitive to a particular antigen. Entry of that antigen will induce massive antibody formation. Antigen- antibody reaction causes release of histamine and other mediators of allergy.
- In a severe form of allergy, there may be systemic allergic reaction resulting in anaphylaxis.
- **Autoimmune diseases**:
  - Normally, the immune system has the ability to distinguish between self and non-self. However, in some individuals, the immune mechanisms get directed toward some self protein. E.g. myasthenia gravis.

HEMOSTASIS 01:12:23

(Stoppage of bleeding by platelets; clot formation, and related issues)

- When a blood vessel is ruptured, and bleeding starts, some events occur in that region to stop the bleeding. These events may be collectively called "hemostasis" (hemo= blood; stasis = stoppage)

Events occurring in process of hemostasis 01:14:26

Following events occur in all overlapping sequence, in the process of homeostasis:

1. Vasospasm or vasoconstriction
2. Platelet plus formation
3. Clot formation (coagulation of blood)
4. Organization, retraction, and eventual dissolution of the clot.

Vasospasm or vasoconstriction

- When a blood vessel is ruptured, within a few seconds the vessel undergoes spasm or constriction. The vessel lumen is narrowed so that the amount of blood loss can be minimized.
- Contraction of the smooth muscle in the wall of the vessel is responsible for the vasoconstriction.

Platelet plug formation (Stoppage of bleeding)

- **Within 1-3 minutes** of the injury, the platelets in that

region form a small mass that plus the ruptured part of the vessel. This platelet plus stops the bleeding.

Platelets (Thrombocytes) [morphology, functions, applied aspects] 01:18:00

- Platelets are round or oval disc shaped blood cells; 2-4 μ in diameter
- Non-motile, non – nucleated
- Formed in the bone marrow, from a large precursor cell called **megakaryocyte**;
- **Thrombopoietin**, a protein formed in the liver & kidneys, stimulates thrombopoiesis (formation of platelets in bone marrow)
- Life span of a platelet: about 9-12 days (Half – life is about 4 days)
- **Normal platelet count**: 1.5 to 4 lacs/ mm^3
- **Critical platelet count** : When the platelet count falls to about 50,000 / mm^3 or less, it is considered to be a "critical" platelet count.

Morphology of platelets

a. **Platelet canalicular system**: There are two types of canaliculi in platelets

i. Open canaliculi: These are open on the platelet surface; the secretory products will be discharged by the platelets, to the exterior, when the platelets are **activated**.

ii. Dense tubules: (closed canaliculi) These tubules or canaliculi are not open to the exterior. They maintain a **high concentration of Ca^{++}** within them.

b. **Platelet granules**: Platelets contain two types of granules:

1. **Dense granules**: contain non-protein substances (serotonin, ADP, etc) which are secreted in response to platelet activation, and
2. **α-Granules**: contain secreted proteins which include clotting factors and platelet – derived growth factors and platelet – derived growth factor (PDGF). [Note: PDGF is also secreted by macrophages and endothelial cells; it stimulates wound healing.]

c. **Contractile filaments** – actin, thrombosthenin. These contractile filaments are involved in clot **retraction** (discussed later).

- Platelet membranes contain **receptors for collagen, ADP, fibrinogen**, and **von Willerbrand factor (vWF) of the vessel**

Platelet activation & aggregation: "Platelet plus formation"

- When a blood vessel is ruptured, platelets come in contact with the exposed collagen and vWF in the vessel wall. This results in **platelet activation**.
- **Platelet – activating factor (PAF)**, secreted by neutrophil , monocytes and platelets increases the production of **thromboxane A_2**.
- Ca++ is released into the cytosol of these activated platelets via the via the canaliculuar system.
- This increased cytosolic Ca++ will be utilized for the following

a. To cause degranulation: the contents of the platelet granules will be discharged to the exterior. Two important contents in this context are
   - **ADP & thromboxane A_2** release of these chemicals will attract nearby platelets to come into this area and adhere to these activated palettes. **A positive feedback cycle will follow**. The new platelet will be activated; they will release the chemicals, further attracting more and more platelets to come into the region and adhere to the platelet already activated. Finally, a platelet plug will be formed; it will seal the gap in the injured vessel

b. Contraction of the platelets in the platelet plus. **"Clot retraction"** – The increased cytosolic Ca^{++} is utilized by the contractile proteins (actin, throbosthenin). Once platelet plug is formed, a blood clot is formed on the surface of the platelet plug. The contractile proteins within the platelet plus will contract so that:

1. Clot size is reduced and
2. Injured & separated ends of the vessel wall are pulled toward each other, reducing the gap size.

Function of platelets: 01:28:35

1. Platelet plug formation and arrest of bleeding: It occurs within 1-3 minutes after the vessel injury.
2. Release of platelet phospholipids and other factors that initiate and aid in clot formation: Plateletes play a role in intrinsic pathway for clot formation.
3. Strengthening of the clot: Platelets (entrapped in the clot) release a factor called **fibrin – stabilizing factor**. Clot is a meshwork of fibrin threads. The fibrin – stabilizing factor causes covalent bonding between the strengthening the clot.
4. Clot retraction: Platelets entrapped in the clot are also responsible for reducing the size of the clot. The contractile proteins within these platelets would cause contraction of the platelet plug. The clot size is reduced and the broken ends of the vessel wall are pulled closer.

Clinical Application 01:32:54

i. Bleeding time:

- The time interval between onset of bleeding.
- Normal bleeding time is 1-3 minutes.

- Stoppages of bleeding is the function of platelets; with platelet deficiency the bleeding time will prolong.

ii. Thrombocytopenia & Purpura

- As a result of a decrease in platelet count, the bleeding time is prolonged. Bleeding into the skin, after minor injuries, leads to appearance of purple colored spots in the skin. The condition is called purpura.

iii. Anti – platelet agents and "platelet aggregation inhibitors" in the treatment of myocardial infarction and stroke:

- An abnormally formed (platelet plug + clot), within intact vessels, is referred to as a **thrombus**.
- Such a thrombus threatens to interfere with the blood supply to an organ.
- When a thrombus formus inside coronary vessels, it may result in myocardial infarction ("heart attack"); thrombus within cerebral vessels may result in stroke ("paralysis" or hemiplegia).
- Aspirin is known to be an anti – platelet agent; it reduces the stickiness of platelets, preventing their coming together in a thrombus formation. Clopidogrel is the drug that is called 'platelet aggregation inhibitor'.

Clot formation and coagulation

- Platelets are the cellular elements of blood. The platelet plug is an important early tool for a quick limitation of blood loss.
- The platelet plug is a quicker but temporary response. The platelet aggregation and adhesion properties have a limited time – span. However, the injury in the vessel wall

Coagulation of blood : Clot formation 01:40:50

- Clot formation occurs in 3 essential steps:

1. As a result of certain reactions occurring at the site of injury, there is formation of prothrombin activator (it is a complex of substances)
2. Prothrombin activator then converts prothrombin to thrombin,
3. Thrombin, once formed, acts enzymatically to convert fibrinogen to fibrin threads. The fibrin threads then enmesh blood cells and plasma to form the clot.

Note a few points:

- Prothrombin and fibrinogen are the plasma proteins synthesized by the liver.
- Once thrombin is formed from prothrombin, the thrombin then acts as an enzymes to convert fibrinogen to fibrin monomers.
- There is polymerization of the fibrin monomers, resulting in the **fibrin threads**. Fibrin threads form the meshwork of the clot.
- The fibrin meshwork is strengthened by fibrin – stabilizing factor (FSF). The FSF is an enzyme present in small amounts in plasma; it is also released by the platelets that are entrapped in the clot. Fibin- stabilizing factor causes covalent bonding between the fibrin monomer molecules and the adjacent fibrin threads, resulting in strengthening of the fibrin meshwork.

Formation of prothrombin activator is possible in two ways: The "Extrinsic" and the "Intrinsic" pathway. Therefore, blood coagulation (clot formation) is said to occur via these two mechanism, extrinsic & intrinsic.

1. Extrinsic pathway for coagulation: When there is trauma to the vessel wall and to the surrounding tissues, it will initiate the clot formation; the mechanism for such a clot formation is called "extrinsic" pathway (The reason for initiation is 'extrinsic' to blood.)
2. Intrinsic pathway for coagulation: When there is trauma to blood itself, or if blood comes in contact with the collagen in the vessel wall (or blood coming in contact with a water – wettable surface, such as, glass), it will initiate the process of clot formation; the mechanism is called Intrinsic pathway.

- Tissue trauma releases tissue thromboplastin which initiates extrinsic pathway.
- Trauma to blood, or its exposure to vessel wall collagen or glass, causes clotting factor XII to be activated. This initiates intrinsic pathway. Thus, blood taken in a test tube will clot by intrinsic pathway for clotting.

The clotting factors in p-lasma: 01:48:51

Refer Table 13.1

- The clotting factors are present in inactive forms in the plasma. When coagulation is initiated, these factors are activated. The activated factor is mentioned with a subscript 'a'; for instance, Factor X to Xa.
- All the factors are synthesized by the liver, with the exception of factor VIII which is synthesized by endothelial cells.
- Vitamin K – dependent factors: factors II, VII, IX, and X are called vitamin K is a necessary co-factor for the enzyme that catalyzes the conversion of glutamic acid residues to -carboxyglutamic acid residues.

1. Extrinsic pathway for coagulation:

i. Tissue injury / trauma to vessel wall: It causes release of tissue thromboplastin or tissue factor (TF) from the fibroblasts and vascular smooth muscle cells (VSMCs).

ii. Activation of factor VII : Tissue thromboplastin then activates factor VII.

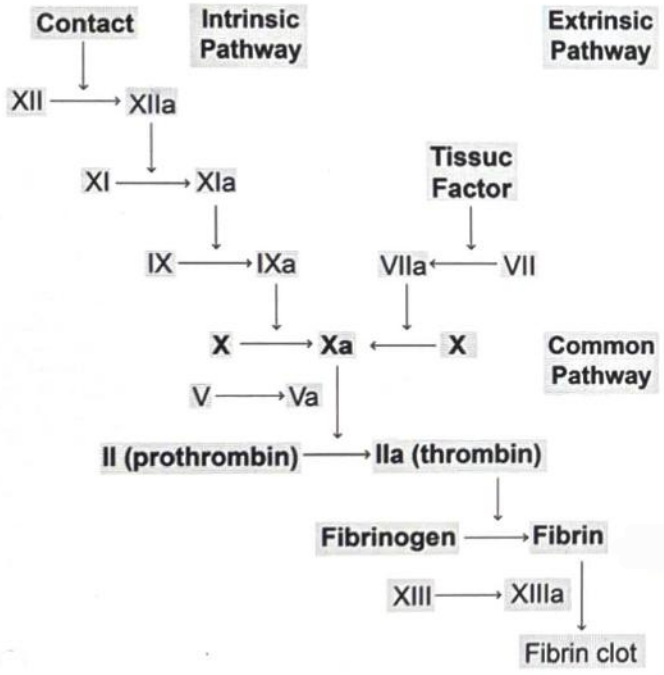
iii. Formation of prothrombin: Factor VIIa then, in the presence of tissue thromboplasin and Ca++, converts factor X to Xa. (Factor Xa+tissue thromboplastin + factor V) is the complex that is called prothrombin activator.

iv. The remaining steps are common for extrinsic & intrinsic pathways. Prothrombin activator acts on prothrombin and converts it to thrombin. Thrombin converts fibrinogen to fibrin.

Role of factor V:

- In a positive feedback manner, factor V forms more and more thrombin.

2. Intrinsic pathway for coagulation: (Formation of prothrombin activator is initiated with trauma to the blood itself, or exposure of the blood to subendothelial collagen in the injured vessel wall, or exposure of the blood to a water – wettable "enzyme cascade reaction" (previously also called as "waterfall sequence theory"). "Enzyme"- Once a factor is activated, it acts 'enzymatically' to activate the next factor, and so on. Subsequent step the reactions become larger so as to make a large final product.



Coagulation pathways intrinsic and extrinsic

Note: factor VIII is activated when it is separated from VWF.

- In absence of factor VIII, there will be deficient formation of Xa / prothrombin activator. The clot formation would thus be deficient or delayed.
- Deficiency of factor VIII is the condition called classic hemophilia.

Role of Ca^{++}:

- Calcium ions are necessary for all the steps in clotting, except for the first two steps in the intrinsic pathway.
- Without the ionic calcium, clot formation will not be possible.

Clinical Application 02:07:15

Abnormalities of hemostasis

- Thrombosis
  - A clot formed, under abnormal circumstances, inside a vessel is called thrombus; the phenomenon is called thrombosis. An abnormal clot or thrombus is formed within a vessel under following conditions.
    i. Sluggish blood flow; it allows the activated clotting factors to accumulate
    ii. Injury to the intima of a vessel : For instance, as occurs in atherosclerosis. A thrombus in coronary vessel, blocking blood flow to myocardium, result in myocardial infarction. A thrombus in cerebral circulation leads to stroke.
- Liver disease and clotting abnormalities
  - Severe liver disease result in clotting defect and excessive bleeding. In severe liver disease, bile salt deficiency causes a deficient absorption of fats soluble vitamins. Vitamins K is a fat soluble vitamin. Its deficiency leads to insufficiency of the vitamin K dependent factors (II, VII, IX, X, and protein C). This can lead to a severe bleeding tendency.
- Hemophilia : ("phil" = love or attract: Excessive bleeding occurs into tissues as if the tissues 'attract' blood). It is an inherited disorder that results from a congenital deficiency of factor VII or factor IX.
- Hemophilia A or classic hemophilia is caused by factor VIII deficiency. About 15% cases of hemophilia are caused by deficiency of factor IX (Christmas factor)- hemophilia B or Christmas disease.
- Von Willebrand disease results from deficiency of von Willebrand factor (vWF).
- Factors VIII & IX are transmitted genetically via the female chromosome as a recessive trait. Hemophilia occurs almost exclusively in males. Females do not have hemophilia because at least one of their two X chromosomes has the genes that code for these clotting factors. Hemophilia is manifested as excessive bleeding tendency.

After 3 steps in hemostasis (vasospasm, platelet plug formation, and clot formation), the next event is:

- Clot retraction; dissolution of the clot:

a. Clot retraction; SERUM

- Within 20-60 minutes after clot formation, the clot begins to retract; it reduces in size retract; it reduces in size.
- The contractile filaments- actin thrombosthenin- of the platelets within the platelet plug would contract. Two things are achieved by this
  i. The injured ends of the vessel are pulled closer so as to reduce the gap size.
  ii. Clot size is reduced, so that it does not obstruct the eventually, the clot is invaded by fibroblasts, which will form connective tissue throughout the clot.

Dissolution and lysis of the clot:

- Plasminogen is a plasma protein; it is activated to form plasmin. Plasmin is a proteolytic enzyme (similar to trypsin). It digests the fibrin threads in the clot, and the clot will be lysed.

Why doesn't the blood clot spontaneously with vessels?

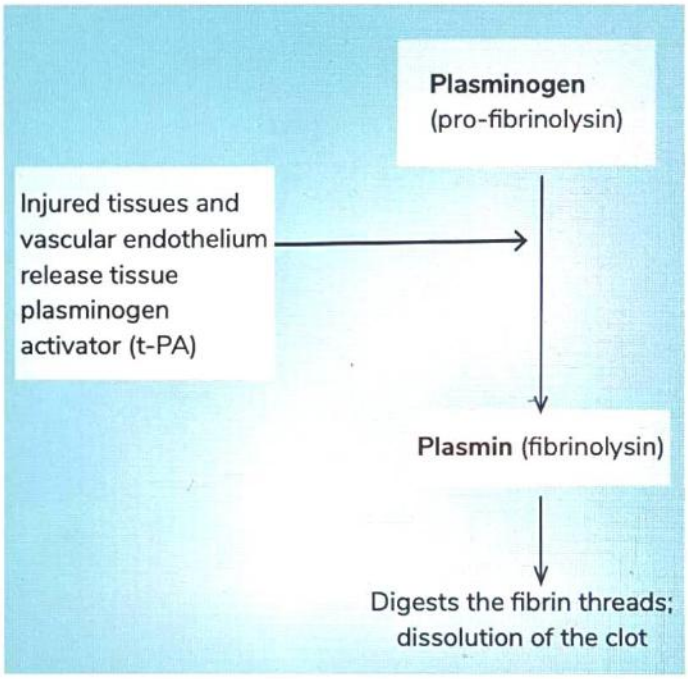
1. Plasma contains clotting factors that cause clot formation. However, they are in inactive forms.
2. Factors that promote clot formation and the factors that prevent clot formation are both present in the plasma. Normally, the balance is titled in the favor of the factors that prevent clot formation.

- Natural (in vivo) anticlotting mechanisms:
- Smoothness of the endothelium: It prevents the contact activation of factor XII and thus prevents initiation of intrinsic mechanism of clotting.
- Thrombomodulin – thrombin complex: All endothelial cells have a protein called thrombomodulin bound to their surfaces. (The only exception is cerebral microcirculation) Thrombomodulin binds thrombin. Thrombin is a procoagulant that activates factors V and VIII. However, when thrombin binds to thrombomodulin, thrombin becomes an anticoagulant. The thrombin + thrombomodulin complex activates a plasma protein called protein C.
- Activated protein C(APC), along with its cofactor protein S, inactivates factor V and VIII. Clotting mechanism is a "positive feedback" process. How is the process limited? How is excessive spread of the clot prevented?
- Antithrombin III: It is a protease inhibitor present in plasma. It binds to and inactivates some clotting factors. Activated factors IX, X, XI, XII are the factors that areinhibited by antithrombin III, thus blocking them after a certain amount of clot is formed.

Role of Heparin : 02:21:22

- Heparin is an naturally occurring anticoagulant in blood
- It is produced by
  a. Basophils in blood
  b. Mast cells located in the pericapillary connective tissue.
- Heparin acts via antithrombin III. It facilitates the binding of clotting factors to antithrombin III, thus inhibiting the active forms the clotting factors IX, X, XI, XII.
- Heparin also removes thrombin via its facilitation of antithrombin III.
- Dissolution of the clot: fibrinolytic system
  - Plasminogen is a plasma protein ; it is an inactive precursor that when activated forms a substance called plasmin or fibrinolysin.
  - Plasmin is a proteolytic enzyme that resembles trypsin. Plasmin digests the fibrin threads, which will result in dissolution of the clot.

Also note: Plasminogen receptors are present on intact endothelial cells. When plasminogen binds to these receptors, it becomes activated. Thus, intact blood vessels are provided with a mechanism that discourages clot formation.



Clinical Application

- Streptokinase and urokinase are tissue plasminogen activators (t-PA). Streptokinase is a bacterial enzyme produced by some strains of streptococci.
- Human t-PA is produced by recombinant DNA technology

Anticoagulants: 02:24:30

A. In-vitro : (These anticoagulants are used outside the body to store blood, as a sample for lab analysis)

1. Dilution of blood up to 20 times or more:
   - It does not allow the clotting factors to come together in sufficient quantities and initiate / form a clot. Note: RBC pipette and WBC pipette are used for collection of blood sample; a diluting fluid is added to the sample. Since, dilution of blood is 20 times or more in those pipettes, the diluting fluid does not need to contain an anticoagulant
2. Prevention of contact
   - The container for blood collection may be coated from inside with such a material (e.g. silicon) that will prevent contact activation of factor XII, thus blocking the initiation of coagulation.
3. Ca^{++} removing agents: (used for collection of blood samples)

[Ca^{++} is necessary for almost all steps in coagulation. When these anticoagulants are added to blood samples, ionic calcium is removed so as to make it unavailable for clotting]

i. Oxalates : (double oxalate)
   - Double oxialate is a mixture or ammonium oxalate (3 parts) + potassium oxalate (2 parts)
   - Mechanism of action: precipitation of Ca^{++} as insoluble oxalate crystals

ii. Citrates: (trisodium citrate)
   - **Mechanism of action**: Converts Ca++ in the blood sample into non – ionized form

iii. Ethylene diamine tetra acetic acid (EDTA):
   - Sodium and potassium salts of EDTA are strong anticoagulants

Table 13.1

Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Tissue thromboplastin or tissue factor
Factor IV	Calcium
Factor V	Labile factor (proaccelerin)
Factor VII	Stable factor
Factor VIII	Anti hemophilic factor (AHF) or anti-hemophilic globulin
Factor IX	Christmas factor
Factor X	Stuart – Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA)
Factor XII	Hagmen factor (contact factor)
Factor XIII	Fibrin – stabilizing factor
Other factors involved in coagulation	High molecular weight kininogen (HMWK), prekallikrein, Platelet phospholipids

14 BLOOD PHYSIOLOGY PART - 3

Introduction 00:02:42

- The population is divided into various groups, based on the presence of certain antigens on the RBC membrane.
- Carl Landsteiner discovered the first blood group system (ABO system) in the year 1900. Since then, about 20 blood group systems have been devised. (ABO, Rh, Kell, Duffy Lewis M and N system, etc).
- Each blood group system has some specific significance. For instance, the M and N system is mostly used in paternity disputes.
- The two systems that are clinically most important are – ABO and Rh systems.

ABO blood groups system

- Antigens
  - → The ABO blood group system is based on two antigens – A and B.
  - → The blood group antigens are present on the surface of RBC. These antigens present on red cell membranes are called agglutinogens. [they react with agglutinins or antibodies; the reaction is "agglutination reaction".]
  - → Based on the presence or absence of the antigens, there are 4 blood groups in the ABO system – A, B, AB and O.

  If a person has only A antigen on his red cells, his blood group is A.
  If only B antigen is present – blood group B.
  Both A & B antigens present - blood group AB.
  Neither A nor B present – blood group O.
- Antibodies: (agglutinins)
  - → There are antibodies against antigens A and B. Antibody against A is called "anti – A" or alpha (α); antibody against B is called "anti-B" or beta (β).
  - → The antibodies α and β are present in the plasma.

LANDSTEINER'S LAW 00:09:27

- Only applicable to the ABO system
- 2 laws:
  - 1st Law: when an agglutinogen is present on the membrane of RBC. The corresponding agglutinin must be absent in the plasma of the person.
    E.g.: RBC contains A – Ag: plasma must not contain ⟨ agglutinin; otherwise there will be death
  - 2nd Law: when the RBCs in an individual are devoid of agglutinogen, plasma shall contain the corresponding agglutinin.
    E.g.: RBCs contain no B or A antigen. In the plasma of this individual; there must be anti-A and anti-B agglutinins.
- Therefore: "A" group blood must contain β - agglutinin in the plasma and group O blood must contain both α and β agglutinins in the plasma.
- Thus, antigen and antibody put together, blood groups can be written as follows: Aβ, Bα, AB. Oαβ

Blood group	Antigen (on RBC)	Antibody (in plasma)
A	A	Anti-B (or β)
B	B	Anti-A (or α)
AB	A and B	-
O	-	Anti – A and anti-B (α& β)

~ Concepts of "universal donor" and "universal recipient":

- These concepts were put forth after the discovery of the ABO blood group system. This is regarding blood transfusion – giving one person's blood to another. Donor is the person giving blood; recipient is the person who receives the blood.
- With understanding of immunity (behavior of antigens and antibodies), "O" blood group was called "universal donor"- can give blood to any other blood group individual. And, "AB" was
  Called "universal recipient" can receive blood from any other blood group individual
- Bombay blood group, is a rare blood type
- The h/h blood group, also known as Oh
- Was first discovered in Bombay in 1952
- H- antigen which is present in blood group O and precursor for A,B & AB
- O antigen genotype is HH
- Bombay genotype is (hh), do not express H antigen
- H antigen is absent in Bombay group, but antibody – A and B are present in serum
- Bombay group cannot receive blood from any member of the ABO, since they have Anti-H
- Cause is FUT1 gene mutation on H locus

- Frequency = 0.0004%

Rh system: 00:29:16

- The Rh blood group system is based on the "Rh" antigen. [Rh~ Rhesus; the Rh antigen was found to be present in the Rhesus species of monkeys; hence the term "Rh".]
- If Rh antigen is present on the red cells, the person is called "Rh – positive"; if it is not present, the person is said to be "Rh – negative".
- 85-90% of the population is Rh – positive; 10-15% is Rh-negative.
- While noting the blood group of an individual, antigens of both ABO system and Rh system are mentioned. E.g. B+ve means B antigen and Rh antigen present.
- Rh antigen is of 6 types, structurally. The 6 types are: C, c, D, d, E, e.
- In majority individuals (almost 95%) – D type is found.

Erythroblastosis fetalis: [hemolytic disease of newborn]

- It is a disease occurring in a fetus / newborn baby.
- It occurs due to "Rh incompatibility between mother and fetus". (That is, Rh blood group of mother and fetus not compatible)
- C/F
  - → anemia
  - → Jaundice
- Preventive measure
  - → Anti D Serum given to mother after delivery of 1st body
- TREATMENT
  - → Exchange transfusion for anemia

Blood transfusion 00:57:18

- "giving one person's blood to another".
  - Indications of blood transfusion (when is it required?)
    - → Blood loss due to any reason (accident, surgery, etc)
    - → Severe anemia (Hb <5 gm%)
- **Transfusion of blood products:**
  - Sometimes, transfusion of whole blood is not advisable. Instead, blood products are transfused. Blood products: Red cell transfusion, fresh frozen plasma (FFP), platelet transfusion, cryoprecipitate.
  - Transfusion is given to improve tissue oxygenation: in severe anemia, acute blood loss. FFP is used for reversal of anemia, acute blood loss.
  - FFP is used for reversal of anticoagulant effects.
  - Platelet transfusion: To prevent hemorrhage in thrombocytopenia or defects in platelet function
- **Cryoprecipitate:**

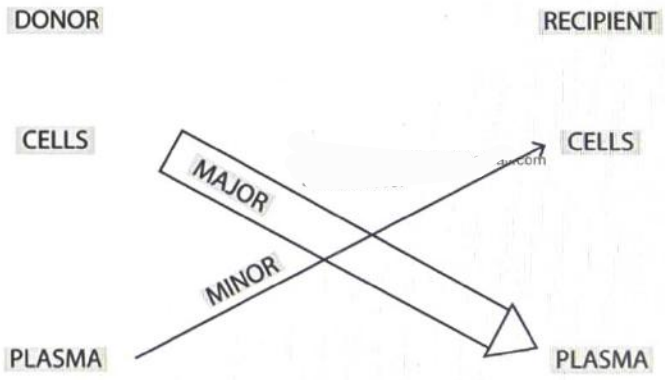
Hypofibrinogenemia (consumptive coagulopathy) [cryoprecipitate is prepared by thawing fresh frozen plasma and collecting the precipitate. It contains high concentrations of factor VIII and fibrinogen.] Its transfusion is indicated in surgical bleeding.

  - Screening of the donor: (who can or can't donate blood?)
    - → The person should not be underweight (what should not be less than 45 kgs)
    - → The person's hemoglobin should not be less than 12 gm%
    - → The person should not be suffering from any communicable disease. Also, he/she should not have suffered from any infectious disease for the last 1 month.
    - → If the person has donated blood previously, the gap between 2 blood donations should be at least 4 months.
    - → Donor's written consent should be obtained.
- **Collection and storage of blood:**
  - A vein in the donor's cubital fossa is selected for blood collection. The skin is sterilized properly in the region. 16 no. (wide gauge) needle is inserted in the vein, blood starts flowing out into the bottle that contains anticoagulant. About 480 mL of blood is collected in the bottle that contains 120 mL of anticoagulant. Throughout the procedure, the bottle is shaken gently so that blood and anticoagulants are used: Acid-citrate dextrose [ACD].
  - Blood is then stored in the refrigeration at 0 to 4 degree C.

Matching: 01:05:02

Blood samples of the donor and the recipient are collected.

- Blood grouping
  - Blood groups of both donor and recipient should be preferably the same. (if the recipient is Rh-ve, he/she should not receive Rh + ve blood).
- Cross matching
  - Blood sample of donor separate cells and plasma
    Blood sample of recipient separate cells and plasma
    {recall: blood group antigens are on red cells and antibodies are in plasma.}



- Blood transfusion orders
  - → The recipient's case papers should have the note prescribing the rate of transfusion – e.g. 20 drops / min.
- Hazards of blood transfusion: [complications in the recipient, after receiving blood]
  - → Thrombophlebitis – inflammation of the vein through which the blood is given. If the inserted needle is left in the vein for a long complication.
  - → Congestive heart failure – it may occur in elderly patients with cardiovascular status compromised.
  - → Transmission of infection – HIV, hepatitis B (if the donor's blood was not screened properly);

CLINICAL QUESTIONS

Q. A 28 year old male was brought to the emergency bay after a road traffic accident; he had multiple lacerations to his both upper extremities and sustained an open fracture to his lower extremity. Initial CBC revealed WBC to be at 22 x 103 /µl, and subsequent CBC analysis after 5 hours revealed the WBC count to be at 7 x 103 /µl. Why there is an increased WBC count in the first CBC analysis?

A. Increased production of WBCs by the bone marrow
B. Release of pre-formed, mature WBCs into the circulation
C. Decreased destruction of WBCs
D. Increased production of selectins

Answer: B

Solution:

- In bone marrow, majority of the WBCs are stored. When there is stimulation, like increased level of cytokines, these stored WBCs are released into the circulation.
- But still, a physical traumatic event can result in the release of WBCs into the circulation.
- The increase in the given case may not be due to any particular inflammatory response, but instead the increase is due to the mechanical trauma and associated stress responses.

Reference: Guyton and Hall Textbook of Medical Physiology 13th Edition, Page No. 456

LEARNING OBJECTIVES

UNIT 4 CARDIOVASCULAR SYSTEM

GASTROINTESTINAL TRACT

- Innervation
- Electrical activity
- Reflexes
- Motility in digestive tract
- Secretions in GIT
- Digestion and absorption

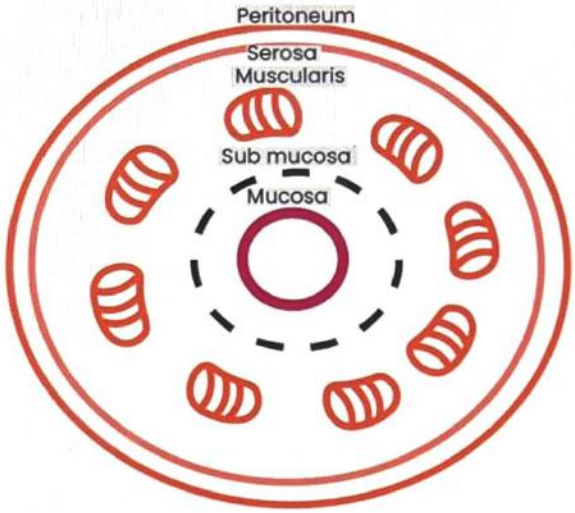
15 GASTROINTESTINAL TRACT

Introduction

00:01:30

Layers

1. Mucosa
2. Submucosa
3. Muscularis mucosa



4. Serous layer

Innervation

00:04:25

Enteric nervous system

- Branch of ANS
- aka Peripheral / mini brain
- Sub mucous / meissner's plexus (sensory)
- Myenteric plexus / Auerbach's plexus (motor)

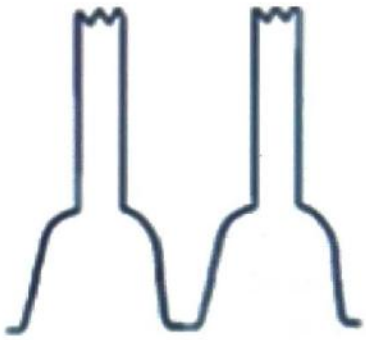
Hirschsprung disease-congenital megacolon characterized by lack of ganglion cells/enteric nervous plexuses (Auerbach and Meissner plexuses) in distal segment of colon.

Achalasia cardia– failure of LES to relax due to degeneration of inhibitory neurons (containing NO and VIP) in the myenteric (Auerbach) plexus of the esophageal wall

Electrical Activity

00:07:00

- Pace maker cell → Interstitial cell of CAJAL
  Electric activity occurs at a frequency. Frequency differs at different parts of GIT
- BER (Basal Electrical Rhythm)



- Frequency
  Stomach → 3-4 times/min
  Duodenum → 12/min
  Jejunum → 9/min
  Illeum → 7/min
- The decrease in the frequency from oral to anal direction of peristalsis – Law of the Gut except colon (antiperistalsis)

Antiperistalsis

- Naturally occurs in colon (From hepatic Flexure of colon to caecum)
- Frequency at Sigmoid → 6-9 /min
  at Asc. colon → 2-6/ min
- Significance → to reabsorb water (1.5 ltr/day)
  MAXIMUM ABSORPTION OF WATER TAKES PLACE AT JEJUNUM (6.6 LTR /DAY)

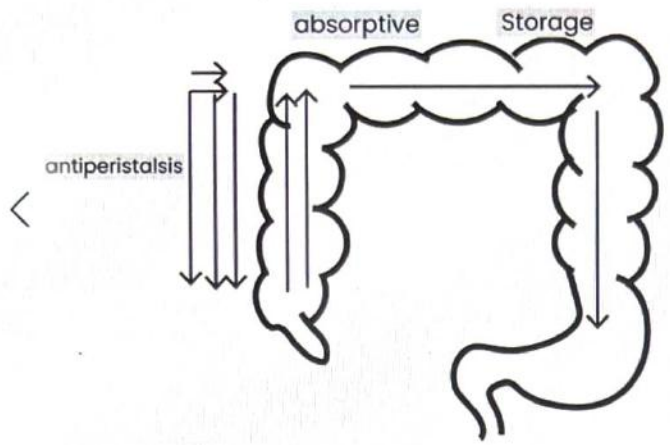
REFLEXES

00:19:14

Q. Defecation is initiated by which reflex Upon rising up From bed in morning

a. Gastroileal reflex
b. Gastrocolic reflex
c. Orthocolic reflex
d. Mass peristalsis

TYPES OF REFLEXES



1. LOCAL REFLExES
   - Entirely confined to digestive wall
   - EX: Peristalic reflex
2. ULTRA LONG LOOP REFLEXES
   - ENS → Spinal cord → Higher centres
   - Ex: Defecation Reflex
3. LONG LOOP REFLEX
   - ENS → Spinal cord and back
   - Ex: orthocolic reflex

NEUROTRANSMITIERS
Excitatory NTs → Ach
Substance P
Inhibitory Nts → VIP (inhibits motility)
NO

Motility in digestive Tract

00:24:45

Deglutition (10-12 sec)

Causes of difficulty in swallowing:

1. Esophageal potholopies-Achdado Sderodermal esophageal dysmotility (Part of CREST syndrome), Diffuse esophageal spasm
   (dysphagia and angina-lke chest pain, Schatzki rings, Eosinophilic esophagitis, Gastroesophageal reflux disease, plummer–vinson syndrome,
   Esophageal carcinoma, Escalloped stricture
2. Food impaction
3. Zenker's diverticiium
4. Epiglottitis
5. Polymyositis
6. Clostridium Botulinum (4 D's - Displopia
Dysarthria, Dysphagia, Dyspnea)
7. Enlargement of the LA (eg. in mitrol stenosis) can lead to compression of the esophagus (dysphagia)
8. Neuro-Stroke, Osmotic demyelination syndrome, Amyotrophic lateral sclerosis

➔ 3 phases

1. Oralphase — voluntary
2. Pharyngeal } Involuntary } Swallowing
3. Oesophageal } (Reflex Phases) } Center in medulla

ORAL PHASE

- Tongue is pressed upward & backward, bolus of Food pushed into posterior pharynx

PHARYNGEAL PHASE

- Sensitive part → Tonsillar pillar
- When Food touches tonsillar pillars, the Swallowing centre in the medulla is activated. This causes Deglutition apnea which sends signals for co-ordinated contractions that are seen in pharynx & oesophagus.
- IX & X CN involved
- EVENTS AFTER UPPER ESOPHAGEAL SPHINCTER RELAXATION

1. Soft polate moves upwards & the posterior nares are closed
2. Epiglottis falls & closes the respiratory passage
3. Potato pharyngeal folds approximate in mid line & Leaves a narrow slit for the passage of bolus
4. Opening of oesophagus widened & wave of peristalsis sent down wards

OESOPHAGEAL PHASE

- LOWER/ GASTRO OESOPHAGEAL SPHINCTER
- Physiological sphincter/ functional sphincter
- No anatomical entity
- acts as a high pressure sphincter area
- Food enters the stomach by 1 & 2 peristalsis

MOTOR FUNCTIONS OF THE STOMACH

1. STORAGE
2. MIXING
3. SLOW EMPTYING

Stomach functions are NOT essential for life EXCEPT secretion of intrinsic factor

1. STORAGE
- RECEPTIVE RELAXATION OF STOMACH WALL
- 1-1.5 Ltr Food is accumulated without much rise in intra gastric pressure.
- Pack maker to stomach is located in mid portion of body

2. MIXING → RETROPULS1ON
- Chyme empties From pyloric sphincter, some of it goes back to stomach & the process repeats

3. SLOW EMPTYING
- (N) → 4- 6hrs
- Upto 8hrs for fatty Foods

Factors influencing emptying

1. Weak factor (Gastric Factor)
- Gastrin
- Promotes emptying

2. Strong (Duodenal Factors) – inhibit emptying

a. (Pancreatic enzymes in duodenum needs alkaline environment)

Acidic chyme
↓
Secretin (S cells)
↓
Constriction of Pyloric sphincter

b. Irritation of duodenal mucosa (e.g. Poisons)
↓

c. Initiation of enterogastric reflex
(e.g. Post-Gastrectomy)
Cause lot H_2O pulled by osmosis
Causes decrease in blood volume & causes DUMPING SYNDROME

Hypertonic Contents
↓
Osmoreceptor (in duodenal wall)
↓
Entero Gastric Reflexes

Fat break down products in duodenum
↓
CCK (cholecystokinin) released
↓
↓Gastric motility
↓
Feeling of fullness (satiety)

MOTILITY OF SMALL INTESTINE

01:00:00

Length a SI in living - 2.77 mts
Length a SI after dearth -6 mts(Loss of villi & microvilli)

1. FED
- Peristalsis (Propulsion)
- Segmentation (Mixing)

2. FASTING → Migrating Motor Complex (MMC)
1st - hunger pangs

MMC(MIGRATING MOTOR COMPLEX)

01:07:05

- house keeper a Intestine (similar in colon and has haustrations)
- in post absorptive phase, it clears the debris
- 90 min cycle

3 Phases

1. PHASE I → 70 Min
→ Quiescent phase, only slow waves
→ No contractions
2. PHASE II → 10-15min
→ Irregular contractions
3. Phase III → 5-10 min
→ Activity front

The contractile ring will travel from MMC to the whole length of the intestine (vs peristalsis – travel only a few cms)

MOTILIN
- Hormone that strengthens the MMC Contraction
- Erythromycin binds with Motilin Receptors (Hence, used as Pro kinetic drug)

Erythromycin is used to stimulate intestinal peristalsis
Gastrin secretion is increased in chronic PPI use, in chronic atrophic gastritis (e.g H pylon) and in Zallinger-Ellison syndrome (Gastrinomal)

Regulatory Peptide secretions digestive Tract

01:14:15

Cell secretion Stomach	Functions
	Acts H_2, receptors on parietal cell
1. ECL Cells secrets → Histamine →	↑ Gastric acid secretion (paracrine) Potentiating effect of ACH, gastrin
2. G cells secrets Gastrin → →	↑Gastric acid secretion ↑Motility
1. Stomatosin [Pro insulin as well as anti insulin] synthesized by	Octreotide is an anolog used to treat acromegaly, carcinoid syndrome, gastrinoma,
- D-cells in pylorus duodenum →	glucogonoma, esophageal varices
- δcells in pancreas →	↓ Gatsric acid secretion (pH <2)
- Hypothalamic neurons →	Suppresses the insulin & glucagon secretion Secrets GHIH (inhibit anti insulin – hence, proinsulin)

Cells in small intestine
Duodenum

1. S cells secretes SECRETIN (1st hormone to be discovered)	→ Stimulated by acidic chime → Maintains alkaline pH in duodenum → Constricts the pyloric sphincter of HCO_3, rich pancreatic
2. I cells secretes Secrete CCK Stimulated by fat breakdown products	→↓Gastric motility → ↑intestinal motility Causes enzymes rich pancreatic juice to be secreted Bile flow from gall bladder (cholagogue)
3. M cells secretes MOTLIN→	↑ MMC contraction

Choleretics - ↑bile acids from hepatocytes (eg. Vagus)

BOMBESIN/ GRP
- Gastrin releasing peptide (neuropeptide)

PEPTIDE YY (Tyrosine Residues).
- Ileal mucosa in response to fat
- Prevents further gastric emptying
- Prevents steatorrhea
- Also regulates hunger

INCRETINS
- Released by G1 mucosa in response to oral glucose
- They will go to pancreas & Insulin Secretion
  Oral glucose has double effect- insulin in pancreas (Incremental insulin)

GLP 1 or
GIP (Glucose dependent insulinotropic peptide)
GLP-1 analogs (exenatide, lira glutide) are used in Diabetes mellitus therapy DPP-4 inhibitors (Linagliptin, saxagliptin, sitagliptin) – Inhibit DPP-4 enzyme that deactivates GLP-1 and are used in Diabetes mellitus therapy

SECRETIONS IN GIT:

01:35:30

SALIVA
- Secretes highest volume of k' (vs. Max K concentration in colonic secretion)
- It has no endocrine control, only neural control
- In Sialorrhea, no ductular modification
  pH → 6-6.5, hypotonic (N) isotonic
  2 ions → K; HCO_3
  2 enzymes → ptyalin (α - amylase)
  Lingual Lipase (for Lipid digestion)
- Defense mechanism- Thiocyanate ions, IgA, Lysozyme

M3 (muscarinic) increases exocrine gland secretions

(eg., Lacrimal, sweat, salivary, gastric acid),
- Pilocar pine (cholinomimetic Agents) – patent stimulator of sweat, tears and saliva- used in xerostomia (Sjogren syndrome)
- Saliva can be a route of transmission for various viral infcetions like Roseola infantum
- (Human herpesvirus 6 and 7), Mononucleosis, herpes simplex virus - 1

High flow rate
↓
No ductular modification
↓
Final will resemble primary secretion (rich in Na^+, Cl^- H_2O)

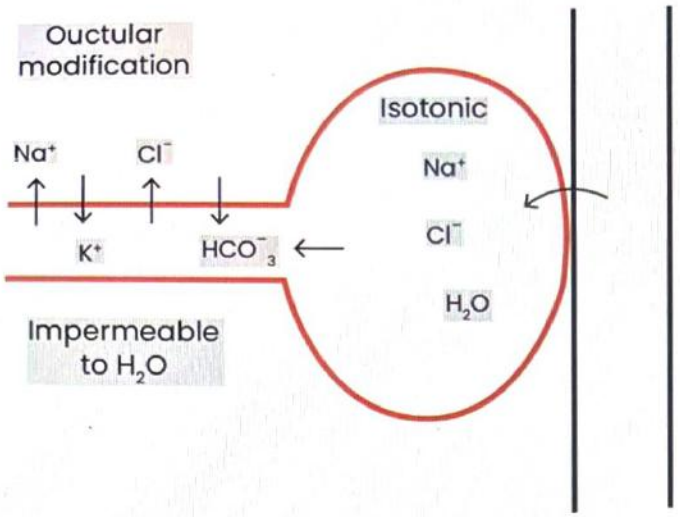
Amylase cannot act in acidic environment like stomach
Lingual lipase can act in stomach & duodenum

Iodides are concentrated in salvia (Na-I symptoms)
Mech. of salivary secretion

2 forms

10 salivary secretion
Rich in Na^+, Cl^-, H_2O (isotonic)

Ductular modification
Na^+ → reabsorption
Cl^- → reabsorption
K^+ →secretion
HCO_3 →Secretion



Functions of saliva
1. Forms bolus of food
2. Helps in swallowing
3. S. amylase
3. Digestion of polysaccharides $\xrightarrow{\text{S. amylase}}$ oligosacchrides

   Digestion of lipids → because of lingual Lipase
4. Speech
5. Temperature regulation
6. Defense mechanism

Regulation of secretion of saliva
- Exclusively neural regulation
  - X N. – afferent fibres
  - VII N. Efferent fibres (motor)
- Conditioned reflex

GASTRIC SECRETION

01:52:48

GATSRIC GLANDS
1. MUCUS NECK CELLS → Secretes Mucus
2. PEPTIC OR CHIEF CELLS → Secretes pepsinogen
3. PARIETAL OR OXYNT1C CELLS → Secretes HCL & Intrinsic Factor a castle

Phospholipase- only enzyme not prepared in inactive precursor form

PEPSIN
- Aids in 10-20% of protein digestion
- Needed For Further gastric acid secretion & digestion of meat protein (collagen)

RENNIN
- Secreted in stomach
- Helps in digestion of milk protein (Casein)

GASTRIC LIPASE
- A Tributyrase
- Digest tributiric acid/ Butter fat

PHASES OF GASTRIC ACID SECRETION:
1. CEPHALIC (20%) → Mediated by vagus (site & smell of food) Can be prevented by vagotomy

2. GASTRIC PHASE (70%)
- Partly mechanically → by distension a stomach wall
- Partly chemically → by protein breakdown products
- Mediated by gastrin hormones

3. INTESTINAL PHASE (10%)
- Mediated Partly by Gastrin
- Inhibited by neurotensin

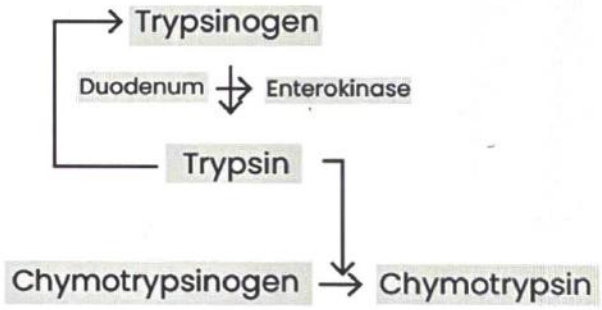
Q. How does Tomato soup with bread crumbs act as appetizer?

Ans: The soup will flow along lesser curvature (liquid). The bread crumbs will mop up the acid & disintegrate (Solid should not fill & should not remain in stomach).This will initiate hunger.

PANCREATIC JUICE

02:28:26

- pH → 8.0, isotonic
- HCO_3 rich (for chyme) in response to secretin
- Enzyme rich (for nutrients) in response to CCk
- Highest protein content by weight (organ - pancreas)



- Trypsin, Chymotryspin are called as ENDOPEPTIDASES (breaks internal bonds)
- Carboxypeptidase, Aminopeptides A & B, Amylase, nuclease
- DISACCHARIDASES → Di & Tripeptidases, trehalase

Phases of pancreatic juice secretion
1. Cephalic → 10%
2. Gastric → 10-20%
3. Intestinal → 70%

Lowest pH- gastric juice
Highest pH- Pancreatic juice

BILE

02:46:50

bile secretion is increased by secretin

- Secreted by LIVER
- Gall Bladder
- Stores & Concentrates Bile
- Acidifies bile
- Adds mucus to bile

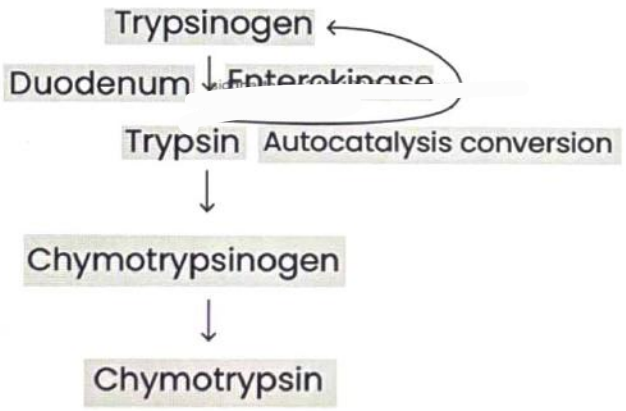
DIGESTION & ABSORPTION

03:04:48

Polyaccharides	Poly peptide
↓ Salivary amylase	↓Pepsin
Oligosaccharides	Oligopeptide
↓ Pancreatic amylase	↓Trypsin/Chymotrypsin
Disaccharides	Dipeptide
↓ Succus enterricus	↓Succus Enterricus
Monasaccharides	Amino acids

FUNCTIONS OF BILE SALTS

1. Digestion of lipids emulsification
2. Absorption of lipids
3. Micelle formation for fat absorption
   a. Ferrying function (20-40 bile salts)
   b. Absorption of nutrients- stomach
   c. Absorption of Alcohol- 20% stomach, 80% jejunum



Duodenum – Absorption of Divalent cations Fe^{2+}, Ca^{2+} (Except Mg^{2+}-in Illeum)

JEJUNUM

All major nutrients

- Max. H_2O absorption (6.6L/day) (1.5L/day from colon) (Total H_2O absorption in GIT is 8.8 L /day)
- Long chain fatty acids absorbed into lymphatic circulation
- Appears milky called LACTEALS
- Lymphatics in form, of chylornicrons

ILEUM

- Mg^{2+} Vit B_{12}, Bile salts absorbed from Ileum
- Enterohepatic cycling occurs 7-8 times a day (a bile)
- Maternal antibiotics are absorbed from Ileum

GUT OR COLON MICROFLORA

Synthesize & absorb

- Vit B_{12}, Folic acid, Vit K & short chain Fatty acids

Decreased absorption of enteric bile at distal ileum (as in short bowel syndrome, Crohn disease) prevents normal fat absorption Calcium, which normally birds oxalate, binds fat instead, so free oxalate is absorbed by gut increasing the Frequency of calcium oxalate kidney stones

Plasma cell dyscrasias- Characterized by monoclonal immunogloubin (Ig) overproduction due to plasma cell disorder

- Multiple myelorna Overproduction of IgG (55% of cases)>Ig
- Woldenstrom macroglobulinema- Overproduction IgM
- Monoclonal gammopathy of undetermined significance- Overproduction of any Ig type

Albumin is decreased in advanced liver disease (marker a liver's biosynthetic function)

CLINICAL QUESTIONS

Q. Bile acids entering into enterohepatic circulating are primary acids synthesized from cholesterol in hepatocytes. They are secreted actively across the canalicular membrane and carried in bile to the gallbladder, where they are concentrated during digestion. Which of the following statements is not true about enterohepatic circulation?

A. Na+ Bile salt cotransporter is involved.
B. 95% bile salts are reabsorbed
C. All the components of bile are reabsorbed.
D. Occurs 6-8 times daily

Answer: C

Solution:

- Bile consists of the bile acids, bile pigments, and other substances dissolved in an alkaline electrolyte solution which is similar to pancreatic juice.
- Per day, about 500 ml is secreted.
- Some of the components of the bile especially bile salts are reabsorbed in the intestine and then excreted again by the liver **(enterohepatic circulation)**.
- 90 to 95% of the bile acids are absorbed from the small intestine.
- Once they are deconjugated, they can be absorbed by nonionic diffusion, but most are absorbed in their conjugated forms from the terminal ileum by an extremely efficient **Na^+–bile salt cotransport system** (ABST) whose activity is secondarily driven by the low intracellular sodium concentration established by the basolateral Na+, K+ ATPase.
- The total bile acid pool of approximately 3.5 g recycles repeatedly via the enterohepatic circulation; it has been calculated that the entire pool recycles twice per meal and 6–8 times per day.

Reference: Ganong's Review of Medical Physiology 26th Edition, Page No. 454

LEARNING OBJECTIVES

UNIT 5 CARDIOVASCULAR SYSTEM

CONDUCTING SYSTEM OF THE HEART

- Properties of Cardiac Tissue
- Conducting System of Heart
- Parts of the Conducting System
- Bundle of Kent
- Hisbundle Electrogram
- Indication of Hisbundle Electrogram
- Timing for Impulses to reach at Different Points
- Depolarization
- Repolarization
- Diagrammatic Representation of Depolarization and Repolarization spreading in opposite direction
- ction Potential in the Heart
- Types of Action Potential
- Pathophysiologic Basis of Arrhythmias
- Rate of Depolarization
- Conduction Speed of Various Parts

ECG

- Leads
- 3 Bipolar Leads
- 3 Unipolar Leads
- 6 Uniipolar Leads
- Waves and Intervals
- Heart Rate Measurement
- Heart Block
- Hexaxial Reference
- Compromised Ventricular Performance

CARDIAC CYCLE PART 1

- Introduction & Duration
- Atrial Events
- Ventricular Systole
- Ventricular Diastole
- Arterial Pulse
- Atrial Pressure Changes
- JVP
- Pressure Wave Forms Of Atria

CARDIAC CYCLE PART 2

- Left Ventricular PV loop
- Frank Starling Curve
- Lusitropy
- Preload vs Myocardial Contractility
- Afterload vs Myocardial Contractility
- Valvular Heart Diseases

CARDIAC OUTPUT

- Factors determining Cardiac Output, Stroke Volume
- Effect of Heart Rate on Cardiac Output
- Bainbridge Reflex
- Effect of Catecholamines
- Methods of measurement of Cardiac Output
- Conditions where the method is unreliable
- Thermodilution Method

CIRCULATION PART 1

- Circulatory Physiology
- Functional Types of Blood Vessels
- Blood flow to Various Organs
- Types of Blood Flow
- Aspects of Viscosity
- Blood Pressure
- Introduction of Blood Pressure
- Determinants of Arterial Blood Pressure
- Types of Blood Pressure
- Measurement of Blood Pressure
- Blood Flow
- Coronary Circulation

CIRCULATION PART 2

- Chemical Regulation of Blood Pressure
- Vasodilators
- Neural Regulation of Blood Pressure
- Chemoreceptor Mechanism
- Cushing Reaction
- Intermediate term reactions for Regulation of BP - ADH & Thirst mechanism
- Long Term Mechanisms
- RAAS
- Kidney- Body Fluids Mechanism
- Cardiovascular changes during Exercise
- Isotonic Exercises
- Isometric Exercises
- Cardiovascular Reflexes
- Starling's Equilibrium
- Lymph and its Functions

16 CONDUCTING SYSTEM OF HEART

00:00:13

Properties of cardiac tissue: 00:02:04

- Excitability
- Contractility
- Autorhythmicity
- Long refractory period
- They have gap junctions (through which there is free rapid passage of ions leading to fast impulse transfer), due to which heart muscle works like SYNSITIUM

SYNSITIUM

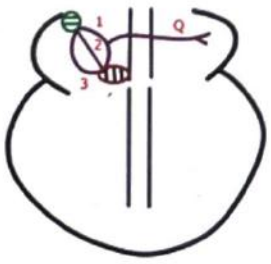
- all fibers contract as a single bundle
- Heart is made up of 2 synitia:
  - Both Atria- contracts together
  - Both Ventricles- contracts together
- Contains intercalated discs: 00:11:57
  - They provide electro mechanical tethering to fibers

Previous Year's Questions

Q heart is made upof how many synsitium?
A. One
B. Two
C. Three
D. Four

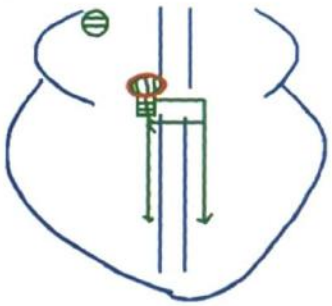
ANATOMICAL PARTS 00:12:14

- SA Node
- AV Node
- 3 Inter Nodal Tracts
- Right and left bundle of his
- Purkenjie fibers



Previous Year's Questions

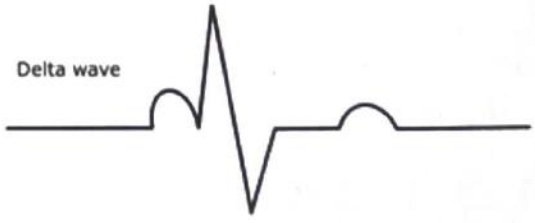
Q Choose the correct statement 00:13:29
A. Rt atrium excites ahead of it Atrium
B. It atrium excites ahead of Rt atrium
C. both atria excites at same time
D. depends on size of the atrium



- SA node sent impulses to AV node through 3 Inter Nodal tracts
  - Anterior - Bachman's bundle
  - Middle - Wenckebach's bundle
  - Posterior - Thorel's bundle
  - Br of Anterior bundle - innervates Lt. Atrium

BUNDLE OF KENT 00:17:31

- Aberrent anomalous path that connects atria directly to ventricle bypassing AV Node
- No AV Nodal delay
- Shortened PR Interval
- Appears as delta wave on ECG
- Seen in wolff parkinson white syndrome



Previous Year's Questions

Q. Which statement is correct? 00:20:44
A. Rt ventricular excitation starts first
B. Lt ventricular excitation starts first
C. Both at the same time
D. depends on orientation

- Explanation: the spread of impulse from left bundle to right bundle through interventicular septum produced Q wave.

Previous Year's Questions

Q. Suspected case of RBBB. which interval is prolonged
A. PA interval
B. AH interval
C. HV interval
D. None of the above

BUNDLE OF HIS
HIS BUNDLE ELECTROGRAM(HBE) 00:25:54

- A Wave - SA Nodal Depolarisation
- H Wave - His Bundle depolarisation
- V Wave - Ventricular depolarization

INDICATIONS 00:30:15

- Heart Block → to Chect wheather the block is above (AVNODE) or below (Bundle branches) the His Bundle
- To differentiate b/w ventricular & supra ventricular tachycarias
- AH INTERVAL- (time taken for impulse to travel from SA Node to His bundle) 55 - 130ms
- HV INTERVAL – (time taken for impulse to travel from His bundle to ventricles) 35 - 55ms
- If AH Interval is prolonged - Block is above (AV block)
  - HV Interval is prolonged - Block is below (bundle branch block)
- Impulse enters left branch first and through IVS goes to Rt. Branch
  - Responsible for Q wave deflection
- Both branches goes to apex; and impulse reaches apex
- Purkinje fibers are present at apex

Previous Year's Questions

Q. Which statement is correct? 00:36:28
A. Rt ventricle excitation ends earlier
B. Lt ventricle excitation ends earlier
C. Both at the same time
D. Sometime Rt & sometimes Left

Previous Year's Questions

Q. Which ventricular ejection starts first 00:40:25
A. Rt ventricular ejection
B. Left ventricular ejection
C. Both ejection
D. condition of vessel wall

- pulmonary valve opens earlier due to down stream pressures
- Aortic valve opens later
- Aortic valve close First
- Pulmonary valve closes later

} S_2 produced due to closure - $A_2 P_2$

Previous Year's Questions

Q. What is the last part of heart to get depolarized? 00:47:01
A. Epicardium of the base of the left ventricle
B. Endocardium of the base of the left ventricle
C. Apical epicardium
D. Apical endocardium

DEPOLARIZATION: 00:48:54

Last part to depolarised

- Epicardium of Base of Left ventricle
- Pulmonary conus
- Upper most of Inter ventricular Septum

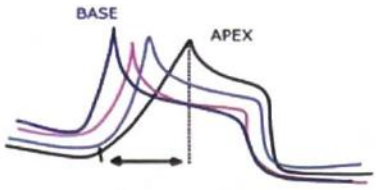
FUNCTIONAL ASPECTS

- Rates of depolarisation
  - Fastest depolarising cell is at base
- Fibre at apex depolarises first, last to complete the depolarisation
- Fibre at base repolarises first

REPOLARISATION:

00:53:54

- Last to repolarise - Apex endocardium
- Repolarisation starts from base to apex and epicardium to endocardium

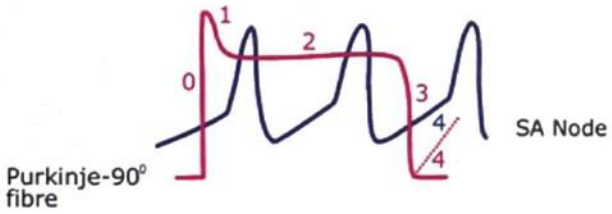


ACTION POTENTAL IN HEART:

Previous Year's Questions

Q. SA node is pace maker d/t ? 00:55:25
A. Slow depolarization & slow repolarisation
B. Rapid depolarisation & rapid repolarisation
C. Slow repolarisation & rapid repolarisation
D. Rapid repolarisation & slow repolarisation 01:02:06

SLOW RESPONSE TYPE	FAST RESPONCE TYPE
SA Node	Purkinje Fiber
AV Node	Ventricular Fiber
Rmp -55 to -65 mv	RMP -90 mv



- Amplitude of Purkinje fiber is more than SA Node
- Natural excitability of Purkinje fiber is half that of SA Node
- Slop of phase 4
- Flat in purkinje Fibre
  - At the end of repolarisation, it can't depolarise by itself
- Steep in SA node
  - determines automaticity
- Under certain circumstances ↑in Slope of Phase 4 in purkinje result in enhanced / abnormal automaticity
- fast response fibre get converted to slow response fibre & result in Arrythmias

CONDITION LEADING TO ENHANCE ABNORMAL AUTOMATICITY

Eg:- ISCHEMIA

01:29:50

ISCHEMIA
↓
$Na^+ K^+$ pump fails
↓
K^+ starts accumulating in ECF
↓
Electric gradient created
↓
I/C K+ accumulate at inner aspect of membrane
↓
Membrane begins to depolarise

ARRYTHMIAS - PATHOPHYSIOLOGICAL BASIS

01:35:20

- Enhanced abnormal automaticity
- Triggered activity (After depolarisation (early / delayed)
- Re entry & circus movements

Rate of depolarization: 01:39:24

- Determines conduction speed of 1 impulse

Previous Year's Questions

Q. Fastest conducting part in the heart is?
A. SA node
B. AV node
C. Bundle of His
D. Pukinje fibre

Previous Year's Questions

Q. Slowest conducting part in the heart is? 01:41:25

A. SA node
B. AV node
C. Bundle of His
D. Pukinje fibre

- AV NODE-Slowest conducting velocity
  - Smallest conducting velocity
  - Least no. of gap junctions

Rate of Repolarisation: 01:45:15

- Determines INTRINSIC RHYTHMICITY of that Part 01:47:10

- Fastest repolarising part → SA Node (Pace maker)
- SA Node & AV node has equal AP but SA Nodes recovers earlier→PACEMAKER
- After cardiac denervation, HR Increases (80-100/min)
- SA Node normally under vagal tone; i.e. why HR is 70-75 / min, IF vagal tone is lost HR increases to 80-100 beats / min
- After cardiac denervation, vagal tone is lost

IONIC BASIS OF AP 01:52:58

Slow response type : 01:54:02

- **Phase 1:** Repolarisation K+ exit
- **Phase 2:** K+ exit stop
  - starts accumulation
  - inside the membrane

- **Phase 3:** Na+ Funny current
  - Hyperpolarisation activated cyclic nucleotide gated (HCN) Channels
  - More the hyperpolarisation, more the activation
  - equally permeable for Na+ & K+

- **Phase 4:** Reaching threshold through Ca2+ T (transient) Channels
- **Phase 5:** Ca2+ L (long lasting) channels - Depolarisation above threshold
- Major current caused by which ion for SA node & Av node -$Ca2^{+}$
- Major current caused by which ion for Purkinje fibres- Na^{+}

PRE POTENTIAL / PACEMAKER POTENTIAL / DIASTOLIC DEPOLARISATION

- The potential that automatically reaches threshold at the end of every repolarisation

Fast response type: 02:00:04

- Rapid upstroke-by Fast Na+ channels (Tetradotoxin sensitive)
- Early repularisation- by K+ exit
- Plateu Phase→by slow Ca2+ channels
- Rapid Repolarization
- Resting membrane potential

Phase 2

- By slow Ca2+ channels
- slow inward movement of Ca2+ (ECF Ca2+)
- Causes electrical & contractile activity (Ca2+ Sparks)

Arryhmias- Pathophysiological Basis

- Enhanced abnormal automaticity
- Triggered activity (After depolarisation (early / delayed)
- Re entry & circus movements

TRIGGERED ACTIVITY: 02:04:53

- Results in AFTER DEPOLARISATIONS
- AD → EAD- in phase 2 or early phase
- AD → DAD- phase 4
- Misnomer
- AP are triggered early
- causes extra systoles 02:06:54
- Factors responsible are

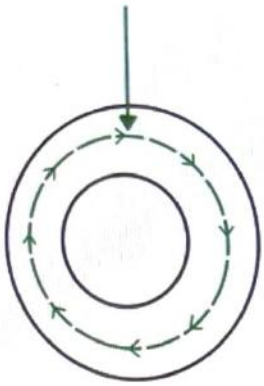
- Drugs which increase intracytoplasmic or sarcoplasmic calcium
  - Eg:- Digitalis (↑ i/c Ca2+)

02:10:02

- There can be extra systole in the atria & ventricle called as atrial pre-mature beat and ventricular pre-mature beat respectively.
- VPB is followed by a compensatory pause while this pause is not seen in APB

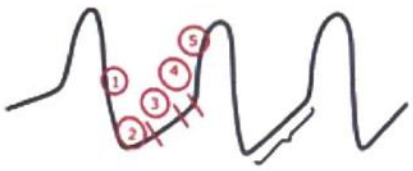
RE ENTRY & CIRCUS MOVEMENT OCCURS 02:11:35

- Path length increased
  - Ex: cardiac dilatation
- Damaged the purkinje system
- Slowed down conduction velocity



ADVANTAGES OF PLATEAU PHASE 02:16:05

- LONG AP duration (Purkinje fibres 200-300 ms)
- Long repolarization
- Long refractory period (heart cannot be excited at very high frequencies and heart muscle can't be tetanized)



CLINICAL QUESTIONS

Q. A 55-year-old man has been diagnosed with Stokes- Adams syndrome. Two minutes after the onset of syncopal attack, among the following, which becomes the pacemaker of the heart?

A. Sinus node
B. A-V node
C. Purkinje fibers
D. Cardiac septum

Answer: C

Solution:

- During a **Stokes-Adams syndrome** attack, the **total A-V block suddenly begins.**
- After a few seconds, some part of the **Purkinje system** beyond the block, usually in the distal part of the A-V node beyond the blocked point in the node, or in the A-V bundle, **begins discharging rhythmically at a rate of 15 to 40 times per minute** and acting as the pacemaker of the ventricles.
- This phenomenon is called **ventricular escape**.

NOTE: When **A-V block** occurs—that is, when the cardiac impulse fails to pass from the atria into the ventricles through the A-V nodal and bundle system—the **atria continue to beat at the *normal* rate** of the rhythm of the sinus node, while a new pacemaker usually develops in the Purkinje system of the ventricles and drives the ventricular muscle at a new rate somewhere between **15 and 40 beats per minute**. After a sudden A-V bundle block, the Purkinje system does **not** begin to emit its intrinsic rhythmical impulses until 5 to 20 seconds later because, before the blockage, the Purkinje fibers had been "**overdriven**" by the rapid sinus impulses and, consequently, are in a suppressed state. During these 5 to 20 seconds, the ventricles fail to pump blood, and the person faints after the first 4 to 5 seconds because of a lack of blood flow to the brain. This delayed pickup of the heartbeat is called **Stokes-Adams syndrome.** It may lead to death, if the delay period is too long.

Reference:

- Guyton and Hall Textbook of Medical Physiology 13th Edition, Page No. 157
- Berne & Levy Physiology, 6th edition, SECTION 4 - The Cardiovascular System, CHAPTER 16 Elements of Cardiac Function. Pg. 317-318.

17 ECG

00:00:15

RECORDING OF EGC

00:01:40

- Graphic record of electric activity of heart from body surface
- Summated activity
- EINTHOVEN recorded 1st ECG (1905)
- electric activity carried to the surface through body Fluids
- The condition that can be diagnosed with ECG are
  1. CAD
  2. Arrhythemias
  3. Chambered abnormalities
  4. Electrolyte disturbances
- CARDI JELLY-decreases the resistance offered by the skin
  - Normal saline also can be used

LEADS

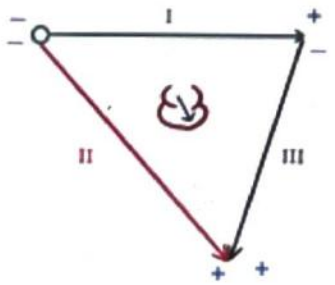
00:06:25

- An electrode | pair of electrodes placed on a specific body position
- EINTHOVEN'S ECG
  - created 3 Bipolar leads by placing 2 electrodes at 2 different points
- Bipolar leads measures potential difference b/w 2 points

- 1st bipolar leads:

00:08:18

  - Lead I- Right arm negative and left arm positive
  - Lead III- left arm negative and left leg positive
  - Lead II- right arm negative and left leg positive
- These 3 leads create EINTHOVEN triangle
- KIRCHHOFF'S LAW: the sum of all the potential in a closed loop is zero
  - I + II + III = 0
- Wave of depolarisation towards positive electrode gives upward deflection
- Wave of depolarisation towards negative electrode gives down ward deflection



- He reversed polarity of Lead II, to get upward deflections
- Kirchhoff's Law
  - I+III + (-II) = 0
  - II = I + III → Einthoven Equation

EINTHOVEN EQUATION

- IF potential of 2 leads are known, 3rd lead potential can be calculated
- Lead II will have high potential because of max amplitude - Long Lead II recorded to identify the changes

UNIPOLAR LIMB LEADS

00:22:10

- Positive electrode placed on Rt. arm [VR], Left arm [VL] & Foot {VF] K/a Exploring electrode
- Negative electrode [k/a Indifferent electrode] created by connecting 3 point & passing it through wilson's terminal (5000Ω)
  - negative electrode reward nothing
  - RA - (RA+LA+LL)
  - Amplitude recorded are less

Auggmented Unipolar Limb Leads

- Positive electrode on one arm
- Negative electrode created by joining the other two- Amplitude of waves ↑ 50%
- aVR, aVL, Avf
- 3 Bipolar
- 3 Augmented Unipolar } 6 Limb Leads
- Limb Leads: Record cardiac activity in 2 dimensions [from above download]
- Chest Leads: Record cardiac activity in antero - posterior direction

CHEAST LEADS/ PRE CORDIAL LEADS

00:30:30

- electrode placed on anterior wall of heart
- V1 to V6
- all are unipolar
- aka Anterior leads
  - V_1 - Right sternal border

- V_2 - Left sternal border
- V_3 - b/w V2 & V4
- V_4 - 5th intercostal space, mid sternal line
- V_5 - anterior axillary line
- V_6 - mid axillary line

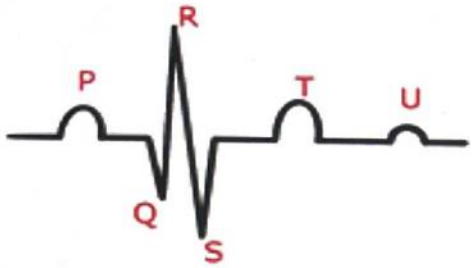
- Cheast leads - Anterior Leads
  - II & III, avF - Inferior Leads
  - V_2 & V_4 - Septal Leads

Important Information

- In posterior wall Infarct, reciprocal changes seen in anterior leads Long lead II recorded separately, to diagnose anomalies, since it has the highest potential

NORMAL ECG

00:39:05



- P - Atrial depolarization
- QRS - Ventricular depolarisation
- T - Ventricular repolarisation

  U - Repolarization of papillary muscles, not always seen

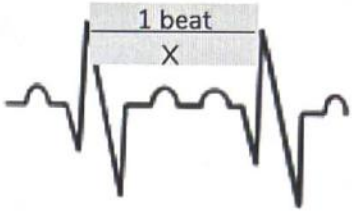
ST SEGMENT

ISO Electric Segment	• all the ventricular fibres have completed depolarization • all the fibres are equipotential at this time
J-Point	• End of 5 wave : ISO electric point / reference point
Peak of T Wave	• Vulnerable point of the heart • all Fibres are in different stages of thier electrical activity [some are repolarized, some depolarized] • at this stage, if an extra systole is initiated, it leads to ventricular fibrillation

HEART RATE

00:52:16

- The distance b/w Two successive 'R waves → 1 Beat
- Speed of paper - 25 mm / sec
- In 1 min - 1500 mm
- 1 heart beat - x



- in 1500 mm, no. of heart beats = $\frac{1500}{x}$
- Serves are proof (authentic way of calculation HR)

WAVES OF ECG

P Wave / Atrial Depolarization

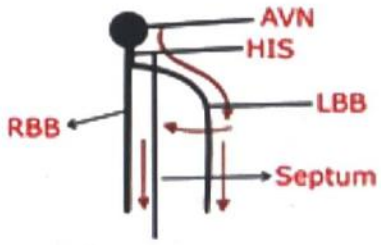
- P = 0.1sec
- P wave is the summated potential of both the atria depolarization
- BIFID/ M Shaped P Wave
  - Seen in mitral stenosis
  - d/t hypertrophy of left atrium
  - This increase in mass - increase depolarization time of LA - Bifid P Wave
- Saw Toothed P Wave: Seen in Atrial Flutter

Atrial Repolarization

- Not seen normally
- Marged with QRS complex
- Can make it visible by changing the speed of paper
  - (N) speed 25 mm/Sec

QRS Complex / Ventricular Depolarization

- represented by QRS complex
- Normal → 0.08 - 0.01 Sec
- SAN → AVN → BUNDLE OF HIS —(continues down as)→ RBB
- LBB —(gives it branch)→



- Implus enters LBB 1st, via interventricular septum, enters RBB This produces download deflection of Q wave
- R & S wave: Ventricular depolarizated

Ventricular Repolarization: represented by T wave

QT Interval

- Normal: 0.41 - 0.43 Sec
- includes Ventricular Depolarization + Ventricular Repolarization aka Electro Mechanical Systole

PR Interval

- Signifies AV nodal delay
- From the start of P wave to start of R wave
- (N) →0.12 to 0.16 Sec (max accepted→ 0.2 Sec)
  - 0.24 Sec → AV Block

HEART BLOCK

01:03:40

- 1°: pr Interval prolongation [0.24 sec]
  - All P waves are followed by QRS complex
- 2°: Not All P wave are followed by QRS complex [aka Imcomplete Heart Block]
- Mobitz Type 1
  - PR interval goes on increasing in successive
  - In 1 beat P wave not followed by QRS complex
- Mobitz Type 2
  - Atria to ventricular Ratio: 8:7 (inconsistent) → 8th beat not reaching the ventricle
  - PR Interval is Fixed
  - but, Infrequently, one QRS complex is dropped
- Mobitz Type 3
  - Consistent (3:2, 4:3)
  - Every 3rd beat will not reach ventricle
  - P wave not followed by QRS Complex
- 3°: No P wave is followed by QRS complex
  - Complete heart block

HEXAXIAL REFERENCE SYSTEM

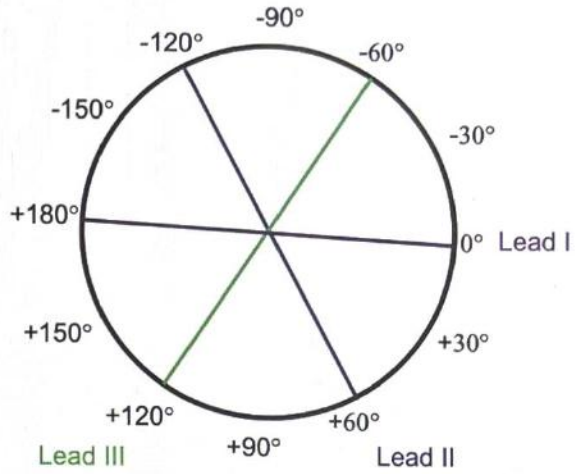
01:10:37

- Used to determine

1. CARDIAC AXIS represent the 3D Orientation of Heart
2. CHANGES like hypertrophy, bundle branch block etc.

- The Means QRS vector is piotted on a 360° Plot, where
- Lead I, II, III are poltted according to thier vectors
- Amplitude of R waves recorded in any 2 leads &
- plotted arbitarily on the graph

Perpendicular lines from the point of amplitude are drawn so that the perpendicular lines from the 2 leads intersect the line connecting the centre of hexaxial reference system, to the point of intersection of perpendiculars, is the means QRS vactor



Normal QRS vector	+ 59 degrees
Normal Range	- 30 to +110 degrees
Right axis deviation	Clockwise deviation of means QRS
Left axis deviation	Anti - clockwise deviation of means QRS Vector

COMPROMISED VENTRICULAR PERFORMANCE

01:22:10

1. ECG record
2. Carotid pulse record
3. Phonocardiograph (heart sound)

- To calculate PEP (Pre-Ejection Period) : LVET (Left Ventricular Ejection Time)
  - QS_2: start of ventricular depolarisation (Q Wave) & entire ventricular systole to the start of ventricular diastole (S_2)
- QS_2 - LVET = PEP
- Normal PEP: LVET ratio = <0.35
- >0.35 = ↓LVET (left ventricular performance is reduced)

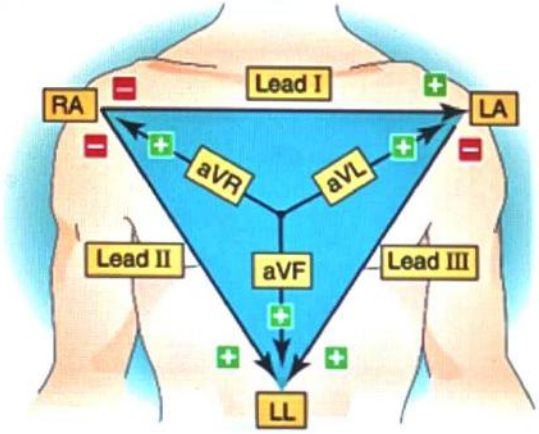
CLINICAL QUESTIONS

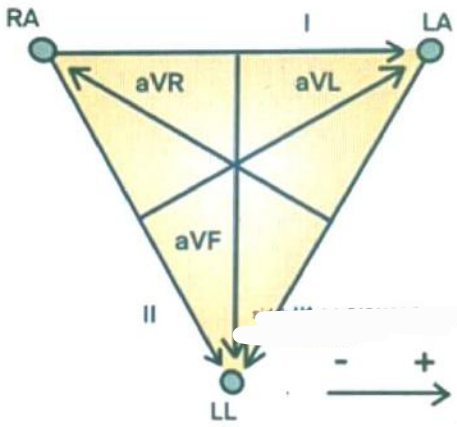
Q. The cardiac axis refers to the mean direction of the wave of ventricular depolarisation in the vertical plane, measured from a zero reference point. The zero reference point looks at the heart from the same viewpoint as lead I. When recording lead I on an ECG, the right arm is the negative electrode and the positive electrode is which one of the following?

A. Left arm
B. Left leg
C. Right leg
D. Right arm + left leg

Answer: A

Solution:
By convention, the left arm (option-1) is the positive electrode for the lead I of an ECG.





Reference:

- Guyton and Hall Textbook of Medical Physiology 13th Edition, Page No. 134.
- Medical Physiology, A Cellular and Molecular Approach, UPDATED SECOND EDITION. Walter F. Boron, Emile L. Boulpaep. Section IV - The Cardiovascular System, Chapter 21 - Cardiac Electrophysiology and the Electrocardiogram. Pg. 517.

18 CARDIAC CYCLE

Previous Year's Questions

Q. 2nd heart sound occur in which phase? 00:00:13

Proto diastole
isovolumic relaxation
Diastasis
1st rapid filling

CARDIAC CYCLE

00:03:07

The changes that sweep over the heart in 1 single beat and repeated in the subsequent beat

- Duration- 0.8 sec (72 beats per 60 sec)

Systole-Contraction	↑Pressure
	Ejection of blood
Diastole- Relaxation	↑Pressure
	Blood received

- At higher heart rates both systole & diastole decreases (cardiac cycle↓), but diastole decreases more than systole.

EVENTS OF CARDIAC CYCLE

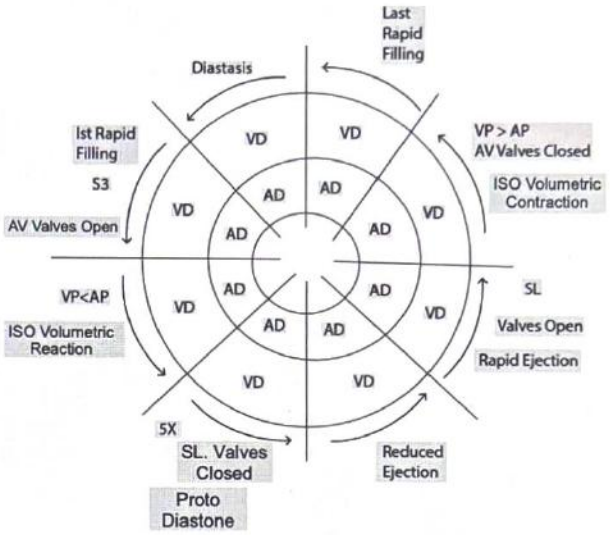
- Atrial Events (0.8 sec)
  - o Systole (0.1 sec)
  - o Diastole (0.7sec)
- ventricular events (0.8sec)
  - o Systole (0.3sec)
  - o Diastole (0.5sec)

ATRIAL EVENTS

00:08:29

1. Atrial Systole

- Myotonic contraction
  - o Strength of contraction goes on decrease
  - o Eg:- Atrial systole
    - → First-0.05sec- Dynamic
    - → Late-0.05sec-Adynamic



2. Atrial diastole: 0.7 sec

VENTRICULAR EVENTS

00:17:10

- Ventricular systole-0.3sec
  - o Ventricular systole starts after atrial systole d/t AV nodal delay
  - o AV valves close -ventricular pressure> Atrial pressure
  - o S_1 produced (S_1-1st heart sound)
  - o Isovolumic contraction
    - → All valves are closed
    - → Aortic pressure > Lt ventricular pressure
    - → In Aortic regurgitation, blood enters LV during isovolumic contraction
- Ventricular pressure increases than Aortic pressure
- Semilunar valves open
- Ejection starts
  - a. Rapid ejection
  - b. Reduced ejection

AUXOTONIC CONTRACTION:

- strength of contraction
- Eg:- Ventricular systole ejection

Ventricular diastole: (0.5sec) 00:34:29

- 75-80% of ventricular filling is passive
- Last 20-25% of filling is active due to atrial contraction

a. Proto diastole

- Sudden change in the direction of blood
- Semilunar valves closes- produces 2nd heart of sound

b. Isovolumic relaxation

- All valves closed (ventricular pressure > atrial pressure)
- In Mitral regurgitation, blood moves from LV to LA, even while ventricles are relaxing
- In regurgitant conditions, there is no true Isovolumic contraction or relaxation

c. Ventricular pressure decreases than atrial pressure

- AV valve opens (VP<AP)
- Filling of ventricle starts
  - 1st rapid filling- causes S_3 (d/t turbulence)
  - Diastasis
  - Last rapid filling

    → Due to atrial systole

    → causes S4 (atrial sound)

    ↓

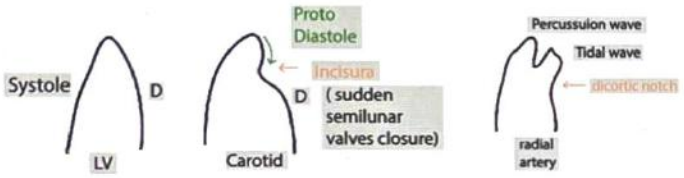
    caused by atrial contraction

PRESSURE VOLUME CHANGES

00:48:45

1. Arterial Pulse Tracing

- It is recorded by DUDGEONS sphygmograph
- Most common artery used-Radial artery



Radial Pulse Tracing

- Percussion wave – true systolic peak
- Tidal wave- d/t oscillation of vessel caused by meeting of the ongoing pulse & reflected pulse wave

ATRIAL PRESSURE CHANGES

00:57:54

Previous Year's Questions

Q. 'V' wave in the LA is larger than 'V' wave of RA?

Because the left side have higher pressure than the right side

Because the mitral valve has got different dynamics compared to tricurpid value

Because left atrium receives blood from the lungs

Because left side of heart pumps the blood to the Aorta

Previous Year's Questions

Q. CVP changes with breathing are?

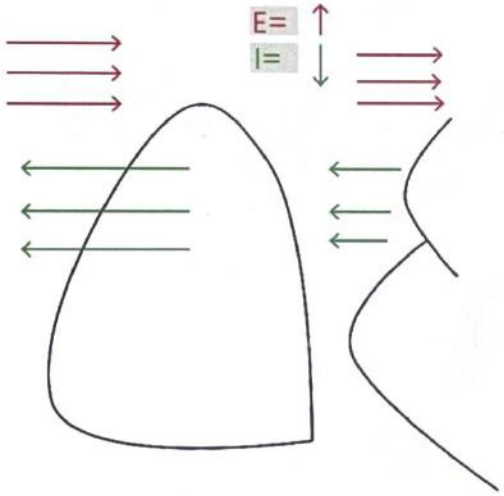
E= +6 I= +2

E= -6 I= -2

E= +6 I= -2

E= -6 I= +2

- Right Atrial pressure decrease with inspiration
- Right Atrial pressure increase with expiration



JVP (JUGULAR VENOUS PRESSURE)

shows right atrial pressure)

01:04:54

- RA pressure are recorded from internal jugular veins
- N= 0-5cm H_2O (±5cm H_2O) →0-2mm of Hg
- Internal jugular vein has no valve so, the pressure of right atria is reflected in internal jugular vein

PCWP (PULMONARY CAPILLARY WEDGE PRESSURE)

- Records the pressure of LA
- Not a natural occurring pressure
- A inflated balloon tip catheter is inserted into a vein & its taken into the right atrium →Right ventricle→ Pulmonary artery→where it wedges→Block's the blood flow temporarily→creating no pressure difference b/w left atrium & the point after the wedge→ there by calculating LA pressure
  - Normal value -5mm of Hg or 5-8cm of H_2O

PRESSURE WAVEFORMS OF ATRIA 01:09:54

A wave

- atrial systole
  - Tricuspid stenosis
  - AV Dissociation
  - Larger 'a' waves
  - cannon 'a' waves seen in

C wave

- isovolumic contraction of rt. ventricle
- (ballooning backward of the tricuspid valve into Right. atrium)

X downslope

- ventricular ejection

V wave

- venous blood accumulates in rt. atrium dlt ISOVOLUMIC RELAXATION of Rt. ventricle.
- V wave is larger in Lt. Atrium
  - receives 2% (of bronchial venous circulation) more blood in left atrium
  - also receives some amount of venous admixture of blood

Ventricular filling

- cardiac tamponade ⟶ Abnormal y Downslope
- constrictive pericarditis ⟶ Abnormal y Downslope
- **$\bar{x}$ wave** → As ventricular systoles, the Apex of heart goes upward and the base goes downward, as the base goes downward it pulls the right atrium leading to $\bar{x}$ wave

Previous Year's Questions

Q. A patient of constrictive pericarditis is brought to you: which wave in JVP will be abnormal?
A wave
V wave
X downslope
Y downslope

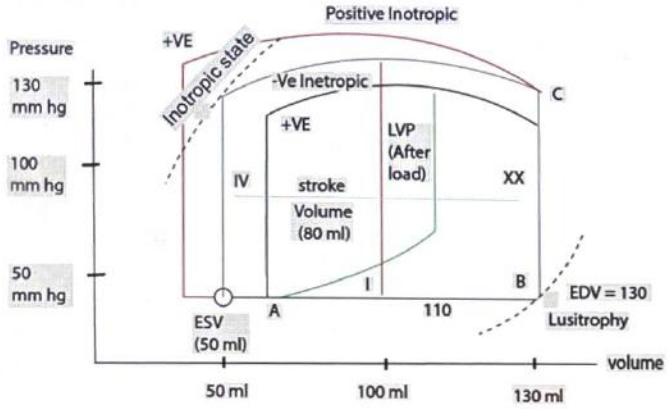
19 CARDIAC CYCLE PART 2

LEFT VENTRICULAR PRESSURE VOLUME LOOPS

00:03:31

Previous Year's Questions

Q. left ventricular PV loop is shifted to left in which of the following conditions?
Mitral stenosis
Mitral regurgitation
Aortic stenosis
Aortic regurgitation



Phase –I	Phase of filing (but no pressure rise)
Phase-II	Isovolumic contraction
Phase-III	Phase of ejection
Phase-IV	Isovolumic relaxation

- EDV- Indicates pre load
- ESV- Myocardial contractility of ventricle

PRELOAD

- Load on muscle before contraction starts
  - EDV (End Diastolic volume)
  - EDV (End Diastolic pressure)

After Load

- Load against which ventricle contracts
  - Aorta pressure for LV
  - Pulmonary artery pressure for RV

Stroke volume: Indicated by width of loop

LV Pressure

- Indicated by height of loop
- Height of loop indicative of afterload

Comparison of RV & LV:

- Preload is same on both ventricles
- Afterload of LV is 5-7 times higher than RV
- Therefore work output by LV is 5-7 times than that by Rt. Ventricle

Left Ventricle loop (LV)

- increase Preload → increase Stroke volume; → by FRANK STARLING LAW
  - More the filling, mre the fiber length, more the stroke volume
- increase Afterload - increase Stroke volume

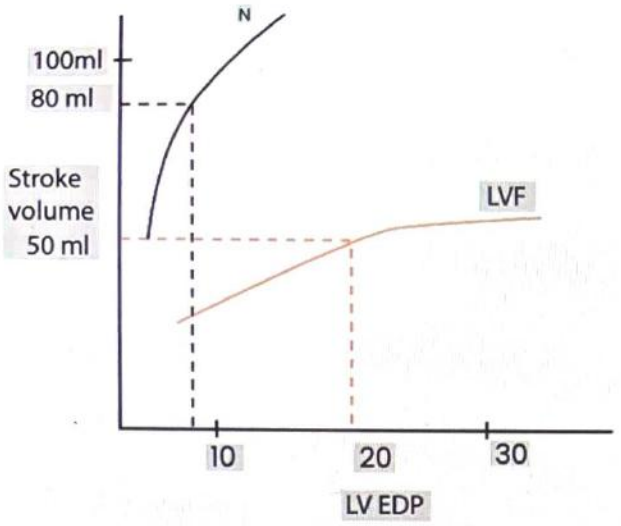
INOTROPIC STATE / CONTRACTILITY STATE

- Positive inotropism / increase myocardial contractility
  - Height of loop & width of loop increase; stroke volume & LV pressure increase
  - DECREASED END SYSTOLIC VOLUME
  - Catecholamines, Digitalis, cardiac glycosides
- Negative Inotropism / LEFT VENTRICULAR FAILURE
  - height & width of Loop decreases; stroke volume & LV pressure decrease
  - INCREASED END SYSTOLIC VOLUME
  - In heart failure

FRANK STARLING CURVE

00:40:02

- 80 ML of stroke volume
  - corresponds to 5-10 mm of LVEDP
- In negative inotropism stroke volume decreased & End systolic volume increases,
  - End systolic pressure also increases



LUSITORY | LUSIOTROPY | RELAXABILITY & DIASTOLIC FUNCTION

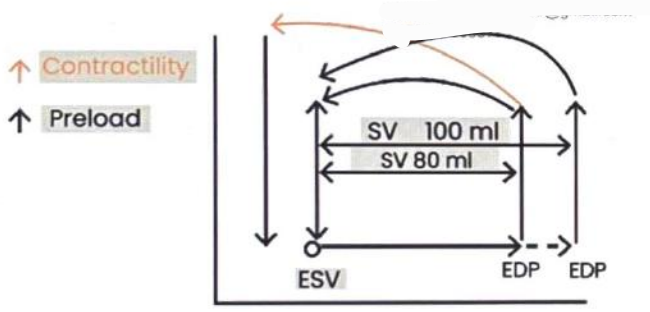
00:45:03

- ALTERED LUSITROPY
- occurs in constrictive pericarditis & cardiac tamponade
- EDV decreases, End diastolic pressure increases
- Catecholamines have positive lusitropic effect

LV PV LOOP

00:52:06

- increase: Preload
- increase Contractility



Increase Preload

- increase Stroke volume
- Increase EDV
- increase height
- Normal End Systolic volume
- characteristic Feature of Frank Starling's law

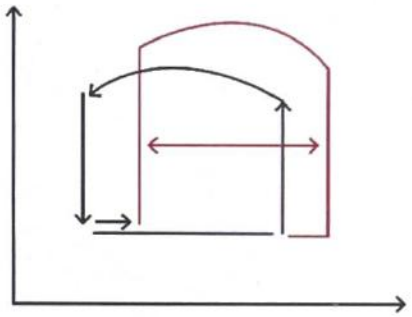
Increase Myocardial Contractility

- increase Stroke volume
- Increase Height
- Normal End Systolic volume
- increase End Systolic volume

Increase Afterload

01:02:58

- Decrease Stroke Volume
- Decrease Width
- increase End Systolic volume
- increase End diastolic volume
- Increase Height



VALVULAR HEART DISEASES

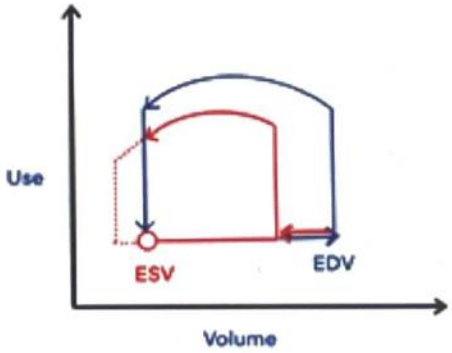
01:06:58

1. Mitral Stenosis

- Decrease EDV (↓Preload)
- Decrease Stroke volume
- Decrease Width slightly
- Decrease Height
- ESV constant (normal)
- Compensatory changes

(over a period of time)
↓
Decrease aortic pressure (↓after load)
↓
Increase stroke volume

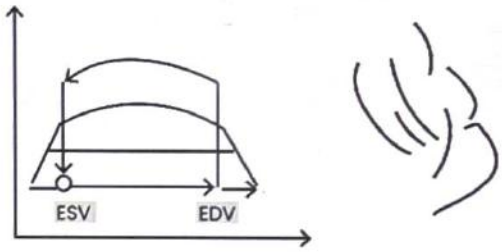
- LV PV LOOP SHIFTED TO LEFT
- Decrease EDV > Decrease ESV



2. Mitral Regurgitation

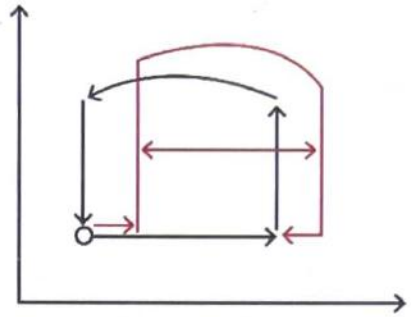
- ESV decreased
- Increase Stroke volume

- EDV increased
- Decrease Height
- SV increased
- Increase Width
- No true isovolumic contraction
- blood goes into LA
- No true isovolumic relaxation
- blood goes into LA
- Height decreases
- Increase Preload
- Decrease Afterload



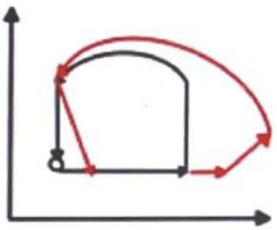
3. Aortic Stenosis

- Increase Afterload
- Increase Height (left ventricular pressure)
- Decrease SV
- Decrease ESV
- Width narrowing



4. Aortic Regurgitations

- Increase EDV
- No true isovolumic contraction
  - blood received into LV
- No true isovolumic relaxation
  - blood received into LV
- Increase Preload
- Increase Height (left ventricular pressure)
  - ↓Afterload



20 CARDIAC OUTPUT

00:00:13

Previous Year's Questions

Q. Dye Dilution technique. Dye leaks out of capillaries rapidly. How will it affect CO & ECF Volume?
A. Both high
B. Both Low
C. No error in CO
D. No error in CO & ECF volume

CARDIAC OUTPUT

00:03:01

- CO = SV x HR
  = (70-90) x 72
  = 5 ltr/min
- Cardiac vol. remains the same ≈ 5 ltr
- Cardiac output can alter (↑↓) according to the needs of the person
- Cardiac index

$$\frac{CO}{BSA} = \frac{5L}{1.7\ m^2} = 2.9\text{-}3.3\ ltr/min/m^2$$

FACTORS DETERMING CARDIAC OUTPUT

00:08:50

- Stroke volume
- Depends on strength of contraction

Intrinsic / Heterometric Regulation

- by changing Length
- SV α EDV
  α EDL
  α Preload

  $\alpha \frac{1}{afterload}$ (aortic / PA pressure)

- More the filling, more the SV
- More the venous return, more the SV
- Determined by Frank Starling Law
  - In normal physiological conditions, greater the blood returning to the heart, greater the blood pumped out from the heart
- Venodilators reduce the preload
- Arterial dilators reduce the afterload

Extrinsic Homeometric Regulation

- No change in length
- Positive inotropic effect

Factors

- Increase Sympathetic Discharge
- Increase Circulating catecholamine's
- Cardiac glycosides Eg. Digitalis

INDICES

1. EJECTION FRACTION

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

- Normal →60-65%
- Decreases in LVF

2. LEFT VENTRICULAR SHORTENING FRACTION

$$LVSF = \frac{LVEDL - LVESL}{LVEDL} \times 100$$

LVEDL- LV End Diastolic Length
LVESL- LV End Systolic Length

- Normal → 40%
- Decreases in LVF

HEART RATE

00:22:18

1. 72 bpm → 130 BPM
- Increase HR → increase SV
- STAIRCASE EFFECT
  - D/t increase sarcoplasmic Ca^{2+} → contractions becomes stronger
  - Reaches peak at 130 bpm

2. 130 bpm -160 bpm
- Increase HR - SV Constant
- Even though diastole duration decreased, diastasis disappears to maintain SV (filling)

3. 160 bpm -180 bpm
- filling suffers
- Decrease SV -increase HR

4. >180 bpm -CO is virtually 'O'
- HR Max = 220 – age (Karvonen formula)

Q. HR_{max} on stress test of 40yr old man (220- age)
A. 160
B. 180
C. 200
D. 220

EFFECTS 00:37:38

- **CHRONOTROPY**- Effect on HR
  - Catecholamines → increase HR
  - Vagus → decrease HR
- **DROMOTROPY** - Effect on impluse conduction speed
- **INOTROPY**-Effect on contraction
  - Sympathetic → increase contraction
  - Vagus → do not increase directly
- **BATHMOTROPY**- Effect on excitability
  - Sympathetic → increase
  - Vagus → decrease
- **LUSIOTROPY**-Effect on relaxability & diastolic function

CATECHOLAMINES 00:41:52

- Increase HR
  - Decrease Systole
  - Decrease Diastole
- Increase SV -During systole
- Increase rate of tension development
  - During diastole
- Decrease duration, yet filling remains unaffected
  - Increase rate of relaxation
- Acts on PHOSPHOLAMBAN (SERCA Related protein)
  - Keeps check on SERCA
  - Phosphorylates, Phospholamban → check of SERCA lifted
- More remove of Ca^{2+} removed from sarcoplasm
- Has effect on cross-bridge cycling →peak tension development → increase SV

PHYSIOLOGICAL INFLUENCE: 00:50:58

1. Respiration:
   - Forcefull inspiration increase venous return to heart result in increased venous return increase SV
2. Muscle as a pump:
   - Increase venous return increase SV
3. Exercise, anxiety
4. Sleep:
   - Basal metabolic rate decrease result decrease CO
5. Posture:
   - Venous return decrease to heart decrease SV
6. Pregnancy

Pathological influence:

Increase CO	Decrease CO
Anemia	hypothyroidism
hyperthyroidism	Congestive cardiac failure

METHOD OF MEASUREMENT 00:55:42

1. DIRECT FICK METHOD 00:56:05

Named after Adolf fick & the fick's principle

- based on law of conversation of mass

$$CO = \frac{\text{O2 consumption (ml/min)}}{\text{A-V O2 difference}}$$

O_2 consumption by entire body

- Arterial sample can be collected from any artery
- Venous sample can't be taken from peripheral veins
- Different for different parts of the body
- Should be collected from PULMONARY ARTERY
  - Mixed venous blood
  - Representative of entire body

2. STEWART - HAMILTON DYE DILUTION TECHNIQUE / INDICATOR DILUTION METHOD 01:03:45

$$V = \frac{I}{C}$$

I= Initial volume of dye
C= Concentration of dye

- A known initial volume of dye (I) is injected into vein

↓

Heart

Decrease SV dilutes the dye

Artery

- Mean concentration calculated by serial measurements from continuous samples
- More the stroke volume, more the dissipation of dye

$$F = \frac{I}{Cxt} \times 60$$

I= Initial volume of dye
C= Mean concentration of dye
t= Time in seconds at which the dye appeared for the 1st time in artery
- For conversion to minute

After injecting leaves via systemic capillaries rapidly

- No change on CO measurement.
- We collect the sample from artery before it reaches capillaries
- No change in ECF volume measurement
- When it leaks out of systemic capillaries , it reaches interstitial fluid

Q. What if the dye leaks out of even pulmonary capillaries?

Ans. Lesser dye will reach collection point

↓

Concentration will be erroneously ↓ed

CO will also be erroneously ↓ed

Q. What if dye is sticky and attaches to the vessel wall?

Ans. Concentration will be erroneously ↓ed

CO will also be erroneously ↓ed

- UNRELIABLE in

1. VSD (Ventricular Septal Defect) (Dye will go from LV → RV)
2. Regurgitation conditions

21 CIRCULATION

00:00:13

Previous Year's Questions

Q. The greatest resistance to the blood flow in the systemic circulation occurs in which segement of the circulation?
A. Artery
B. Arterioles
C. Capillaries
D. Venules

Previous Year's Questions

Q. Critical closing pressure is?
A. 0mm Hg
B. 20 mm Hg
C. 40 mm Hg
D. 60mm Hg

FUNCTIONAL TYPE OF BLOOD VESSEL

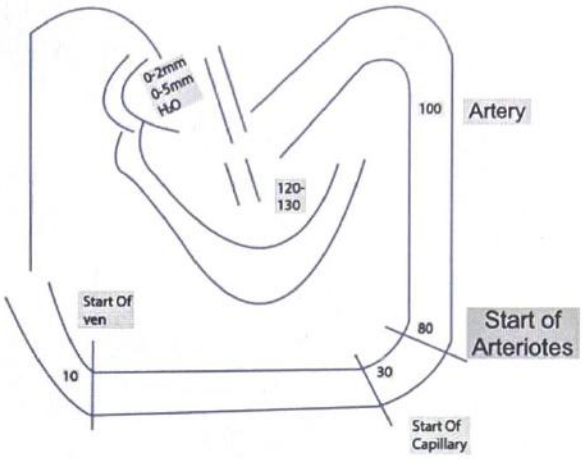
00:00:51

1. Windkessel vessels:

- Aorta, large arteries
- Shows WINDKESSEL EFFECT
- aorta distends & accumulates the blood during ventricular systole without rising pressure much
- during left ventricle diastole, aorta coils back & pushes the blood forward
  - (potential energy → kinetic energy)

2. Resistance vessels:

- Arterioles
- Offer greater resistance to blood flow
- Has maximum effect on blood pressure (pressure head drops maximally)
- Greatest drop of pressure occurs at
  - Arteriolar Segment (Resistance vessel) Average capillary pressure
  - 15-20 mm of Hg
  - Pressure of circulation in dead person 6-7 mm of Hg d/t TISSUE PRESSURE



Critical closing pressure

- Atrial pressure of 20mm of Hg
- Pressure below which blood flow stops & vessels close down

Previous Year's Questions

Q. In the recumbent posture, max pressure difference is at
A. Saphenous vein to Rt side of heart
B. Femoral artery to femoral vein
C. Rt side of heart to cerebral vessels
D. Rt. Side of the heart to the pulmonary vein

3. Capacitance vessels

- Veins
- more than half the volume of blood (54%l is presents in venous compartment

Blood volume:

- Arteries & Arterioles : 10-15%
- Capillaries : 5-8%
- Lungs : 15-18%

4. Exchange vessels

- Capillaries

5. Thoroughfare vessels

- A-V anastomosis / shunt vessels

BLOOD FLOW

00:22:10

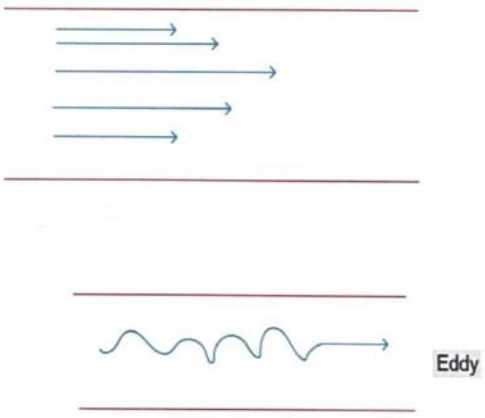
- Velocity:- highest in Aorta= 33cm/s; Capillaires = 0.33mm/sec
  - Largest fraction of blood flow goes to → LIVER
  - Liver: 25-27% →BSP (Bromsulphthalein)
  - Kidney: 25% →PAH
  - Blood flow per 100g | min
    - → Carotid body (Tissue) = 2000ml| 100gm | min
    - → Kidney (Organ) = 400 ml | 100 gm | min

Types of blood flow

00:28:52

- Laminar / Streamline Blood Flow
  - Follows Parabolic path
  - Silent (stetho)

- Turbulent blood flow
  - Eddy currents produced
  - Sounds heard



- Reynolds number:
  - Determine the type of blood flow/ tendency of turbulence
  - Re < 2000 → Laminar
  - >3000 → Turbulent
  - 2000-3000 → transition

- Depends on
  - Re $\alpha \frac{VDP}{\mu}$

    → V = Velocity
    → D = Diameter
    → P = Density
    → μ = Viscosity

Fourth power law

- Flow $\alpha (r)^4$. α = radius

Viscosity

00:34:20

- Unit -Poise (absolute viscosity)
- Relative viscosity of water, plasma, whole blood - 1:3:5

BLOOD PRESSURE

00:37:50

- Lateral pressure exerted by the moving column of blood on the vessel walls

Pressure in circulation – 3 Dimensions:

- P1- P2
  - blood flows from high pressure to low pressure

- Hydrostatic Factor
  - Beneath the surface of water, pressure increase
  - at Tricuspid valve level - 'O' pressure level | Reference
  - below this level - positive pressure
  - above this level - negative pressure
- Transmural pressure
- pressure across the vessel wall

DETERMINANTS OF ARTERIAL BLOOD PRESSURE

00:44:02

Previous Year's Questions

Q. BP→90 MM Hg, Co→5.4 ltr / mn, Peripheral Resistance?
A. 1R
B. 2R
C. 4R
D. 6R

OHM's law

- $Q = \frac{\Delta P}{R}$ $CO = \frac{BP}{PR}$ BP = CO x TPR
- Q CO = 5.4 L/min, BP = 90 mm of Hg, PR?
- $PR = \frac{BP}{CO}$
- PR units → PRUS / R
- $1R = \frac{1\ mm\ of\ Hg}{1\ ml/sec}$
- 5.4ur / min = 90ml / sec, $\frac{90}{90}$ =1R

TYPES OF BP

00:52:04

1. Systolic BP

- highest pressure of systole'
- indicates the force of contraction

2. Diastolic BP

- Lowest pressure of diastole
- indicates peripheral Resistance

- Greatest peripheral resistance offered by skeletal muscle contraction (>50%)
- Cutaneous circulation contributes to 20-30% of peripheral resistance
- PULSE PRESSURE → SBP – DBP
- indicates stroke volume
- DBP + Pulse pressure = SBP
- Systole : diastole : pulse pressure = 3:2:1

4. Means Arterial Pressure

- Average pressure
- MAP = DBP + (1/3 rd of pulse pressure)
- Ex: SBP = 120 mm of Hg
  - DBP = 80 mm of Hg
- Arithmetic Average → 200 / 2 = 100 mm of Hg
  - DBP + PP = SBP
  - DBP + 1/2PP = arithmetic mean/average
- MAP
  - DBP + 1/3 rd of PP
  - 80 + 1/3 x 40
  - 80 + 13 = 93 mm of Hg
- MAP is not the exact arithmetic average d/t longer duration of Diastole
- MAP is closer to diastolic Blood pressure

MEASUREMENT OF BP

01:09:53

Previous Year's Questions

Q. A patient is admitted in ICU and his blood pressure is being monitored continuously and simultaneously by an intravascular catheter and sphgmomanometery. What will be your recordings?

A. Sphgmomanometery will give a higher pressure as compared to intravascular catheter pressure

B. Sphgmomanometery & intravascular catheter will give the same pressure

C. Sphgmomanometery will give lower pressure as compared to intravascular pressure

D. Depends on various factors

Note:- The answer to the above question
Sphgmomanometer pressure (Riva Rocci cuff pressure) are on little higher side than intravascular pressure because some amount of pressure gets dissipated in the intervening tissue
SPHGMOMANOMETERY is used to pressure BP
There are two methods:
Palpatory method
Ausculatory method

Palpatory method

- Lower systolic BP than actual BP
- We tie BP cuff to the arm and the pulse is being palpated at the wrist (Radial artery)
- There is lapse of time between the pulse felt at wrist and the systolic pressure on the cuff; so the pressure will be slightly less than the actual pressure

Auscultatory method:

- Tie the cuff around the arm, ↑the pressure & slowly lower
- Once the cuff pressure same as the intravascular pressure, then blood starts moving in a turbulent format making Korotkoff's sound with systole & not diastole

Korotkoff's sound:

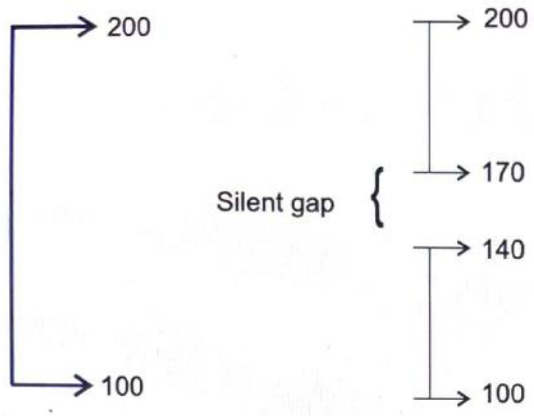
- Phase 4/ muffling of sound is more appropriate for taking as Diastolic pressure
- Phase
  - TAPPING SOUNDS
  - CUFF pressure is b/w Systolic &
  - Diastolic pressure
- Phase 4 - MUFFLING SOUND
  - Cuff pressure reached diastolic pressure
  - Sound is d/t turbulent blood flow
  - Should be taken for DBP measurement
- Phase 5 - Disappearance of sound
  - turbulence converted to Laminar flow
  - majority considered it for DBP measurement as it is easily reproducible (ease of Use) compared to muffling
  - Differences b/w Phase 4 & phase 5 → 5 mm of Hg
  - Phase 4 is considered as DBP in such conditions
- Obesity
  - higher pressure are recorded by Riva Rocci Cuff
- Atherosclerosis
  - Higher pressure are recorded by the cuff

SMALL CUFF- ERRORS

- higher pressure are recorded
  - tends to occlude the brachial artery incompletely

AUSCULTATORY GAP / SILENT GAP

- Sounds disappears & reappears, silent gap persists in between
- Reason not know clearly, might be atherosclerotic
- Low Systolic & normal diastolic BP recorded
- To avoid this, do palpatory method



REGIONAL CIRCULATIONS

CORONARY CIRCULATION

01:41:36

- At base of Aorta, Rt & lt coronary arteries arises
- Lt coronary artery gives lt circumflex artery & descends as
  - Lt. anterior descending artery (LAD) / Windows Artery (Commonly involves in MI)
    - → These 3 artery turn at edge of the heart & anastomose on the posterior wall of the heart
- Heart (Coronary blood flow) receives about 4-5% (225 - 250 ml) of co
- Autoregulation of blood Flow
  - Adenosine→Main Auto Regulator causes vasodilation → K^+, H^+
- Heart receives the blood flow during diastole
- Epicardial vessels receive blood flow during systole
- Endocardial vessels receives blood flow during diastole
  - Endocardial vessels are compressed in systole
  - Endocardial vessel open up during diastole
  - At higher heart Rates, Sub endocardial infarcts are more common as diastole suffers more
- A-V O2 Difference→ 75% (highest in heart)

NUTRITION OF HEART

- Primary source of energy is free fatty acid (67% of energy)
- 30% of energy derived from GLUCOSE

ECONOMY OF MYOCARDIUM / ENERGY EFFICIENCY

- CO= SV x HR
- $\frac{work\ output}{O_2 consumption}$
- Best economy - ↑ SV & ↓HR
- 2nd Best economy - Normal SV & Normal HR
- Bad Economy - any SV & ↑ HR (O2 Consumption ↑ proportionately)
- Worst Economy - any co maintained against ↑ afterload

CAD

Angina Pain

- imbalance in O_2 consumption & O_2 delivery
- Since lack in O_2 delivery; anaerobic metabolism takes place leading to lactic acid accumulation which irritate the nerve endings – causing pain

CLINICAL QUESTIONS

Q. Absolute organ blood flow in mL/min equals flow velocity (cm/s) multiplied by the arterial cross-sectional area (cm^2). When organ blood flow and oxygen delivery are severely compromised, increased tissue oxygen extraction cannot fully compensate for the decreased oxygen delivery, and if tissue oxygen demands remain the same, organ O_2 consumption will decline as a direct consequence of inadequate delivery. Which structure has the Maximum blood flow/100 gm/min?

A. Brain
B. Heart
C. Kidney
D. Liver

Answer: C

Solution:

Organ	Blood flow (during rest) (ml/min.)	Blood flow (maximal vasodilatation) (ml/min.)	Blood flow (ml) per 100 gm of tissue per min.	% total cardiac output
Brain	750	1500	55	14
Heart	250	1200	80	5
Liver	1300	5000	85	23
Kidneys	1200	1500	**400**	22
Muscle	100	20,000	3	18
Skin	200	4000	10	4

- **The highest amount of blood flow (ml/min):** Liver
- **The highest amount of blood flow (ml/100 gm of tissue/min.):** Kidneys.
- However, the **Carotid body receives 2000 ml/100 gm of tissue/min., highest for any tissue** in the body.
- **Highest arterio - venous O_2 difference is seen in the heart; it is least in the kidneys.**

Reference: Guyton and Hall Textbook of Medical Physiology 13th Edition, Page No. 204

22 CIRCULATION PART 2

REGULATION OF BLOOD PRESSURE 00:00:58

Previous Year's Questions

Q. Two Students A &B. they are performing 2 different experiments on dogs
1. A cuts carotid baroreceptor (i.e. 9th CN) when the pressure was 80mm Hg on that dog
2. B cuts arotic baroreceptor (10th CN) when the pressure was 80mm Hg on that dog
What will be the result that they get after sectioning of those respective nerves in 2 different dogs

Both will get ↑BP
Both will get ↓BP
↑BP in the 1st dog but no change in the 2nd dog
No change in the 1st dog but ↑BP in the 2nd dog

Previous Year's Questions

Q. At what existing BP the impulse- discharge frequency from the baroreceptor will be maximum?
A. 60 mm Hg
B. 100 mm Hg
C. 150 mm Hg
D. 180 mm Hg

Previous Year's Questions

Q. Baroreceptor system is most sensitive / efficient at what BP?
A. 60 mm Hg
B. 100 mm Hg
C. 150 mm Hg
D. 180 mm Hg

1. Chemical
2. Neural | short term

VASOCONSTRICTORS-INCREASE BP 00:04:56

Previous Year's Questions

Q. Angiotensinogen is synthesized by which organ?
A. Liver
B. Kidney
C. Lungs
D. Heart
E. Brain

- Vasopressin
- Noradrenaline
- Angiotensin
- Endothelin (most potent local vasoconstrictor)
- ET_{2B} ®
  - only endothelin Receptor that causes vasodilation
  - It is for inherent check
- Urotensin (most potent circulating vasoconstrictors)
- Q Angiotensinogen formed by LIVER - Plasma protein

VASODILATORS 00:10:15

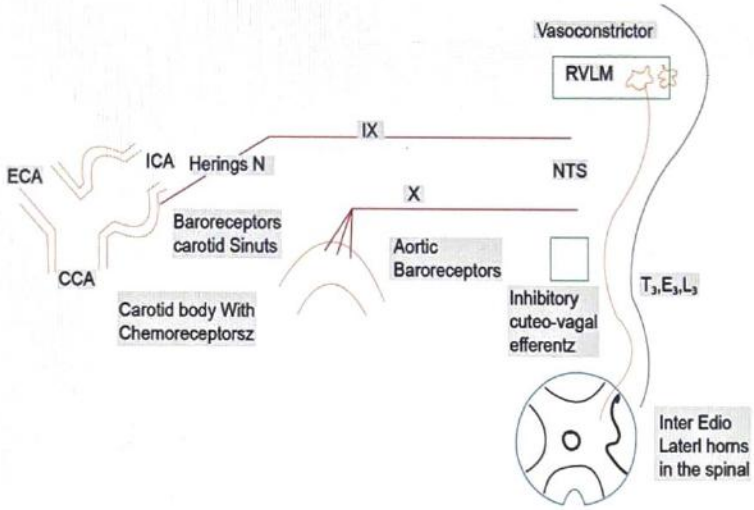
- HYPOXIA
  - CAUSES VD every where EXCEPT in LUNGS-ATP Sensitive K+ channels are present everywhere→ r/F VD
  - O_2 Sensitive K+ channel in the membrane of pulmonary vessel - r/F VC
- Co2
  - Local Vasodilator
  - Systemic vasoconstrictor (if it accumulates in medulla)'
- H+
- Lactic Acid
- Histamine
- Adenosine- Coronary vasodilator EXCEPT in afferent arteriole of KIDNEY)
- Nitric Oxide / Endothelium derived Relaxing factor (strongest VD)

NEURAL / SHORT TERM REGULATION

00:13:33

Baroreceptor Mechanism

- Mechano sensitive receptors
- Stretch receptors
- Spray type endlings
- IX & Xth Nerves are called as BUFFER NERVES (Buffer the changes of BP)
- Operational Range
  - Carotid baroreceptors
    → 60 - 180 mm of Hg
  - Aortic baroreceptors
    → 90 - 210 mm of Hg



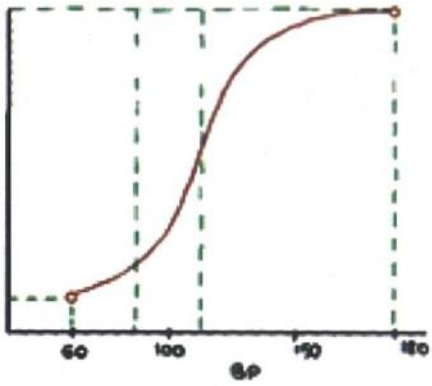
- RVLM (Rostral ventro lateral medulla) - Vasoconstrictor area
- NTS (Nucleus of tractus solitarius) - IX & X CN
- Vasomotor tone
  - VM Center is continuously tonically active
  - Blood vessels are 50% constricted state
- CARDIO ACCELERATOR AREA -Present in medulla behind-cardioinhibitory area

SET POINT

- BR system is most sensitive at 100 mm of Hg
- This is the NATURAL SET POINT for BR
- BARORECEPTOR RESETTING to New BP-done within 1-2 days

FREQUENCY MODULATED SIGNALING

- At 100 mm of Hg, Steady impulse discharge from baroreceptors & maintains the VASOMOTOR TONE
- VASOMOTOR TONE / VASOCONSTRICTOR TONE
  - VM Center is continuously tonically active
  - Blood vessels are 50% constricted state
- When BP increases, impulse discharge frequency also increases
- When BP decreases, impulse discharge frequency also decreases
- Least impulse discharge is at - 60 mm of Hg
- Highest impulse discharge is at - 180 mm of Hg
- Steepest impulse discharge is around - 100mm of Hg



- Any homeostatic regulatory mechanism ; operates best near its natural set point
- Sleepest around 100 mg of Hg (very sensitive)

EFFECT OF CUTTING / SECTIONING OF IX & X Nerves

- Decrease impulse to Vmc,
  - Sensed as a fall in blood pressure, with in 1 Sec BP increased

2. CHEMORECEPTOR MECHANISM

00:39:01

- **Carotid body**
  - Operates >60 mm Hg
  - They have massive blood flow
  - Present in common carotid Artery
  - Chemosensitive cell
    → GLOMUS CELL
    → They have O_2 – sensitive K^+ channel
    → Sensitive to hypoxia (O_2)
    → BP from < 60-30mm, causes ↓ Blood Flow (hypoxia)
  - upto 60mm of Hg→ controlled by Baroreceptor mechanism
  - From 60- 30 mm of Hg → controlled by chemoreceptors
  - < 30 mm of Hg→controlled by CNS ISCHEMIC RESPONSE

3. CNS ISCHEMIC RESPONSE / LAST DITCH STAND

- If BP is > 30mm Hg-0 mm Hg
- at such Low BP, Blood Flow to vmc is Decreases & Co2

accumulates around vmc & stimulates vasoconstrictor center BP rises immediately

- CUSHING's REACTION 00:46:08
  - ↑ICT
  - (↑ CSF pressure)
  - ICT > Cerebral artery pressure

  } CNS ISCHEMIC RESPONSE

INTERMEDIATE TERM REGULATION 00:48:03

- ADH & Thirst mechanism (↓BP)
- Capillary fluid mechanism
  - ↓circulating volume, ↓BP
- Atrial Natriuretic Peptide mechanism
- Increase Atrial filling → ANP → Kidney →Natriuresis Diuresis

LONG TERM REGULATION 00:51:53

RAAS 00:52:42

- ↓Blood volume & ↓BP → renal BR → JG cell → Renin

  ↓

  Angiotensinogen (Liver) →Angiotensin I lungs →(ACE) Angiotensin II
  - Salt & water retention
  - Vasoconstriction
  - Adrenal cortex (Aldosterone release from kidney leading to salt & water retention)

KIDNEY BODY FLUID MECHANISM 00:53:55

- Urine output adjusted on a long term basis
  - at 100 mm of Hg, Urine output →1 - 1.5 ltr / day (normal)
  - at 60 mm of Hg, Urine output → Zero
  - at 160 mm of Hg, Urine output →5 - 6 times the normal
- ↑BP = hypertension; DBP = >90 mm Hg
  - 90-104 mm Hg-mild hypertension
  - 105-114mm Hg - moderate hypertension
  - >115mm Hg- severe hypertension

CARDIOVASCULAR CHANGES DURING EXERCISE 01:00:12

Previous Year's Questions

Q. 30yr old athlete is performing strength training. which of the following indicators will not increase during exercise

A. Heart rate
B. CO
C. MAP
D. SVR

ISOTONIC / DYNAMIC EXERCISE	ISOMETRIC / STATIC EXERCISE
• shortening occurs	• Length remains Same
• Tension constant	• tension develops
• cycling, running, aerobics	• pulley, weight lifting

ISOTONIC EXERCISE 01:05:25

- ↑ HR
- ↑ SV
- ↑ CO

} ↑ sympathetic discharge

MUSCLE CHEMOREFLEX

- (H+, Co2, Lactic acid)

↓

- vasodilation in skeletal muscles

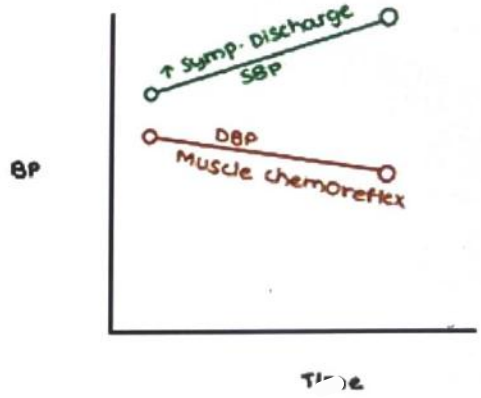
↓

↓PR

↓

↓DBP

- Advised in Hypertensive individuals



ISOMETRIC EXERCISE 01:11:11

- Contraindicated in hypertensives

Isometric

↓

Sustained Tension development

↓

sustained compression of blood vessels in skeletal muscles

↓

Increase Peripheral Resistance

↓

Increase DBP

↓

MEAN ARTERIAL PRESSURE – increase

- increase HR
- Cardiac output not increases
- As muscle is under Sustained Contraction
- ↓ SV due to ↓ venous return

CARDIOVASCULAR REFLEXES: 01:17:46

Bainbridge reflex

- Sudden increase in heart rate and cardiac output because of increase in venous return
- Mechanical stimulus
  - Eg: if the patient in IV saline has increase in venous return cause sudden increase of heart rate

Bezold jarisch reflex or ventricular chemoreflex

- In ventricle and coronary arteries the receptors sent signal via vagus nerve nucleus of tractus solitarius finally efferent fibers results bradycardia ,hypotension,apnea
- Non mechanical stimulus
  - eg: Injection veratrum given result in patient bradycardia , hypotension,apnea

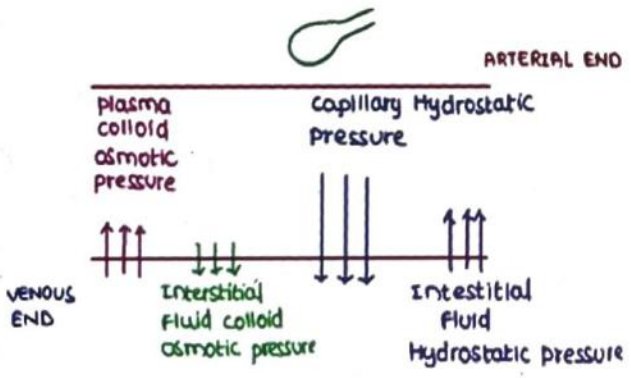
Vago-vagal reflex

- Sudden withdrawal of sympathetic charge result excessive activity in vagus cause bradycardia and hypotension sudden fall of blood pressure decrease in cerebral blood flow result in syncope

STARLING's FORCES (STARLING'S EQUILIBRIUM) 01:24:26

1. Hydrostatic pressure

- Force exerted by accumulated fluid
- Moves the fluid away into neighboring Compartment more the accumulated fluid, more the pressure



2. Colloid osmotic pressure

- Osmotic pressure→exerted by all osmotically active molecules Oncotic pressure → exerted by macromolecules
- Exerted by protein
- Pulls the H2O back into capillaries by Osmosis

- Interstitial Fluid hydrostatic pressure plasma
- colloid osmotic pressure

} Pulls Fluid in the capillary

- capillary hydrostatic pressure Interstitial
- fluid colloid osmotic pressure

} pushes the fluid away from capillary

- At Arterial end, net force pushes Fluid out of capillary At venous end, net force pulls fluid back into capillary
- Net Sum Of Force On Arterial End & Net Sum Of Force On Venous End Are Not Equal (NET force on arterial end is little greater)
  - some amount of fluid stays in interstitium forming ss Interstitial fluid

LYMPHATICS 01:50:44

- accessory routes by which extra interstitial fluid drains out of the tissue & finally into venous system
- Lymph Interstitial fluids (include proteins)
  Digestive tract & Liver lymphatics contains more protein in lymph & Interstitial mode Protein content in Lymphatics & interstitial fluid of
  - GIT & Liver [illegible]
  - Other: 2-3%

FACTORS INCREASING FORMATION OF LYMPHA (CAN CAUSE edema)

- ↑capillary hydrostatic pressure
- ↓ plasma colloid osmotic pressure Foot massage (Flow increased)

FUNCTIONS OF LYMPH

- Return the substances into the venous system
- Helps in macromolecular absorption (fat soluble vitamins)
- LACTEALS (milky appearance) → GIT Lymphatics
- help in absorption of Long Chain fatty Acids (> 18 carbon) in the from of chylomicrons

CLINICAL QUESTIONS

Q. A patient presents with right to left shunt. Oxygen content in arterial and venous side are 18 and 14 ml/100 ml respectively. Oxygen content at pulmonary capillary is 20. What is the percentage shunting of cardiac output?

A. 23%
B. 33%
C. 43%
D. 53%

Answer: B

Solution:

- **Normal O_2 content**
  - Arterial → 20ml
  - Venous → 14 ml
  - Arteriovenous difference → 6 ml
- **In the given condition, O_2 content**
  - Arterial → 18 ml
  - Venous → 14 ml
  - Arteriovenous difference → 4 ml
- I.e. 1/3 of the normal is reduced in the given shunting.
- So, there will be a reduction of 33% (option-2) or 2 ml

Reference: Guyton and Hall Textbook of Medical Physiology 13th Edition, Page No. 256

LEARNING OBJECTIVES

UNIT 6 RESPIRATORY SYSTEM

- **INTRODUCTION**
  - First 7 divisions
  - Next 16 divisions
  - Alveolar epithelial cells: Pneumocytes
  - Dendritic cells and alveolar macrophages
  - Toll – like receptors

- **RESPIRATORY SYSTEM PART 1**
  - Mechanism of Breathing
  - Thoracic cage of its movements
  - Pressures involved in Breathing
  - Surfactant
  - Compliance

- **RESPIRATORY SYSTEM PART 2**
  - Lung volume & capacities
  - Timed Vital Capacity
  - Pulmonary Function Test
  - Flow volume loops
  - Dead Space

- **RESPIRATORY SYSTEM PART 3**
  - Pulmonary circulation
  - Ventilation pressure ratio
  - Gas transport in blood
  - Alveolar air equation
  - Tissue utilization coefficient
  - O2 dissociation curve

- **RESPIRATORY SYSTEM PART 4**
  - Regulation of breathing
  - Hering breuer reflex
  - Head paradoxical reflex
  - Acclimatization to high altitude hypoxia
  - Mountain sickness
  - Prevention
  - Types of breathing

23 RESPIRATORY SYSTEM INTRODUCTION

Introduction 00:03:31

- ~ The trachea divides into 2 bronchi; the respiratory passage then divides and re-divides into successive small – diameter branches. There are 23 divisions between trachea and alveoli, referred to as generations of the respiratory trend.
- The trachea and the first 16 generations make up the. "Conducting zone". It performs an important function of warming and humidification of inspired air. The zone ends with a terminal bronchiole.
- The last 7 generations make up the "respiratory zone". It consists of respiratory bronchioles, alveolar ducts, and alveolar sacs. The gas exchange occurs in this region (mainly in alveoli).

First 7 divisions; the bronchi have-

- Walls containing cartilage and smooth muscle.
- Epithelial lining with cilia and goblet cells
- Submucosal mucus secreting glands
- Endocrine cells – Kulchitsky or APUD (neuroendocrine cells; secrete biogenic amines dopamine, serotonin)

Next 16 divisions: the bronchioles have 00:09:62

- No cartilage, and a thinner muscular layer
- Single layer of ciliated cells
- Granulates clara cells: these cells produce surfactant – like material; they may play a role in epithelial regeneration after injury. They also contribute to the composition of mucus
- Small openings called pores of kohn in the alveolar walls connect adjacent alveoli; canals of lambert connect terminal airways to adjacent alveoli. The pores of kohn and canals of lambert provide collateral ventilation and prevent alveolar collapse.
- The cilia beat with a coordinated oscillation in a characteristic, biphasic and wave-like rhythm called metachronism.
- The "Achilles heel" region of the respiratory system – the region from the terminal bronchioles to the alveoli; it is devoid of ciliated cells (and mucociliary clearance system is weakest here). The relatively slow rate of particle clearance in this area renders the terminal respiratory unit the most common location of airway damage for all types of occupational lung disease.
- Resistance for air flow in the nose: it accounts for about 50% of the total respiratory system resistance, during quiet breathing = 8 cm H_2O /L /sec.

Alveolar epithelial cells: Pneumocytes 00:16:06

- Type I
  - 93% surface area
  - Gas exchange
- Type II –
  - Occupy 5-7% of the surface area of alveolus
  - Synthesize Surfactant
- Type III cells
  - Also called brush cells
  - May function as chemoreceptor

Normally, type I and type II cells exist in a 1: ratio. Cytotoxic agents cause injury to type I epithelial cells; type II cells are responsible for regeneration

- Dendritic cells and alveolar macrophages are the first non-epithelial cells to respond to a foreign substance. The dendritic cells are located, in a diffuse pattern, in the lung interstitium. Their role in immune mechanism of lung ~ antigen presentation to T cells and immunoregulation (tolerance).
- Toll – like receptors: The body has developed a recognition system to identify potentially harmful pathogenic substances that are inhaled (because, most inhaled substances are nonpathogenic). The system is based on the recognition of pathogen associated molecular patterns (PAMPs) on the organism / particle. These PAMPs are recognized by a family of receptors on host cells, called Toll-like receptors (TLRs). Activation of this system initiates inflammatory host defense mechanisms to fight off the pathogen. (An important link in innate immunity (in Drosophila) is a receptor protein named toll, which binds fungal antigens and triggers activation of genes.

24 RESPIRATORY SYSTEM PART 1

Mechanism of Breathing 00:03:38

- Muscles for Breathing

00:06:07

  - Diaphragm
  - External intercostal
- Types of breathing
  - Thoracic: Seen in Peritonitis
  - Abdominal: Seen in Pleural effusion

- **Thoracic cage of its movements** 00:14:01
  - Bucket handle movement
  - Pump handle movement
- Forceful breathing muscle
  - Ala nari
  - Sternomastoid
  - Scaleni
  - Serratus anterior
  - Abdominal } Expiration
  - Internal intercostal }

Pressures involved in Breathing

Q. What is the intrathoracic Pressure of in first Cry of baby
- −100cm H2O
- -60 cm H2O
- +60 cm H2O
- +100 cm H2O

Q. The greatest positive intrthoracic pressure is in which of the following
- Sneeze
- Cough
- Opera singing
- Valsalva manessver

- **Intrathoracic / Intrapleural Pressure** 00:21:58
  - Pressure between two layers of pleura / around the lungs
  - Pressure is mostly negative except for forceful expiration
  - Keeps the lung distended
  - Negative pressure is generated by classic recoil of the lung.
  - During inspiration: the role of pleural fluid
    → Hydraulic traction phenomenon
  - Pressure in forceful inspiration
    → Sighing -30 cm H_2O
    → Yawning
    → First cry of neonate is -60cm H_2O
    → Muller's maneuver is – 100 cm H_2O
    → Forceful expiration
    → Cough / sneeze = +30 to +50 cm H_2O
    → Opera singing = +60 to + 80cm H_2O
    → Valsalva maneuver = +100 to +150cm H_2O

- Intra-**Alveolar Pressure** 00:50:55
  - At start of inspiration is -1cm H2O
  - At end of inspiration is +1cm H_2O
- Trans – pulmonary pressure
  - [alveolar]- [intra pleural]
  - Minimum at start of inspiration
  - Transthoracic pressure = Atmosphere pressure
  - Transural pressure
  - Pressure across wall of the airway
  - (Pairway)- (P interstitium)

Surfactant 01:01:17

- Measured by stalagmometer
- A surface active material present in fluid living alveoli which reduce surface tension within alveoli / reduce surface tension within alveoli / reduce the collapsibility which increase expansibility

- **Composition and synthesis**
  - Type II Pneumocyte
  - Clara cells
  - DPPC: Dipalmitoyl phosphatidylcholine / lecithin.
  - Surface apoproteins [SPs]
    → Regulate the surfactant turnover
  - $Ca2^{++}$
    → Faster speed
- **Functions and clinical applications** 01:15:37
  - Reduce surface tension
  - ↑ Compliance

- Keeps alveoli dry
- Stabilizes the alveolar system of interdependence
  → Laplace law

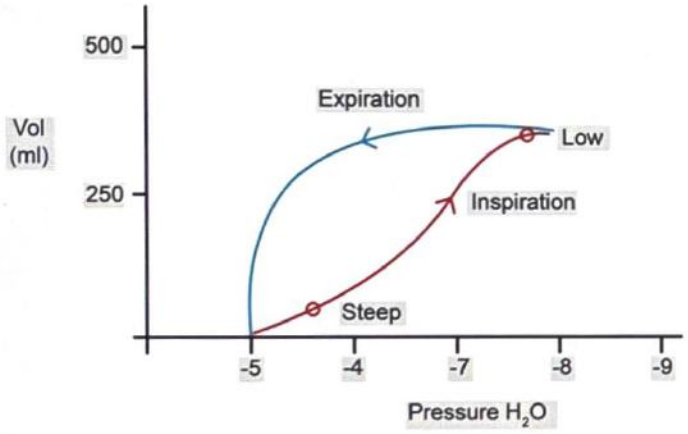
$$P = \frac{2T}{R}$$

- **Clinical Application** 01:24:40
  - ARDS
    → No surfactant production
  - Hyaline membrane disease [HMD]

- **Compliance** 01:27:05
  - Measure of Distensibility
  - Compliance $\propto \frac{1}{Surface\ tension}$
    → $\otimes V / \otimes P$
    → Change in lung volume per unit change in pressure

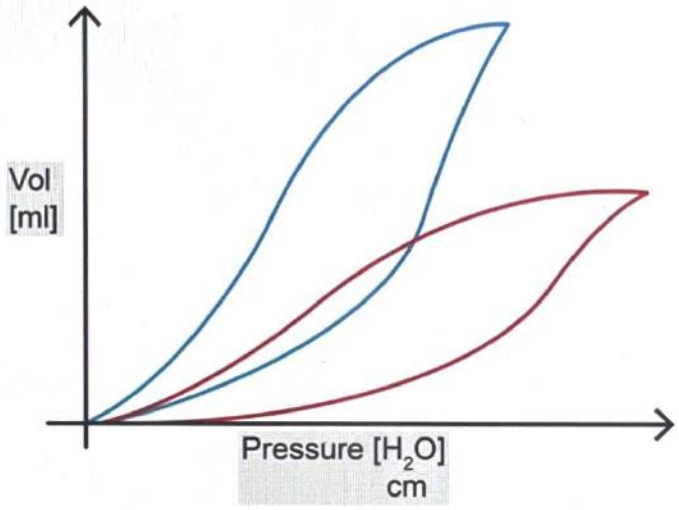
- **Types of complications**
  - Static compliance : 200 ml / cm H2O
  - Specific compliance
    → $\frac{Compliance}{FRC}$
  - Dynamic compliance
    → Changing compliance with the stage of breathing

- **Compliance / Hysteresis Diagram** 01:43:59

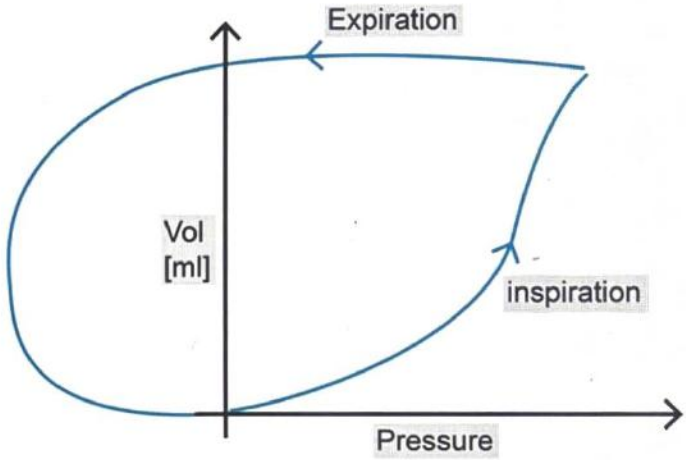


Q. Compliance is greatest at?
Start of inspiration
Mid of inspiration
End of inspiration
Start of expiration

- **Clinical Application**
  - Restrictive lung disease
  - Intestinal lung disease [Fibrosis]
    → Compliance ↓
    → Shallow, rapid breathing, near the lower lung volume
  - In restrictive disease



- In COPD



- **Work of Breathing** 02:18:03
  - Compliance / elastic work [elastic work]
    → 65%
  - Airway resistance work
    → <5%
  - Tissue resistances work

  } [Non – elastic work]

CLINICAL QUESTIONS

Q. A 31 yr old male, came in with history of RTA. On examination, subcutaneous emphysema (+). Pneumothorax was suspected. In a spontaneous pneumothorax, which of the following is expected to occur?

A. Right lung contracts
B. Chest wall on the right contracts
C. Diaphragm on the right moves up
D. Mediastinum moves to the right

Answer: A

Solution:
In spontaneous right lung pneumothorax, volume decreases when normal expansion pressure is suppressed.
All other options are wrong:

- **Increased pressure on the right side causes the chest wall to expand on that side**
- **The diaphragm moves downwards and the mediastinum moves to the left.**
- **Blood flow to the right lung is reduced both because of its small volume and because of hypoxic pulmonary vasoconstriction.**

Reference: Respiratory Physiology The Essentials by John West 9th p 107

25 RESPIRATORY SYSTEM PART 2

- Lung volume & capacities (Diagram)
- Volumes
  - Tidal volume [500 ml]
  - IRV – 3000 ml
  - ERV – 1100 ml
  - Residual volume – 1200 ml
- Capacities
  - Inspiratory capacities: IRV + IV
  - Functional residual capacity [FRC] – ER V + RV = 2300 ml
  - Vital capacity – IRV, ERV, TV: 4600 ml
  - Total lung capacity – IV + IRV + ERV + RV
  - Closing volume just above RV in which the airways at the base will close.
    → 1400 ml is closing volume
  - Residual volume cannot be measured by spirometry.
- Two methods
  - Helium dilution method – $C_1V_1 = C_2V_2$
  - Nitrogen washout method

TIMED VITAL CAPACITY

00:35:44

- FEV_1
  - $FEV_1 = 80 - 83\%$
  - $FEV_2 = 90\text{-}97\%$
  - $FEV_3 = 97\%$

Clinical correlation

- In COPD FEV1 <70%
  - FEV1 / VC =
    → Obstruction disease
  - FEV1 / VC =
    → Restrictive disease

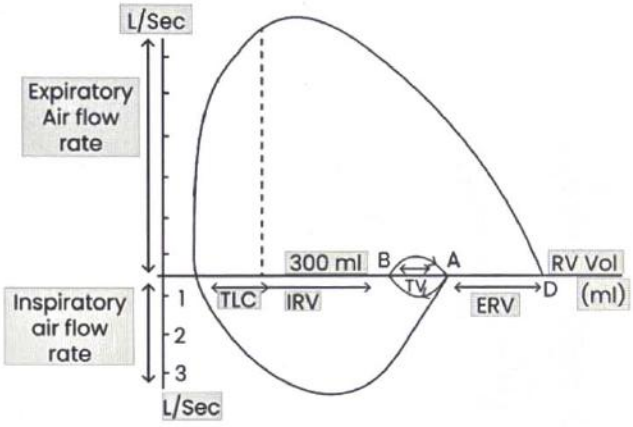
PULMONARY FUNCTION TEST

00:41:39

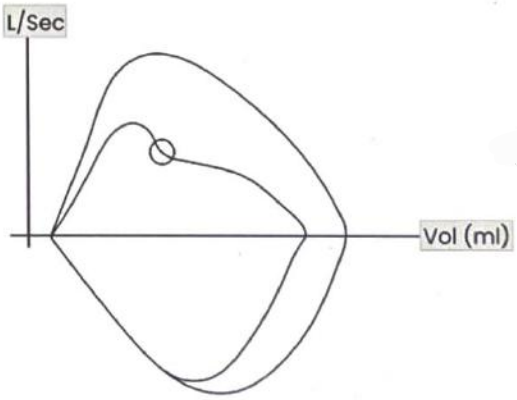
- First 20% is effort dependent flow rate
- Later is effort independent flow rate
- Equal pressure point
- COPD patients
  - Bronchial asthma
  - Chronic bronchitis
    → Inflammation & narrowing, edematous of airways
  - Equal pressure points normally occurs in first 7 generations
  - In COPD, equal pressure points shift downwards in non-cartilaginous airways
  - Breathing in COPD
    → Slow, deep, heavy and prolonged inspiration
    → More negative, ITP, reach higher lung volumes
    → Exhale slowly
    → Pursing of lips
- Bronchitis vs emphysema
  - RV will eventually cause over distention of alveoli
  - Resulting in emphysema
  - TLC

Flow volume loops

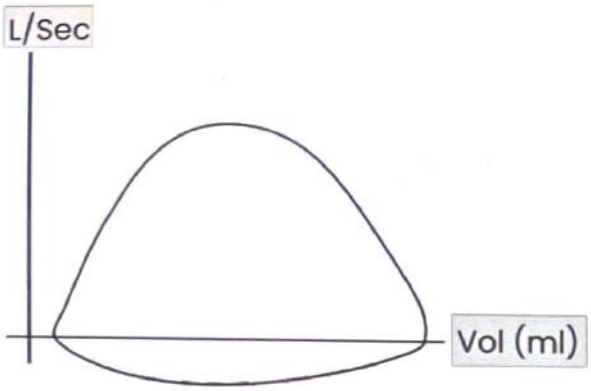
01:06:10



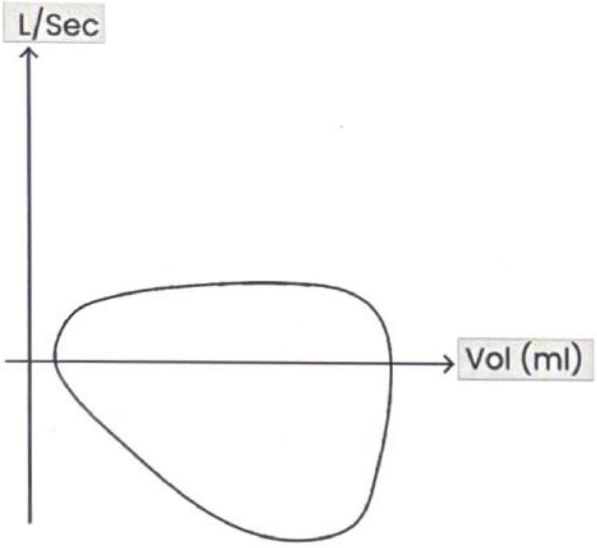
- $\frac{PIFR = 3\ L/sec}{PEFR = 10\text{-}12\ L/sec}$
- $FIV_1 = FEV_1 > 1$
- Flow loop shifting to right in restrictive diseases
- Flow loop shift to left in obstructive disease
- COPD flow loop with small airway obstruction



- Extrathoracic obstruction [variable]



- Intrathoracic variable obstruction
- Extrathoracic fixed obstruction
  → Tracheal tumor men



- $FEV_{0.25-0.75}$
- Maximal mid-expiratory flow rate
  → 3-3.25 L/sec
- The most sensitive indicator for small airway obstruction

DEAD SPACE

01:31:02

- Non respiratory space
- Nose – terminal bronchioles
- 1 ml/pound of body weight
- 150 ml for 70 kg
- Types
  - Anatomic
    → First 16 generation
    → Fowler's method: N2 analysis
  - Physiologic / total
    → Anatomic + alveolar
    → Bohr's method: expired CO_2 analysis
- Disadvantages of dead space
  - 150 ml out of 500 ml is wasted
  - Expiratory
    → For removal of blood gases
- Clinical application
  - Tracheostomy

VENTILATOR INDICES

01:55:03

- Respiratory minute volume [RMV]
  - TV x RR
    → 6-8 L/min
- Alveolar ventilation
  - [TV – dead space] x [RR]
    → 4-4.2 L/min
- Maximum voluntary ventilation [MVV/MBC]
  - 125-170 L/min
- Breathing reserve
  - MVV – RMV
- Dyspneic index
  - MVV – RMV / MVV x 100
    → Normal = 95%

CLINICAL QUESTIONS

Q. A 34 yr old male, mountain climber have started climbing Mount Everest. Before his climb, he takes acetazolamide. What response is expected with the drug, before the climb?

A. Alkalotic blood
B. Normal ventilation
C. Elevated ventilation
D. Normal arterial blood gases

Answer: C

Solution:
Acetazolamide

- Carbonic Anhydrase inhibitor
- Forces kidneys to excrete bicarbonate, the base form of CO_2.
- This excretion reacidifies the blood, balancing the effects of the hyperventilation that occurs at altitude in an attempt to get O_2.
- Such reacidification acts as a respiratory stimulant, particularly at night, reducing the periodic breathing pattern common at altitude.
- This would increase ventilation, resulting in a $\downarrow pCO_2$

Reference: Guyton 13th pg. 563

26 RESPIRATORY SYSTEM PART- 3

PULMONARY CIRCULATION 00:01:40

- Lesser circulation
- Pulmonary arte y
  - deoxygenated blood
- Pulmonary vein
  - Oxygenated blood
- High compliance [24 times]
- Low resistance
- Lungs are reservoir of blood
- Pressures
  - Pulmonary artery: 25/8 mm Hg
  - Pulmonary capillary pressure: 15 mm Hg
  - PCWP – 5 mm Hg [5-8 cm H2O
    → Reflex LA pressure
- Dual blood flow
  - Pulmonary circulation for gas exchange
  - Bronchial circulation for O2 supply to tissues
    → Bronchial vein drains to pulmonary vein to left side of heart
    → Left side has 1-2% deoxygenated blood
  - Hypoxia in lungs causes vasoconstriction
    → O_2 – sensitive K+ channel
    → Two factors
    -Hydrostatic factor
    -Alveolar pressure

- ZONES 00:26:16
  - Zone I : No blood flow
    → $P_{alv} > P_{art} > P_{vein}$
  - Zone II: intermittent blood flow
    → P_{art}, capillary $> P_{alv} > P_{vein}$
  - Zone III: Continuous blood flow
    → $P_{art} > P_{vein} > P_{alv}$

VENTILATION PERFUSION RATIO [V/Q] 00:33:59

- $\frac{alveolar\ ventilation}{blood\ flow\ perfusion} = \frac{4\ L/min}{5\ L/min} = 0.8$
  - Apex
    → $\frac{ventilation}{perfusion} = \frac{V}{\square} = 3.5$
    → physiologic dead space
  - Base
    → $\frac{ventilation}{perfusion} = \frac{V}{\square} = 3.5$
    → Physiologic shunt

- Respiratory membrane
  - Fluid containing surfactant
  - Epithelial cells [alveolar] /pneumocystis type I
  - Basement membrane
  - Pulmonary interstitium
  - Endothelial basement membrane
  - Red cell membrane
- Clinical significance
  - Pulmonary edema, interstitial lung disease
    → ↓O_2 diffusion
  - Emphysema
    → ↓ surface area

- **Diffusing capacity of respiratory membrane** 00:57:34
  - 21-23 ml/min/mm Hg
- Measurement of diffusing capacity
  - Diffusion limited carbon monoxide [DLCO]

GAS TRANSPORT IN THE BLOOD 01:13:09

- O2 transport from atmospheric air to blood
  - Po_2 in atmospheric air at sea level
  - Law of partial pressure
    → 1st law: in a mixture of gasses when there are two or more gasses and are not chemically reacting with each other, then each
    → 2nd law: addition of all partial pressure = total partial pressure of the mixture
    → 3rd law: the partial pressure of individual gas proportional to it relative concentration in the mixture
    → P_{O2} in atmospheric air at sea level is 159 mmHg
    → P_{O2} in inspired air in dead space is 149 mmHg
    → P_{H2O} [water vapor] = 47 mmHg
    → P_{o2} in alveolar air is 104 mmHg

- **ALVEOLAR AIR EQUATION** 01:38:20
  - $P_AO_2 = [FIO_2 \times (P_B - P_{H2O})] - [P_ACO_2/R]$
- Respiratory quotient
  - R – RQ
    → CO_2 endued/ O_2 consumed
    → 0.8 [mixed diet]
    → 1.0 [-CHO rich]
    → 0.7 [fat-rich]

- P_{O_2} in arterial blood
- Clinical correlation

	Alveolar P_{O_2}	Arterial P_{O_2}	A_{aDO_2}
ILD	N	↓	↑
Right to left shunt	N	↓	↑
Hypoventilation	↓	↓	N

- Transport of O_2 in blood up to tissues
  - Free / dissolved in plasma is 3%
    - → Dissolved O_2 in plasma = $[P_{o_2}]$ x [solubility coefficient for O_2] [PO2] 0.003 ml/100 ml/mmHg
    - → 0.3 – 0.4 ml/100 ml
  - O2 transport by Hb is 97%
    - → 1 gm Hb = 100% saturation = 1.39 ml of O_2
    - → 1 gm Hb = 97% saturation = 1.34 ml of O_2
  - Total O_2 content

HB	Free
[HB(gm%) x 1.39 % saturation	$[P_{o_2}$ x solubility coefficient]

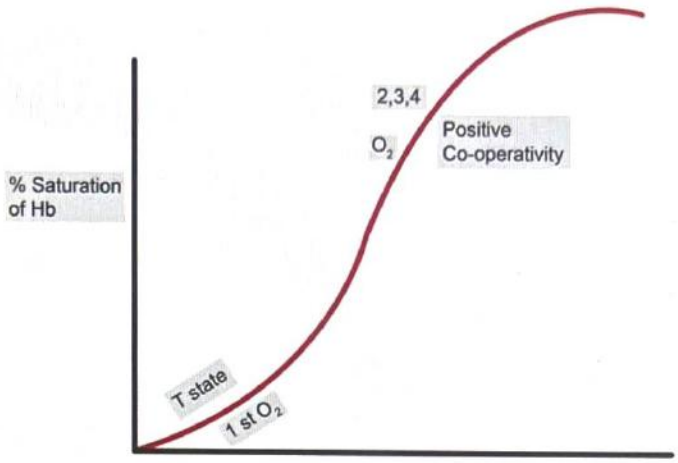
- Minimum required O_2 for survival of tissues is .6 ml /100 ml of blood

TISSUE UTILIZATION COEFFICIENT 02:22:43

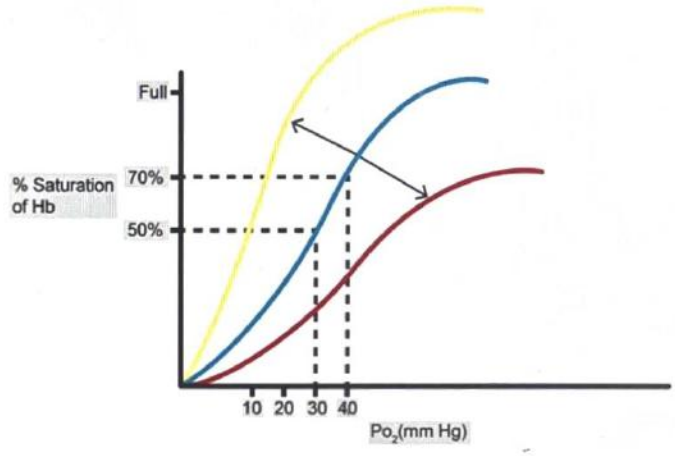
- O2 utilization coefficient is 25%
- A- V O_2 difference
  - Heart A-V O_2 difference
    - → Highest i.e. 75%
  - Kidney
    - → A-V O_2 difference is lowest

O_2 DISSOCIATION CURVE 02:32:13

- 1 molecule of Hb = 4 molecule of O_2



- S shape is because of T – state & R state of globin molecules and principle co-operating
- Advantage of S shape



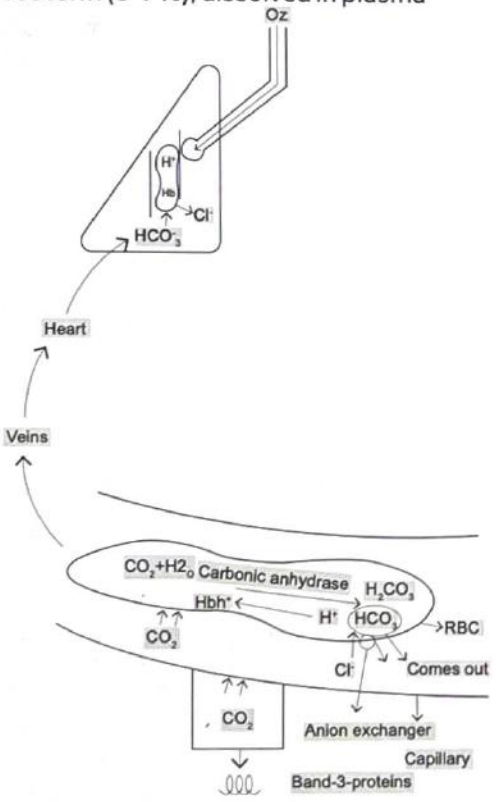
- Shift to right an downward
- → Increase H^+
- → Temp
- → P_{co2} – Bohr's effect
- → 2,3 – BPG
- Shift to upward and left
- → H^+
- → Temp
- → P_{CO2}

2,3 BPG

27 RESPIRATORY SYSTEM PART 4

INTRODUCTION

- CO_2 is generated as the end product of metabolism by the cells and then its released into the capillary blood from where it will come on the venous side via veins it will come into the right side of the heart and then to lungs. From the pulmonary circulation it will diffuse into the alveoli
- From the alveoli it will released out with the expired air
- CO_2 is much more diffusable as compared to oxygen and the pCO_2 is pulmonary capillary blood is only 46 mmHg and alveolar is 45 mmHg and with the difference of only 1 mm gradient CO_2 diffuses in quick time & expelled out.
- When the CO_2 is expelled from cells into the blood, it is transported in 3 forms:
  - HCO_3^- (70%)
  - Carbamino compounds (20-25%)
  - Free form (5-7%), dissolved in plasma



- CO_2 is a volatile acid because it forms H_2CO_3 with water inside the RBC & then converted to H^+ & HCO_3^-
- H^+ combines with deoxy Hb i.e. Hb acts as a extracellular buffer because it is a good acceptor of protons
- Hamburger shift (chloride shift) → Cl^- enters the RBC in exchange of HCO_3^- which enters plasma

Q. MCV of RBC in venous blood is?

A. Same as body average

B. Less than body average

C. More than body average

D. Variable

More than body average because the Cl^- when enters the RBC pulls some water with it into the RBC

- In the lungs, the O_2 we inspire will reach the alveoli and from the alveoli it will reach capillaries from where it will displace the H^+ from Hb
- As CO_2 is not transported as $HbCO_2$ because O_2 will not be able the displace $HbCO_2$ because CO_2 has more affinity for Hb but O_2 can displace H^+ from Hb.
- In lungs HCO_3^- enters and Cl^- leaves the RBC and it combine with H^+ again to from H_2CO_3 which is converted to H_2O & CO_2 by CA & CO_2 is expired from alveoli to outer space
- The H_2O molecules released can line to alveoli & respiratory passages
- Haldane's effect (Reverse Bohr): Effect of O_2 on CO_2 liberation & transport in the lungs

In the absence of O_2 : 2 vol % of CO_2 is liberated in the lungs

In the presence of O_2: 4 vol % of CO_2 is liberated in the lungs

REGULATION OF BREATHING

- Neural Regulation
- Chemical Regulation

Neural regulation

- Heart completely involuntary & automatic where as breathing is partly automatic & partly voluntary
  - Voluntary (cortex)
  - Involuntary (Brain stem) respiratory centre
- Voluntary Motor cortex sends signals to muscles of respiration for voluntary breathing
- Involuntary: There are 4-5 connections of neurons in brain stem which make up the respiratory centre

- Two groups in upper medulla
- One is upper pons
- One is lower pons

Upper Medulla

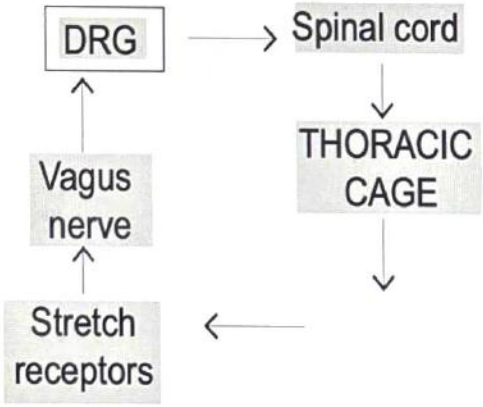
- Dorsal respiratory group (DRG)
- Ventral respiratory group (VRG)

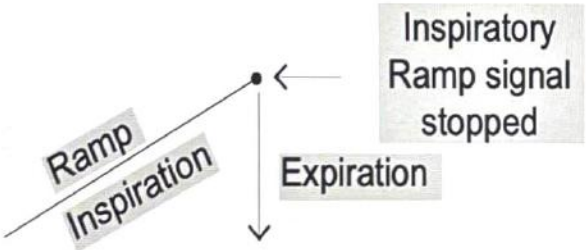
Lower Pons: Apneustic centre

Upper Pons: Pneumotaxic centre

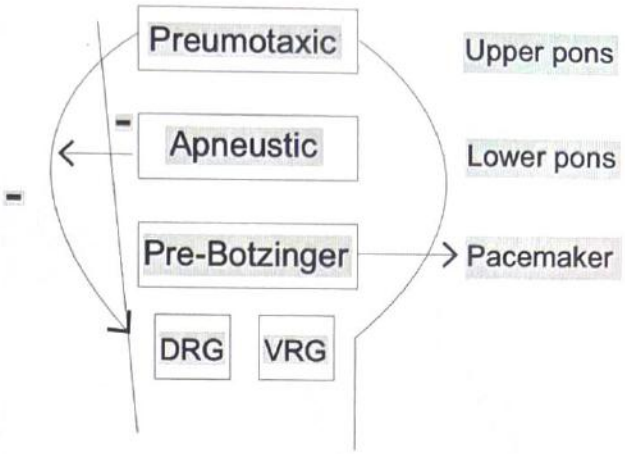
I. DRG: It generates the inspiration signal

- Signal is called inspiratory ramp signal this called Ramp because it increases slowly





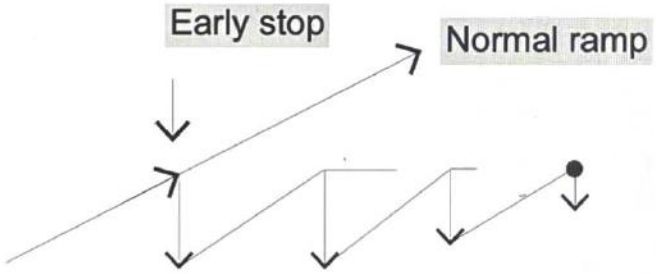
- When the stretch receptors in thoracic cage receive an input they send signal via vagus nerve to DRG & inspiratory signal stops



- **Pre Botzinger** → This complex above the upper medulla & it determines the pace of the inspiration & has connections with DRG & URG i.e. acts as a pacemaker for spontaneous breathing

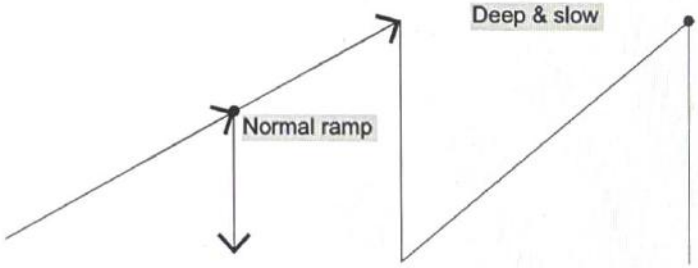
II. VRG: It is not active in normal quiet breathing but activates in forceful breathing. During forceful breathing the strong signals from DRG will pass on URG. Then the URG will send signals to muscles responsible for forceful expiration (e.g. abdominal muscles)

III. Pnemotaxic: It is an inhibitory action on DRG causing an early switch off of the Ramp signal



- Breathing will become shallow & Rapid

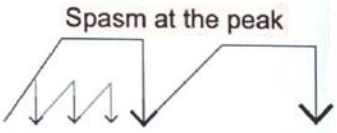
IV. Apneustic centre: It does not allow the early switch off of the ramp signal hence causing long, slow & deep.



Important Information

- The influence of pneumataxic & apneustic centre on DRG will determine the rate & depth of breathing at any moment.

00:40:00

Lesions	Effect
1. Vagotomy	• Prolonged inspiration
2. Transection at lower border of medulla (above C_3) (below DRG & URG)	• Spontaneous breathing will stop
3. Transection at upper border of medulla	• Spontaneous breathing continues but irregular & jerky
4. Mid pontine transection (Above apneustic)	• Long inspiratory spasms 
5. Damage to lower pons keeping upper pons intact	• Rapid, shallow breathing

Important Information

Ondine's curse → Bulbar poliomyelitis

- Damaged automatic breathing

Person has to voluntarily take every breath

Co_2 necrosis increased CO_2 levels for a long time leads to ↓sensitivity of the respiratory

00:48:48

Hering-Breuer Reflexes

Inflation reflex Deflation reflex

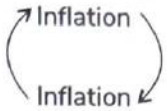
I. Inflation on reflex : If there is overdistension of the lungs, further inflation will be prevented

- It occurs when tidal volume is more than SL
- The stretch receptors send impulses to DRG through vagus nerve

II. Deflation reflex : It usually occurs during yawing

- The deflation of alveoli initiates the reflex causing an increased forceful breath to open up closed peripheral alveoli

HEAD'S PARADOXICAL REFLEX



- It occurs at birth because when a new born starts his / her own breath, the need to open all the collapsed alveoli is required. Hence, inflation leads to further inflation to increase no. of alveoli taking part in breathing. This occurs because the -ve feedback loop has not yet developed completely

CHEMICAL REGULATION

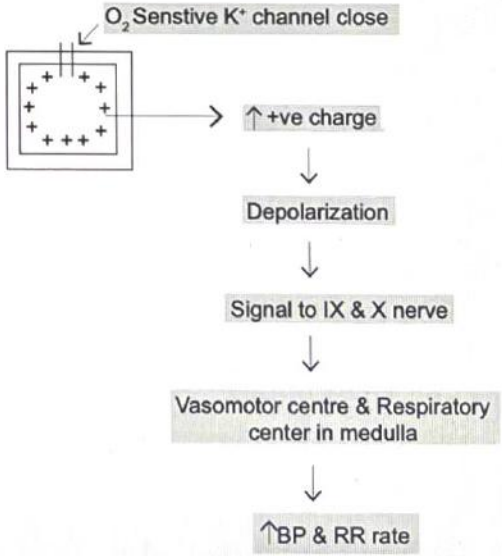
00:56:13

Some chemicals affect the breathing

- CO_2
- H^+
- O_2 / Hypoxia
- Chemoreceptors: Changes in the CO_2 / H^+ are sensed by these receptors

Chemoreceptors { Peripheral, Central }

1. **Peripheral :** They are located near the baroreceptors in the carotid body at the bifurcation of the common carotid and are also present in aortic bodies in the arch of aorta
   - Glomus cells are present in these bodies
   - Sense O_2 / Hypoxia
   - Send signals via IX and X nerve
     - Carotid body: IX
     - Aortic body: X
   - Signal generation: In glomus cell there is a O_2- sensitive K^+ channel. When there is hypoxia, this channel closes hence K^+ inside the cell cannot go out. The +ve charge on K^+ comes near the cell membrane causing its depolarization generating signal in IX & X cranial nerve



- The effect of O_2 on chemoreceptors cannot be seen until the pO_2 is < 60 mmHg O_2 is not the primary driver of ventilation
  - The primary driver is CO_2/H^+
- Peripheral chemoreceptors respond to two stimuli
  - Hypoxia
  - Arterial H^+ (Acidosis)

01:06:08

2. Central chemoreceptors

- Located in medulla (ventral surface)
- Most sensitive to H^+ (locally made in brain)
- Most sensitive to changes in arterial pCO_2 because pCO_2 can cross the blood brain barrier but arterial H^+ can't

Arterial CO_2 → crosses BBB
↓
Enters CSF
↓
$CO_2 + H_2O$
↓
H_2CO_3
↓
H^+ HCO_3^-

- ↑CO_2 / H^+: Stimulates ventilation (via central chemoreceptors)
- ↓CO_2 / H^+: Stimulates ventilation (via central chemoreceptors)
- Hypoxia → but pCO_2 still > 60 mmHg → peripheral chemoreceptors stimulated

↓
↑ventilation
↓
Depress ventilation via central chemoreceptor because
← ↓CO_2/H^+
this is the more predominant signal
(CO_2 effect predominates)

- Hypoxia→pO_2 < 60 mmHg →Stimulate peripheral chemoreceptor

↓
↑ventilation
↓
Tries to still depress ventilation but the
← ↓CO_2/H^+
O_2 effect predominates and still
ventilation increases

ACCLIMATIZATION TO HIGH ALTITUDE HYPOXIA

01:21:13

I. ↑ formation of 2, 3 – Biphosphoglycerate (BPG) leading increased O_2 displacement from haemoglobin
II. ↑ sensitivity of the peripheral chemoreceptors → effect of there receptors on respiratory cells become predominant
III. ↓ sensitivity of the central chemoreceptors

Acclimatization	Adaptation
• Changes physiologic function in response to environmental stress for short term e.g : cold, heat, low pO_2	• Genetic change induced by a long term exposure to environmental stress

- Exposure to high attitude

Decreased atmospheric pCO_2 → ↓alveolar pO_2
↓
↓arterial pO_2

- For every 1000 ft ascent barometric pressure decreases by approx. 26 mmHg (Hypoxia will stimulate ventilation peripheral chemoreceptors)
- Increase in alveolar ventilation would be just noticeable at about 8000 ft. ↓ saturation from 97% to 93% would stimulate chemoreceptors in carotid & aortic bodies
- Hypoxia causes pulmonary vasoconstriction
- At the height of 10000 to 14000 feet (3000-4000 mtrs) the alveolar pO_2 drops to 60 mmHg. The hypoxia induced ventilation is significantly increased (doubled)
- At height of 16000 to 20000 ft, chemoreceptor discharge is maximum & pulmonary ventilation is maximum (65% above normal)
- Hyperventilation occurs in two phases:

I. First immediate effect of hypoxia is to increase ventilation. However hyperventilation causes wash-off of CO_2 and H^+. Decrease in CO_2 and H^+ depresses ventilation via central chemoreceptors. This blunts the effect of hypoxia on ventilation H^+ wash-off leads to alkalosis (Respiratory alkalosis)
II. In slower phase, kidneys excrete more bicarbonate (10-12 hours). A bicarbonate transporter pumps the HCO_3^- out of CSF, pH of the CSF returns to normal and a second phase of hypoxia – driven hyperventilation begins

- **Acclimatization to hypoxic environment:** Their maybe an increase in carotid bodies, sensitivity to arterial pO_2. Hypoxic stimulation of carotid bodies would produce a disproportionately large ventilation response

- An important event in acclimatization (begins in 2-3 days): decreased sensitivity of central chemoreceptors to change in CO_2/H^+, so that even if they are wash-off, they donot influence ventilation
- There is an increase in Cordial output; it maintains the blood flow and O_2 delivery to the tissues
- Hypoxia stimulates the kidneys to produce erythropoietin. Hypoxia induced polycythemia (increased RBC count) is another feature of acclimatization

- There is an increased concentration of 2,3–DPG in RBC. This shifts the O_2 dissociation curve to right and favours unloading of O_2 in the tissues
- For the acclimatization: The golden rule is 'climb high and sleep low'. One should not ascent more than 1000 feet per day to sleep. That is if a climber ascends from 10000 feet to 15000 feet in a day, he/she should descend back to 11,000 feet to sleep
- **Acute Mountain sickness:** Symptoms such as nausea, vomiting, dyspnea. Imp current of mental functions. There may be pulmonary edema (due to increased pulmonary vascular resistance) and cerebral edema. Many symptoms of mountain sickness are due to dilation of cerebral vessels
- Acetazolamide maybe of use in speeding up the acclimatization process and in mild cases of mountain sickness. It will reduce the edema fluid formation. Also, it will cause bicarbonate excretion and will help counter the effects of hyperventilation
- **Chronic Mountain Sickness:** (Monge's disease) extreme polycythemia, cyanosis, malaise fatigue, exercise intolerance. Pulmonary hypertension eventually leads to right ventricular failure. It occur usually above 4500 m or about 14000 ft in natives
- For a person breathing air (20% oxygen) : During ascent the various symptoms caused by hypoxia at different heights, are given below

Ht. in meters	Ht. infect	Symptoms / Conditions
3500-4000	12000	Acute mountain sickness
4000	13000	Acute pulmonary edema
4500	14700	Acute cerebral edema
5000	16400	Flame hemorrhage in retina painless loss of vision
5600	18300	Deterioration (weight loss, anorexia, listlessness)
6100	20000	Loss of consciousness

- **While breathing 100% O_2 at high altitudes:** For a person breathing 100% O_2 the maximum height up to which he/she can ascend and yet a normal alveolar PO_2 (100 mmHg) is possible is 34000 feet (10400 meters) the barometric pressure at this height: 187 mmHg
- At 13700 meters the barometric pressure would be 100mmHg. Maximum alveolar PO_2 attainable at this height would be about 40 mmHg
- At 19200 meters the barometric pressure is 47 mmHg. At or below this pressure the body fluids boil at body temperature. However its only a theoretical possibility. Even before the steam bubbles could cause death, a person would die of hypoxia
- High barometric pressure
  - Usually faced by deep sea drives or people working in mining
  - For gases pressure x volume = constant
  - Hence for every 10 m beneath the surface level of pressure increases by 1 atm pressure and to keep PV constant the volume decreases leading to more dissolution of gases in the blood leading to:

I. O_2 toxicity: Increased dissolution of O_2 in blood causing damage to drugs, cap pillaring & CNS leading to convulsion

II. Nitrogen toxicity:
   → At the depth → (N_2 narcosis) increased dissolution N_2. It has high affinity for lipids & dissolves in adiposites & neural membranes. Symptoms are like alcohol toxicity. Loss of psychosocial inhibitions, intellectual functions are impaired leading to confusion
   → When the pressure is 5 atm, anaesthetic leading to blabbering, confusion etc

- **Martini law**: Every 15 m below the surface there is addition of 1 drink of Martini in the body and effects are same as alcohol intoxication
  - To prevent this divers carry mixture of O_2 & helium because helium dissolves less I body fluids & tissues & effects will be less and diffuses out of tissue very rapidly during decompression phase
  - Suddenly ascends to surface: (Decompression sickness) (dysbarism) (Caissan's disease)
- Pressure suddenly decreases & volume of the gases increases leading to formation of gas bubbles & leaving the solution phase. This leads to formation of N_2 bubbles.

Effects

- **Bones & Joints**: The bubbles get stuck in bones and joints leading to pain causing the diver to bend hence also called "bend's disease"
- **Paralysis**: N_2 bubbles get stuck in the myelin sheath leading to destruction & paralysis
- **Systemic circulation**: Embolic events can be caused by N_2 bubbles
- **Pulmonary circulation**: They cause breathless & choking sensation because N_2 bubbles get stuck in vessels causing Pul. Embolism (CHOKES)

Prevention

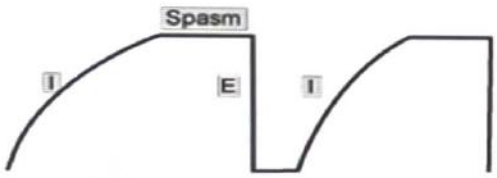
I. Ascend very-very slowly & gradually allowing the N_2 to escape from its body

II. If not possible come slowly immediately after ascend shift the person to decompression chamber and increase the pressure & then gradually decrease the pressure

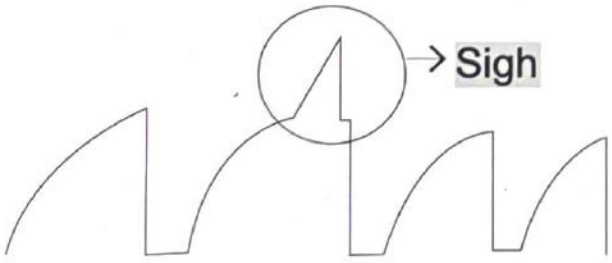
Diagram representation of various breathing patterns:

I. Normal

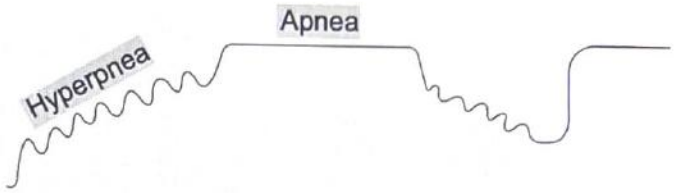
II. Apneustic: Depth of breathing increases



III. Sigh: Sudden increase in pressure (or only one breathing cycle)



IV. Cheyne stokes breathing : Alternate episodes of hyperpnea & apnea

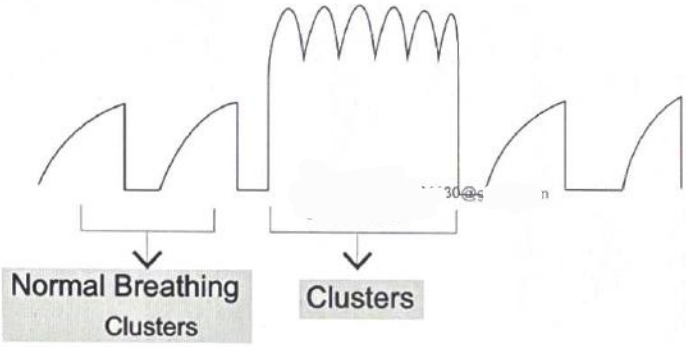


Hyperpnea → CO_2 washes out → apnea

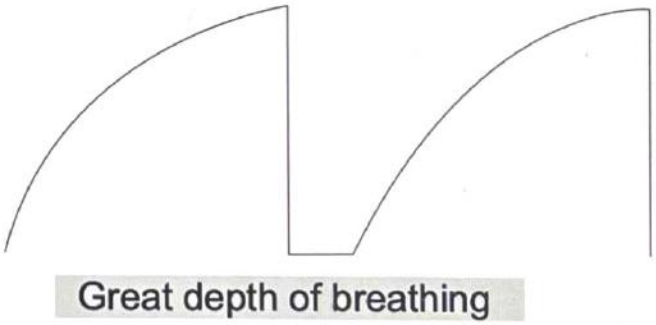
↑ ↓

Chemoreceptor stimulates ← ← Co_2 accumlate

V. Biot's breathing → irregular clusters of hyperpnea usually in meningitis



VI. Kussmaul's breathing (Air hungers) → seen in diabetic ketoacidosis



LEARNING OBJECTIVES

UNIT 7 EXCRTORY SYSTEM

RENAL PHYSIOLOGY GLOMERULAR FUNCTION

- Kidney
- Types of Nephron
- JG Apparatus
- Glomerular Tubular Mechanism
- Type 1 Cortical Interstitial Cell
- Renal Circulation
- Clearance
- GFR
- Factors Influencing GFR
- Measurements of GFR
- Measurement of Renal Blood Flow and Renal Plasma Flow

EXCRETORY SYSTEM

- Tubular Functional
- Glater Handling
- Free Water Clearance
- Concentration of Urine
- Countercurrent flow
- Vasa Recta
- Urinary Bladder & Micturition Reflex
- Effect of Lesions on Urinary Bladder
- Chemical and Physiological Buffer
- Kidney
- Titrable Acidity
- Anion Gap

28 RENAL PHYSIOLOGY GLOMERULAR FUNTION

- Total process – Glomerular filtration + tubular Secretion – tubular reabsorption

NEPHRON

00:01:52

- Basic structural and functional unit of the kidney

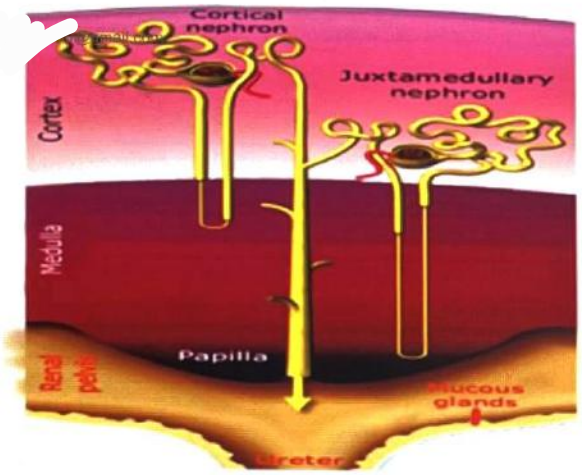
1. Cortical Nephrons

00:07:18

- 85%
- Have short loops
- Entirely located in cortex
- Forms normotonic urine

2. Juxta Glomerular Nephrons

- 15%
- Glomeruli situated in the cortex at the junction of cortex & medulla
- Have long loops
- Forms concentrated urine



BLOOD FLOW TO THE KIDNEY

- Cortex Receives most of blood flow, because of glomerulus
- Medulla consumes more O_2
- O_2 consumption / metabolic rate / ATP load is directly linked to tubular load for Na^+ reabsorption
- Na^+REABSORPTION
  - Na^+ pumped out via Na^+ - K^+ pump on basolateral membrane
  - This creates a concentration gradient
  - Na+ enters the tubular cell through ENaC & NKCC channels on apical membrane
- This Trans- cellular transport is seen in thick ascending limb of Loop of Henle
- Para-cellular transport uses lesser energy so though PCT is the site of absorption of 2/3rd of the glomeruli filtrate, the medulla is the site of maximum O_2 consumption

Previous Year's Questions

Q. Which of the following is also called GOORMAGHTIGH cell?

A. Macula densa cell
B. Lacis cell
C. Granular JG cell
D. Type I cortical interstitial cell

Previous Year's Questions

Q. JG apparatus lies in close relation to?

A. Afferent arteriole
B. Early DCT
C. Collecting duct
D. Glomerulus

JUXTA GLOMERULAR APPARATUS

00:17:15

- Lies in close relation to GLOMERULUS
- has 3 CELLS
  - Cell in Wall of afferent arteriole
  - Cell lining the early DCT
  - Cell between the above two
- Cell in the wall of afferent arteriole
  - JG cell / GRANULAR CELL- synthesizes Renin (enzyme)

Angiotensin II Functions

1. Vasoconstriction
2. Salt & Water Retention
3. Aldosterone Secretion (Adrenal gland) → Na^+ Reabsorption

Cell lining the early DCT

- **Macula densa cell**
  - Sense the Na^+ & Cl^- in tubular Fluids-TUBULO GLOMERULAR FEED BACK (TGF)

BP & RPP keeps fluctuating
increased renal blood flow
↓
Increase GFR & Increase Na^+ filtration
↓
H_2O loss following Na^+ loss
↓
Fluid & electrolyte imbalance
- This is prevented by TGF

TGF
Na^+ reaches early DCT
↓
Sensed by MD cells
↓
Increased Na^+ reabsorption
↓
Increase ATPase (Na^+ - K^+ pump)
↓
ATP→ADP / Increased Adenosine formation (most imp. Lignad in TGF)
↓
Goes to afferent arteriole
↓
Causes constriction
↓
Decrease BF to glomerulus
↓
Decrease GFR & Na^+ filtration / loss

- Ligand → ADENOSINE
- causes vasoconstriction of afferent artioles
- Adenosine is a vasodilator (A_2) everywhere EXCEPT KIDNEY (A_1) where it is vasoconstrictor.

Eg. Burne's hypothesis of coronary vasodilatation initiated by adenosine

ATP itself is sensed by P_2 x (purinergic receptor)
↓
Constriction of afferent arteriole
↓
↓GFR & Na^+ loss

GLOMERULO – TUBULAR BALANCE

00:37:35

Increase GFR
↓
Increase Concentration of proteins in efferents (H_2O & Na^+ filtered)
↓
Peritubular capillaries (increase plasma colloid oncotic pressure)
↓
Reabsorbs Na^+ & H_2O (bulk flow / solvent drag)

Mesangial/ Lacis/ Goormaghtigh/ Pseudo Mesenarian Cell
- Alter vessel diameter
- Has role in immune complex formation

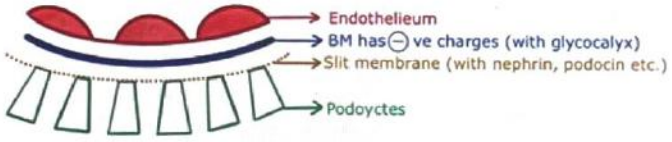
ERYTHROPOIETIN

00:45:57

- Type 1 cortical Interstial cell around peritubular capillaries synthesizes it
- contains O_2 sensitive K^+ channels
- 90% produced by kidney
- 10% produced by Liver
- O_2 sensitive K^+ channels seen in

1. Pulmonary vascular smooth muscle cell
2. Carotid body
3. Type 1 cortical interstitial cell

GLOMERULAR FILTRATION APPARATUS



Proteins- Anionic
- Large molecules (not filtered)
- Lost in nephrotic syndrome

RENAL CIRCULATION

00:54:35

- Along with brain & heart, displays auto regulation of BF
- Only circulation where Capillaries drain into arterioles
- Very high blood flow
  - 25% of Cardiac output (2nd best) (1st – liver 25-27%)
  - 400-450 ml / 100gm / min
  - carotid body – 2000ml / 100gm/ min
- Capillary hydrostatic pressure is 3-4 times the pressure elsewhere
  - 60 mm Hg (highest) (elsewhere – 15-20mm Hg) Blood accumulates in capillaries
  - Afferent is wide & efferent is narrow
- Capillary filtration co-efficient is highest→ 12.5ml/min/mm Hg
- A-V O_2 difference is least (10 – 12.5%) → renal vein carries more Oxygen
  - elsewhere 25%, highest – cardiac 75%
- Metabolic rate is regulated by Blood flow (Na+ Reabsorption)
- cutaneous circulation is regulated by temperature. These two are exceptions because elsewhere blood flow regulates metabolic rate

CLEARANCE

01:11:01

- hypothetical volume of plasma that is completely cleared of a substance per unit time

Previous Year's Questions

Q. What is U in formula for clearance?

A. Urine flow rate
B. Urine concentration in mg%
C. Urine concentration mg / ml
D. Urine concentration in ml /min

$$Cx = \frac{(Ux)(V)}{px}$$

U_x → Urinary concentration of x (mg/ml)
V → Volume of Urine per unit time (Urine flow rate)
P_x → Plasma concentration of x (mg%)

- Eg:(U_x) (V)→ total excretion rate of the substance per unit time
  - Ux =2 mg | ml
  - V = 100 ml / min
  - (Ux) (v) = 200 mg | min
- Interpretation – substance is excreted @ rate of 200mg every minute
- Therefore, clearance is the ratio of total excretion rate per unit time to its plasma concentration

GFR

01:19:57

Previous Year's Questions

Q. The creatinine clearance was 135 ml /min. What is the GFR?

A. 125 ml/min
B. 130 ml/min
C. 135 ml/min
D. d)140 ml/min

Previous Year's Questions

Q. Best substance to measure GFR?

A. Inulin
B. Creatinine
C. PAH
D. Mannitol

- (M/C used – creatinine)

FACTORS – STARLING'S FORCES

1. Glomerular capillary Hydrostatic pressure (60 mm Hg)	→ Favours filtration
2. Plasma colloid oncotic pressure (32 mm Hg)	Opposes Filtration (50mm Hg total)
3. Bowman's capsule hydrostatic pressure (18mm Hg) (50 mm Hg)	

- NET FILIRATION PRESSURE
  - I-II
  - 60-50 = 10 mm Hg
- CAPILLARY FILTRATION COEFFICIENT - 12.5 ml / min / mm Hg
- GFR → 12.5 x 10 = 125 ml /min
  = 180 ltr / Day

FILTRATION FRACTION

- RBF = 25% of CO
  = 1250 ml / min
- Renal plasma flow = 625 - 650 ml / min
- Filtration Fraction $= \frac{GFR}{RPF} = \frac{125}{625} = 1/5 = 20\%$

FACTOR INFLUENCE

01:37:14

Change in arterioles	GFR	RPF	FF
Dilatation of afferent	increase	increase	≈ same
Moderate constriction efferent	increase blood accumulation in G. Cap→ increase HP	decrease	increase
Severe, sustained constriction of efferent	decrease increase Plasma Protein, increase COP, decrease filtration decrease HP → decrease GFR)	decrease	≈ same
Nephrolithiasis	decrease	≈ same	decrease

Nephrolithiasis

Increase GFR ↓ RBF Increase FF ← Crystals decrease flow of tubular fluids ↓ Filtrate stays in BC ↓ Increase HP

MEASUREMENT OF GFR

01:48:06

- Best substance - Inulin (has to be injected)
- Fructopolysaccharide - Freely filtered at glomerulus
  - Neither reabsorbed nor secreted by tubules→ excretion rate closely resembles GFR)
- MC substance - Creatinine (endogenous, need not be injected)

Substaces Used & Criteria

1. Should be freely filtered
2. Neither reabsorbed nor excreted

Creatinine Clearance

- gives 5-10% over estimate of GFR (d/t addition from tubular secretion)
- $\frac{U_{crxv}}{P_{cr}}$ > GFR

1. NUMERRATOR - 20% Over estimate
   - d/t tubular secretion
2. DENOMINATOR - 10% false over estimate
   - PLASMA CREATININE
   - False over estimate
   - d/t JAFFE REACTION
   - In calorimetric method measurement, some non specific chromogens in plasma are added
- Cockroft & Gault Formula

$$C_{cr} = \frac{(140 - Age) \times Body\ Wt}{72 \times P_{cr}}$$

- Unreliable In

1. Extreme obesity
2. Advanced pregnancy

MEASUREMENT OF RENAL BLOOD FLOW (RBF)

01:59:57

Previous Year's Questions

Q. While measuring RBF, 3x ideal amount of PAH was injected. What will be the effect?

A. Falsely high
B. No error
C. Falsely low
D. Depends on RBF

Criteria For Substance

- Numerator
  - consumed by kidney, but not by metabolism, but into urinary excretion (consumption will be same as urinary excretion rate – $U_x \times V$)
- Denominator
  - RA_x
    - → not handled by any other except kidney
    - → $RA_x = P_x$
  - RV_x
    - → RV_x = zero
    - → Completely removed by the Kidney in a single pass
  - $RBF = \frac{(Ux)(V)}{Px - 0}$
  - Best substance → PAH (Para Amino Hippuric Acid)

$$PAH\ Clearance = RBF$$

$$\frac{U_{PAH} \times V}{P_{PAH}} = RBF$$

  - In the question, if PAH given by injection is 2 times →Plasma concentration increase 2 times. →No change in the value
    - → increase P_{PAH}
    - → increase (U_{PAH}) (V) as carrier excretes accordingly
    - → No change In RBF Value
  - But if PAH is given 3 times, then the carriers are saturated
  - (U_{PAH} ≈ same but P_{PAH} increase, therefore RBF will be falsely low)

PAH CLEARANCE

- Occurs
  - 20% by Filtration
  - 80% by tubular Secretion
    - → carrier protein is needed

RBF & RPF

RBF = RPF x

DIRECT FICK METHOD

- Based on FICK'S EQUATION

$$CO = \frac{O_2\ consumption\ (ml/min)}{A - V\ O_2\ difference\ (m1)}$$

$$RBF = \frac{consumption\ of\ x\ by\ kidney\ (ml/min)}{RA_x - RV_x}$$

- Q. U_x, P_x, GFR, V values given

A	B
[P_x X GFR]	[U_x X V]
Total filtered amount of 'x' per unit time	Total excreted amount of 'x' per unit time

- If A > B - Reabsorbed
- If A < B - Secreted

Cockroft & Gault formula

- $C_{cr} = \frac{(140 - \text{Age}) \times \text{Body Wt}}{72 \times P_{cr}}$

CLINICAL QUESTIONS

Q. A 34 yr old male, mountain climber have started climbing Mount Everest. Before his climb, he takes acetazolamide. What response is expected with the drug, before the climb?

A. Alkalotic blood
B. Normal ventilation
C. Elevated ventilation
D. Normal arterial blood gases

Answer: C

Solution:

Acetazolamide

- Carbonic Anhydrase inhibitor
- Forces kidneys to excrete bicarbonate, the base form of CO_2.
- This excretion reacidifies the blood, balancing the effects of the hyperventilation that occurs at altitude in an attempt to get O_2.
- Such reacidification acts as a respiratory stimulant, particularly at night, reducing the periodic breathing pattern common at altitude.
- This would increase ventilation, resulting in a $\downarrow pCO_2$

Reference: Guyton 13th pg. 563

29 EXCRETORY SYSTEM ACID BASE BALANCE

Cockroft & Gault formula

- $C_{cr} = \frac{(140 - Age) \times Body\ Wt}{72 \times P_{cr}}$

Cannot reliably in:
- Extreme obesity
- Advance pregnancy

TUBULAR FUNCTIONS

- Substances that are filtered, reabsorbed & Secreted are - K^+, Urea,uric acid(depents)

1. **Na^+**

- Reabsorption can happen by Paracellular & Trancellular transport
- Na^+ - K^+ pump pumps out Na^+ from cell into plasma
  ↓
  Intracellular Na+ decrease
  ↓
  Na^+ enters from tubular fluids into cell (Transcelluar in thick ascending limb of LOH)
- Paracellular in PCT-driven by trans Epithelial electrical gradient
- In PCT - 67%
  - Sodium-Hydrogen Exchanger
  - Regulatory hormones
    → Angiotensin II
    → NE
- LOH-20-25%
- In descending & thin ascending limb
  - Reabsorption by bulk flow / solvent drag
  - In thick ascending – transcellular – apical - NKCC - Loop diuretics act on it
    → BL side – Na^+ - K^+ pump

- Regulatory hormone- Aldosterone
- DCT- transporter – apical – NCC - Thiazide diuretics act on it
- CD - 3-5%
  - Transporter-apical- ENaC / amiloride sensitive channel
  - Regulatory hormone- Aldosterone
- GLOMERULUS : Isotonic Ultra Filtration

H_2O Reabsorption

PCT	67%	OBLIGATORY H_2O REABSORPTION irrespective of body osmolarity
LH DCT	10-15%	
Thick ascending limb of LOH		Impermeable to H_2O hence the diluting segment
Collecting Duct (ADH)	10-12%	FACULTATIVE REABSORPTION Under the influence of osmolarity

- Under ADH influence, greatest fraction of H_2O is reabsorbed from - PCT
- In the absence of ADH, 88% of water is reabsorbed
- In the presence of ADH, 99% of water is reabsorbed

Free-H_2O clearance

- Solutes are usually dissolved in solvents everywhere & are almost inseparable
- Sometimes solute free H_2O needs to be reabsorbed or eliminated to adjust tonicity.
- Done by kidney @ TAL of LOH & in the CD
- Kidney will keep solute in a minimal vol. of H2O & the solute free H_2O can either be reabsorbed or excreted
  - Urine V = + (solute free H_2O)
    (At any given point of time)
- Hypertonic plasma needs H_2O reabsorption & elimination of concentrated urine – free H_2O clearance will be negative
- Hypotonic plasma - ADH suppressed - diuresis to eliminate solute free H_2O
- Free H_2O clearance will be positive (can go upto 16-18 L/day)

2. **Loop of Henle**

- Descending Limb Some H_2O into interstitium,Na^+ (Bulk flow / solvent drag)
- Thick Ascending Limb

- NKCC Transporter ($Na^+ K^+ 2Cl^-$ Co - transporter)
  - Loop diuretics acts on it
- Impermeable of H_2O
- Fluid reaching the early DCT → hypotonic
  - DILUTING SEGMENT → Thick Ascending Limb

3. **DCT**
- Contains NCC transporter
- Thiazides act on it
- 10% of Na^+ & Cl^- removed
- Removes some H_2O

4. **Collecting Duct**
- Absorbs 10 - 12% of H_2O Under ADH
- CONCENTRATING SEGMENT
- 'P' CELL -PRINCIPLE CELL
- Reabsorbs Na^+
- Secretes K^+
- 'I' INTERCALATED CELL
- Reabsorb K^+
- Secretes HCO^{3-}, H^+
- Buffering cell of Kidney

Glomerular filtrate (Isotonic)
67% Na+
↓ PCT 67% H_2
Still isotonic
TAL of LOH ↓ Na+ removed
↓ H_2O remains same
Hypotonic fluid enters DCT

CD - H_2O under ADH
Hypertonic (Urine / tubular fluid)

TUBULAR / TRANSPORT MAXIMUM (T_{max})
- Maximum rate up to which a substance can be transported across tubule
- Glucose T_{max} → 320 mg / min (373 in males , 303 in females)
- Only substance without transport maximum → Na^+ reabsorption
- K^+ secretion in distal nephron has no transport maximum
  (Value in mg% if in reference to saturation of carriers)

CONCENTRATION OF URINE
- Function of Juxta medullary nephrons (15%)
- Minimum amount of Urine lost
- Achieved by
  1. Hyper osmolarity in medullary interstitium
  2. Role of ADH

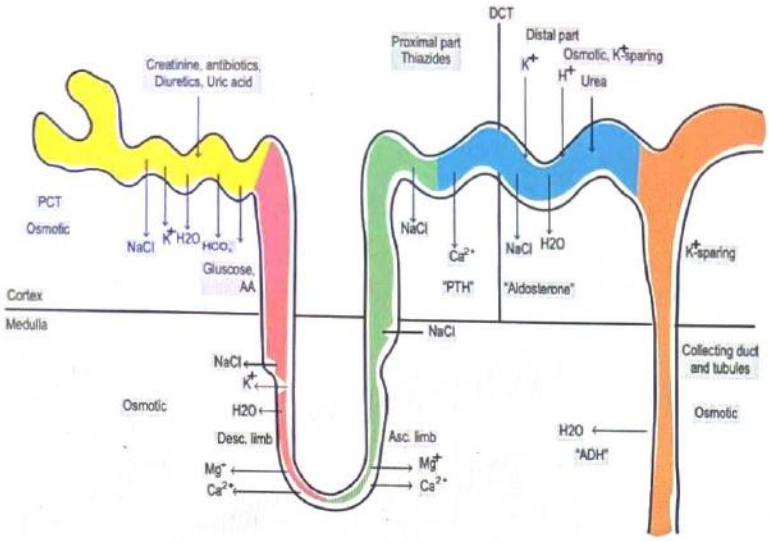
HYPEROSMOLARITY IN MEDULLARY INTERSTITIUM
Achieved By
1. Counter current multiplier
2. Counter current exchanger

Counter Current Multipier
- In the medullary interstitium due to the convoluted structure and the counter current flow, solutes like Na^+ that needs to be retained & solutes like Urea that needs to be excreted are temporarily held to create hyper tonicity.

Multiplier Mechanism
- Starts at thick ascending Limb of LH
- NKCC co-transporter removes Na^+, K^+, $2Cl^-$ into interstitium
- Impermeable to H_2O
- Cl^- being the anion, creates gradient for Na^+ followed by H_2O, hence is of maximum importance
- Tubular fluid is hypotonic (≈ 150 mOsm/L) & Interstitium is hypertonic (≈ 300 mOsm/L)
- At TAL
  - Tubular fluid – 200
  - Interstitium – 400

- Horizontal osmotic gradient → 1 : 2
- Vertical osmotic gradient → 1 : 4
- Max. osmolarity achived at tip of LH - 1200 mos/L
- Max. concentration of urine → 1200 mosm/L at CD
- Urea contributes to 40% of hyperosmolarity
- H_2O moves from descending Limb to attain osmotic equilibrium

UREA
- LOH is impermeable to Urea. In inner medullary CD, is where Urea is 1st taken into interstitium
- Urea transported via UT_1, UT_2
- Urea transport is under the influence of ADH
- Contributes to 40% of interstitial osmolarity
- Recycled & excreted in a concentrated manner
- Urea removes the threat to hyper tonicity due to movement of H_2O
- Urea is highly diffusible (40-50% contribution to hyper tonicity. Remaining- Na^+)



Countercurrent Exchange (for maintenance of the hyper tonicity)

- VASA RECTA (Blood vessels)
- Responsible for counter current Exchange
- Do not actively contribute to hyperosmolarity but prevents its dissipation
- Blood flow is sluggish (if ↑ BF, the solutes could be washed away)
- Blood collects Na^+, K^+, Cl^- & gives out H_2O as it moves down in descending limb
- Hyper osmolarity maintained at tip (maximum)

Blood gives Na^+, K^+, Cl^- & collects H_2O while it moves up in ascending Limb & becomes hypotonic:

1. Maximum concentraed Urine → 1200 mosm /L (4X the normal)
2. Most hypotonic urine → 50 mosm/L
3. At least Avg. 600 mosm of solutes to be excreted by healthy individual daily
4. OBLIGATORY URINE OUTPUT (0.5 L/day)
   - For a young adult, minimum urine output required to excrete at least 600 mosm/ day of solutes of urine is concentrated maximally
5. Oliguria → < 400 ml / day
   Anuria → < 100 ml/day
6. Max. urine output with most hypotonic Urine → 18 L / Day

- If 50 mOsm in 1L therefore 600 mOsm / day → 12 L / Day
- Without ADH - can ↑upto 18 L / Day

Bladder

- Urine brought to bladder with help of ureteric reflex which has pacemakers at the upper part of ureter

Innervation
Micturition

- mainly under Para Sympathetic control (S-2,3,4)
- Forms REFLEX ARC
- Sympathetic innervations not for micturition but carries pain sensation
  (bladder over distention)
- PUDENDAL NERVE
- Nucleus – Onuf's
- Somatic nerve
- Controls external urethral sphincter

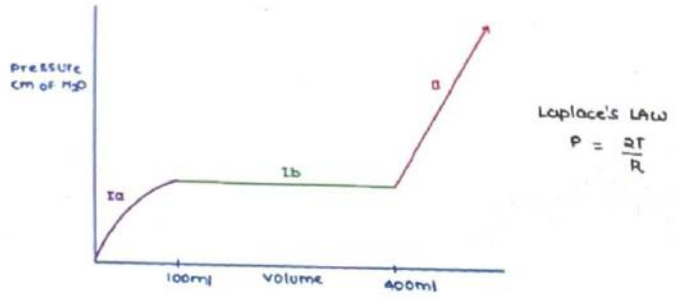
- BRAIN STEM - Pontine center
- BARRINGTON'S MICTURITION CENTER
  - For facilitation or inhibition of reflex arc
  - Micturition reflexes → Barrington's reflexes

Cerebral Cortex

- Para central lobule of frontal lobe has cortical voluntary center for micturition
- Predominanty inhibitory to external urethral sphincter

Bladder fills
↓
Stretch sensed by proprioceptors in bladder wall
↓
Signals sent to SC & higher center
↓ If times and place is convenient
Pontine reflex arc is facilitated
↓
Contraction of detrusor muscle (1st event in micturition)
↓
Self regenerative so impulse becomes stronger
↓
Relaxation of external urethral center
↓
Drops of Urine reach posterior urethra
↓
Wall stretched & reflex strengthened
↓
Bladder emptied

CYSTOMETROGRAM



1. 50 ml → Residual volume
2. 150 ml → First reflex from Bladder wall
3. 250 ml → First desire
4. > 400-450ml → Urgency
5. > 600 ml → Painful urgency
6. 800 - 600 ml → Physiological capacity
7. 900 ml → Anatomical capacity

Lesions

- If Afferents From Bladder are cut
- Transection above S_2,
- Reflex arc intact
- Higher up transection in spinal cord

- Lesion b/w voluntary centre & Brain stem

- Atonic bladder
- Autonomous bladder (some urine is enough to initiate micturition)
- Overflow incontinence (initial tone loss - shock)
  ↓
  Sphincter regains control but bladder will be flaccid
  ↓
  When intravesicular pressure is high enough
  ↓
  Overflow incontinence
- Urge incontinence (or) Spastic neurogenic bladder (or) Uninhibited bladder & mid stream holding lost

ACID BASE BALANCE

Buffer Systems

1. CHEMICAL (within few sec) → 1st to be activated
2. RESPIRATORY (3 - 12) MIN
3. KIDNEY (> 30 min) → Last to be activated

Chemical Buffers

1. HCO_3^-
2. Phosphate
3. Proteins

HCO^{3-}

- pK_a → 6.1
- Most important & plentiful buffer in ECF

Hb

- Is a buffer of ECF
- Oxy Hb is a good donor
- Deoxy Hb is a good acceptor

Phosphate

- pK_a → 6.8
- Intracellular buffering
- Renal tubular fluids

Proteins

- > 70% of intracellular buffering is by intracellular proteins
- pKa → 7.1 - 7.2

Respiratory Buffers

- Physiological buffers
- 3-12 minutes for full activation
- Metabolic acidosis & alkalosis corrected
- If Respiratory rate is doubled → pH increases by 0.45
- If RR is halved, pH decreases by 0.23
- Stronger buffer in acidic pH

Kidney

1. PHOSPHATE AMMONIA
2. REABSORPTION OF FILTERED HCO_3^-
3. GENERATION OF NEW HCO_3^-

Reabsorption of filtered HCO_3^-

- HCO_3^- → 24 mEq/L
- GFR → 180 L/Day
- P_x x GFR → 4320 mEq/Day (total filtered/time)
- for the reabsorption, 4320 mEq H^+ + 80 m.eq secreted at PCT (4400 mEq/day – total acid output/day)
- 80 mEq → NET ACID OUTPUT
- H^+ Secreted in PCT is along the concentration gradient
- H^+ Secreted in collecting duct is against the conc. gradient (1 : 1000 – maximum concentration in plasma : tubule)
- pH of urine becomes 4:5 (Limiting pH) maximally acidic urine pH is 4:5

TITRATABLE ACIDITY

00:00:00

- New HCO_3^- can be generated by kidney
- 1 glutamine → $2NH_3$ → $2HCO_3^-$
- Acidity buffered in the urine by phosphate
- NH_3 → Buffer for chronic respiratory acidosis
  - pka of NH_3 → 9 (only buffer in alkaline pH)
  - Works by non-ionic diffusion / diffusion trapping
  - ($NH_3 + H^+ \rightarrow NH_4^+$ - ionic form and less diffusible hence, trapped and excreted in Urine)

- Collect the Urine Sample, titrate it with NaOH to bring its pH to 7.4
- This will provide the information about phosphate buffer only

ANION GAP

- LAW OF ELECTRO NEUTRALITY
- No. of Cations = No. of Anions
  $(Na^+) + (K^+) + (\text{unmeasured cations}) = (Cl^-) + (HCO_3^-) + (\text{unmeasured anions})$
  Cations can be measured
- Some of anions can't be measured, creating ANION GAP
- It's a virtual gap
- Measured by:
  $[Na^+] - [(C1^- + HCO_3^-)]$

  141 - (105+24)
  141 - 129
  =12 mEq/L± 4 (for K^+)

CLINICAL QUESTIONS

Q. A 60-year-old patient, a known case of hypertension for 25 years, underwent renal artery Doppler, which showed narrowing and turbulence in the right renal artery. If the radius of the artery is reduced by a third, the resistance increases by_____.

A. 3 times
B. 9 times
C. 25 times
D. 81 times

Answer: D

Solution:

- Flow α $(\Upsilon)^4$ (Flow is directly proportional to 4th power of radius; $\Upsilon \rightarrow$ radius)
- Flow= Pressure difference/Resistance
- Resistance is inversely proportional to Υ^4; $R=8\eta L/\pi\Upsilon^4$ (η is viscosity, L is length, π is pi-3.14, Y is radius)

2 times	16 times
3 times	81 times
4 times	256 times

- This **fourth law of power** enables the arterioles to react to the **nerve signal or chemical signals of the local tissue with only small changes in diameter,** either to almost completely cut off the blood flow to the tissue or to increase a large one in the flow at the other end.

Reference: Guyton & hall's textbook of medical physiology, 13th edition, page 176

LEARNING OBJECTIVES

UNIT 8 ENDOCRINE AND REPRODUCTIVE

INTRODUCTION TO ENDOCRINES

- General concepts of endocrine control
- Facts about insulin like growth factors [IGF]
- Hormone synthesis: general principles
- Mechanisms of hormone action
- Cell membrane Receptors
- GPCR (G- Protein Coupled Receptor)
- Catalytic receptors

ENDOCRINE SYSTEM PART 1

- Adrenal gland
- Steroidogenesis in the adrenal cortex:
- Sympathetic alarm reaction
- Adrenal cortex gland secretion of steroids
- Aldosterone
- Glucocorticoids
- Regulation of secretion of cortisol / glucocorticoids
- Disorders of the cortisol secretion
- Endocrine pancreas: (the regulation of blood glucose)
- Insulin :Structure, synthesis, secretion
- Glucagon
- Somatostatin
- Calcium homeostasis

ENDOCRINE SYSTEM PART 2

- Pituitary gland
- Control of pituitary secretion by hypothalamus
- Cell types of anterior pituitary
- Hormones of posterior pituitary
- SIADH
- Hormones of anterior pituitary
- Regulation of GH secretion
- Disorders of GH secretion
- Thyroid hormones
- Synthesis of thyroid hormone
- Metabolism of thyroid hormones
- Functions of thyroid hormones
- Disorders of thyroid hormones

MALE REPRODUCTIVE SYSTEM

- Male reproductive physiology
- Blood test is barrier
- Spermatogenesis
- Difference between male and female spermatogenesis
- Effect of temperature
- Semen
- Sertoli cells

FEMALE REPRODUCTIVE SYSTEM

- The Ovaries
- The biology of oogenesis: (the formation of ova)
- Folliculogenesis
- The Menstrual Cycle

30 INTRODUCTION TO ENDOCRINES

INTRODUCTION 00:00:30

- In classic endocrine signaling, a hormone secreted by an endocrine gland enters systemic circulation and carries the signal to a distant target tissue.
- In paracrine signaling, a hormone acts on nearby cells without ever passing through the systemic circulation.
- In autocrine regulation, a hormone can act on the cell that itself secretes the hormone.
  - Some paracrine factors-interleukins, PDGF; histamine secreted by ECL cells and acting on the parietal cells of stomach, somatostatin secreted by delta cells of pancreas in regulation of insulin & gluacagon secretion.
- Paraneoplastic syndromes: Hormones are produced by nonendocrine neoplastic cells; the clinical syndromes that results from secretion of these hormones are called paraneoplastic syndromes.
  - E.g. Squamous cell carcinoma of lung is associated with hypercalcemia, which results from the secretion of a protein, called PTH related peptide that mimics the actions of PTH.

3 DIVISIONS OR ARMS OF THE ENDOCRINE SYSTEM 00:05:15

- Dedicated endocrine galnds: They synthesize and secrete the bioactive hormones.
- Non-endocrines organs (their primary function is not endocrine): E.g., Kidney synthesis erythropoietin, GIT produces GI hormones, heart synthesis atrial natriuretic peptide (ANP), etc.
- Cells in various organs that modify inactive precursors or convert less active hormones into more active homones: Eg., Formation of angiotensin II by the action of ACE in the lung, formation of vitamin D_3, by hydroxylation reactions successively in the liver and kidney.

GENERAL CONCEPTS OF ENDOCRINES CONTROL 00:07:51

- Functions of hormones : Most hormones have several different target tissues .Many hormones like thyroid cortisol etc have pleiotropic actions (eg multiple phenotypic effects)on numerous cell types

Chemical nature/structural of the hormones

- Hormones may be peptides, metabolites of single amino acids, or metabolites of cholesterol
  - Peptide hormones, proteins, proteoglycans: The peptide hormone families –
    - → Insulin family: insulin, IGF-I & IGF –II, relaxin,
    - → Glycoprotein family: FSH, LH, TSH, hCG
    - → Growth hormone family: GH, prolactin, hPL,
    - → Secretin family: Secretin, glucagon, VIP, GIP
  - Derivatives of a single amino acids, catecholamines and thyroid hormone are derived from the amino acid tyrosine.
  - Steroids or metabolites of cholesterol: synthesis of steroid hormones (from cholesterol) necessitates a number of enzymatic steps. Only very specialized tissues are capable of the series of enzymatic conversions that are necesasary to make active hormones from the starting materials eg adrenal cortex gland synthesize steroids - glucocorticoids and mineralocorticoids

Peptide and protein hormones vary greatly in isze. E.g., thyrotropin releasing hormone (TRH) is a tripeptide; Human chorionic gonadotropin (hCG) has 243 aminoacid residues.]

HORMONE SYNTHESIS: GENERAL PRINCIPLES 00:11:03

- Peptide hormones: within the cell of the endocrine gland the peptide molecule prepared first is usually a larger precursor called "Preprohormone"; it is cleaved to form "Prohormone"; the further cleavage of this peptide forms the final mature hormone. (e.g, preproinsulin – to – proinsulin – to - insulin). The hormone may not be released immediately into the circulation; it is stored in membrane- bound secretory vesicles of endocrine cells and released on demand. The hormone is released by exocytosis through the regukated secretory pathway .that is , the peptide /protein hormone are not secreted continuosly :They are secreted in response to a stimulus -" stimulus "

Peptide / Protein Hormones	Steroid Hormones
• Not bound to plasma proteins • Have a short t½ • Exception IGF (Insulin like growth factors)	• Bound to plasma proteins • Have longer t ½

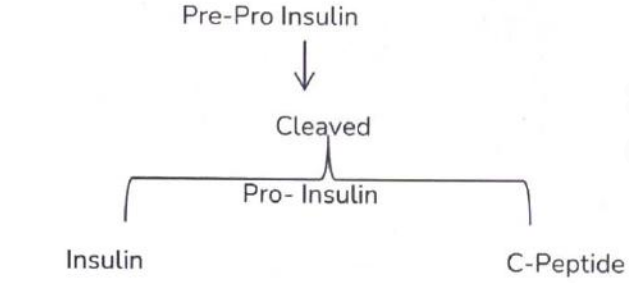
Facts about insulin like growth factors [IGF]

- Types of insulin of Binding proteins [6 IGFBPs] Present in plasma IGFs have longer t ½
- GH has very short t ½ [1-2 min] But in that t ½, it reaches liver & causes IGFs secretion & IGFs exert effect on GH

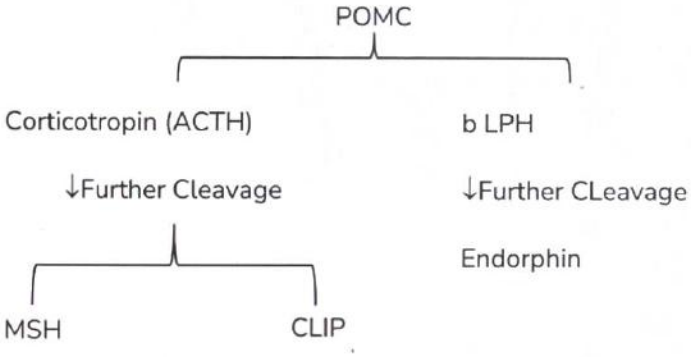
Peptide/Proteins	Steroids
Peripheral Conversion	Peripheral conversion
No further modification once final hormone formed. It acts on the target cells	Further modification occurs before final hormone acts on the target cells Testosterone (active) 5a DHT(active) reduce
Mechanism of action :Peptide/Proteins	**Mechanism of action :Steroids**
Not lipid soluble (can't enter easily) Act via cell membrane receptor	Lipid soluble [enter the cell easily] Act via intracellular receptors [cytoplasmic or nuclear receptors] E.g., Estrogen acts via nuclear R

- Intracellular receptor Progesterone, Estrogen, Testoterone, Cortisol, aldosterone, T3/T4, vitamin D are released immediately into the circulation; it is stored in membrane bound secretory vesicles of endocrine cells and released on demand.

- The hormones are released by exocytosis through the regulated secretory pathway. That is, the peptide/protein hormones are not secreted continuously; they are secreted in response to a stimulus – "Stimulus- secretion coupling".
- Peptides are synthesized in precursor form
  - Insulin + C- peptide produced as a single copy



  - TRH produced as multiple copies [6 copies are formed of TRH]
  - POMC (Pro Opio Melano Cortin) Produces multiple hormones
- IGF: Stimulates linear growth and muscle mass through IGF-1 (stomatomedin C) secretion by liver, increases insulin resistance (diabetogenic).



[Corticotropin like intermediate lobe peptide]

- Intra cytoplasmic receptors of steroids are just primary receptors

Steroids enter the cell easily [Lipid Soluble]
↓ Crossing the lipid Bilayer
Binds with it's receptors
↓
Formation of Hormone receptor complex
↓
H-R complex enter the nucleus
↓
So, anyways steroid hormone enters the nucleus
↓
Attach to specific sites on DNA
(Hormone response elements)
↓
Action of hormone elicited

- Latent period for hormone action- it is the time interval

between the application of stimulus and onset of a response. For instance, oxytocin has among the shortest latent periods; milk ejection occurs in a few seconds. Thyroxine has one of the longest latent periods; its metabolic effects may take as long as 3 days to begin.

- Hormones can circulate either free or bound to plasma proteins. [IGF-I and IGF-II are an exception to this rule: at least plasma proteins bind these peptide growth factors.]
- Forming a complex with a circulating binding protein serves several functions:
  - It provides the blood with a reservoir or pool of the hormone, thus minimizing minute-to minute fluctuations in hormone concentration.
  - It extends the half-life of the hormones in the circulation (as only the free hormone is metabolized by the liver or excreted by the kidney)
- Half-life in circulation: in general, peptide hormones have shorter half-life in circulation; steroids have longer half-life. Epinephrine & norepinephrine have among the shortest half-life (about 10-15 seconds). Thyroxine has a half-life of 7-8 days; 25(OH) vitamins D have a half-life of 15 days.
- Hormones bound to binding proteins in plasma appear to be those whose actions are chronic- in particular, those involving induction of the synthesis of new protein in target tissues. Hormones that play a major acute role in the regulation of body metabolism circulate freely without associated binding proteins.)
- Hormonal rhythms:
  - Circadian (Diurnal) rhythm: (24-hour cycle) – cortisol, GH, prolactin
  - Ultra rhythms: (rhythms with a periodicity of less than 24 hours)

MECHANISMS OF HORMONE ACTION 00:26:46

- All the hormones exert their specific actions on their target cells by binding to specific receptors. The receptor proteins can be divided into two broad categories:
  - Cell membrane receptors – present on the cell membrane,
  - intracellular receptors – present in cytoplasm or nucleus of the target cell.
- The protein/peptide hormones are not lipid- soluble and cannot enter target cells easily. Hence, receptors for these hormones are situated on the cell membranes. Steroids hormones are lipid-soluble; they can cross the cell membranes easily. Their receptors are located inside the cells.
- The protein/peptide hormones (the 'first messengers') exert their effects without entering the target cell. As they combine with the membrane receptors, they activate the so-called "second messengers" within the cells. Second messengers then activate the specific enzymatic machinery within the cell to produce the effect of the hormone..

CELL MEMBRANE RECEPTORS 00:31:04

- Cell membrane receptor Types
  - GPCR
  - Catalytic receptors

GPCR (G- PROTEIN COUPLED - RECEPTOR) 00:34:12

- Aka HETERO TRIMERIC G - PROTEIN [has 3 sub units : a, b,y]
- Has 7 trans membrane segments
  - aka GTP binding protein
  - aka Serpentile receptor
- Ligand + Receptor a sub unit dissociated
- It moves along the membrane & activates EFFECTOR PROTEIN [Adenyl Cyclase / Guanyl Cyclase]
- Adenyl cyclase converts ATP Cyclic AMP [CAMP]
  - CAMP Activates protein kinases Hormonal action ⊕
- Guanyl cyclase converts GTP cyclic GMP [CGMP]
  - CGMP Activates protein kinases Hormonal action ⊕
- CAMP acts as Second messenger For
  - ACTH
  - FSH
  - LH
  - TSH
  - PTH
  - GLUCAGON
  - CATECHOLAMINES
- CGMP acts as second messenger for
  - ANP
  - NO

00:38:34

SECOND MESSENGER SYSTEMS

Adenylyl cyclase-cyclic AMP system	Phospholipase system
ACTH	Angiotensin II
TSH	ADH
FSH & LH	GnRH
PTH	Oxytocin
Glucagon	TRH
Calcitonin, Secretin, Caecholamines	GH-RH

- The plane of the membrane, the a subunit interacts with downstream effectors such as adenylyl cyclase and phospholipases (phospholipase and phospholipase A2)
- There are at least 16 Gα proteins that may activate different types of effector proteins.

G proteins coupled to adenylyl cyclase

- A rather ubiquitous Gα protein is called Gs-α, which stimulates the membrane enzyme adenylyl cyclase. Adenylyl cyclase then acts on the cellular ATP to convert it into the cAMP then acts as the "Second messenger". The cyclic AMP activates an enzyme, protein kinase A (PKA) or cAMP dependent protein kinase). PKA, in turn, catalyzes the phosphorylation of various cellular proteins, ion channels, and transcription factors. This phosphorylation alters the activity or function of the target proteins and eventually leads to a desired cellular response. E.g., parathyroid hormone.
- In some instances, catalytic subunits of PKA may also enter the nucleus, where they phosphorylate and activate the transcription factor, cAMP response element binding protein (CREB protein). Phospho-CREB then increases the transcriptional rate of genes encoding specific enzymes. Synthesis of those specific enzymes will increase.
- Some GPCRs couple to Gi-α, which inhibits adenylyl cyclase. This decreases the levels pf cAMP. E.g., norepinephrine (NE) acting via α_2 receptors, dopamine acting via D_2 receptors.

G proteins coupled to phospholipase C

- A third major hormonal signalling pathway involves receptors coupling to Gq-α, which activates phospholipase C. Phospholipase C acts on the Phosphatidyl inositol biphophate (PIP_2) and generates two second messengers, the di-acyl glycerol (DAG) and inositol triphosphate (IP_3) DAG stimulates protein kinase C (PKC). IP_3 binds to a receptor on the endoplasmic reticulum membrane abd triggers the release Ca^{++} from intracellular stores; Ca^{++} activates calmodulin-dependent protein kinases. E.g, ADH, angiotensin II, TSH.

G protein coupled to phospholipase A2:

- Some peptide hormones (e.g. TRH) activate phospholipase A2. PLA2 then cleaves membrane phospholipids to produce lysophospholipid and arachidonic acid. Arachidonic is converted by certain enzymes, into a variety of biologically active eicosanoids (PGs, prostacyclines, thromboxanes and leukotrienes).
- G protein signalling is terminated by:
  - Intrinsic GTPase activity
  - Desensitization and endocytosis of the receptor.
- GPCR kinases are the membrane receptor proteins are either themselves or part of an enzymatic complex.
- {A category of ion-channel linked receptors may also be included in the 'member receptor' family. It is mostly utilized by neurotransmitters such as Ach. These receptors help regulate the intracellular concentration of specific ions.}

CATALYTIC RECEPTORS

00:44:27

- Receptor tyrosine kinase
  - Receptor for insulin
  - Has 2 sub units α,β
  - Insulin binds with a sub unit, auto phosphorylation occurs
  - βsub unit has the tyrosine kinase activity
- Tyrosine Kinase Associated receptor
  - Receptor for GH
  - Do not have tyrosine kinase activity by itself
  - Tail of receptor a/w tyrosine kinase enzyme
  - Tyrosine kinase activates JAK/STAT Machinery

Many hormones and growth factors bind to cell membrane receptors that themselves have enzymatic activity (or they are a part of an enzyme complex) on the cytoplasmic side of the membrane. 5 classes of such catalytic receptors have been identified:

a. Receptor guanylyl cyclase – when a hormone combines with the receptor, the receptor guanylyl cyclase catalyases the formation of cGMP (cyclic guanosine monophosphate) from the intracellular GTP. E.g., Receptor for atrial natriuretic peptide (ANP) cGMP is used as a second messenger by nitric oxide (NO) and guanylin.

b. Receptor serine/ threonine kinase – when a ligand binds with the receptor, the receptor phosphorylates serine and/or threonine residues on cellular proteins. E.g., receptors for the transforming growth factor (TGF)-β family, which includes the hormones anti-mullerian hormone and inhibin.

c. Receptor tyrosine kinase – when a hormone binds with the receptor, the receptor phosphorylates tyrosine residues on themselves and other proteins. E.g. Receptors for insulin and insulin-like growth factors (IGFs).

d. Tyrosine kinase associated receptor – when a hormone binds with the receptor, the receptor interacts with cytoplasmic (that is, non-membrane-bound) tyrosine

kinases. Eg., receptors for growth hormone (GH), prolactin, erythropoietin, and leptin.

e. Receptor tyrosine phosphate – These receptors cleave phosphate groups from tyrosine groups of cellular proteins.

Signalling from intracellular receptors

- The steroid hormones, thyroid hormones, and vitamins D act through intracellular receptors.
- A steroid hormone enters the cytoplasm of a cell, where it binds with a specific receptor protein.
- The (receptor + hormone) complex then diffuses into or is transported into the nucleus: it binds to specific DNA sequences in the nucleus. Thus DNA sequences in the nucleus. Thus, these intra cellular receptors act as transcriptional regulators.
- There is activation of specific genes to form mRNA.
- The mRNA diffuses into the cytoplasm where it promotes the translation process at the ribosomes to form new proteins: these proteins then function as enzymes or carrier proteins that in turn activate other functions of the cells.
- The glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) are mainly cytoplasmic; the estrogen and progesterone receptors are primarily nuclear. The thyroid hormone receptor (THR) and retinoic acid receptors (RXR) are bound to DNA in the nucleus. The remarkable feature of nuclear receptors is that they bind to specific DNA sequences – called hormone response elements (HREs) in the regulatory region of responsive genes.

Regulation of hormone sensitivity:

- A hormone may decrease the number or affinity of receptors for itself or for another hormone. This is "down-regulation" of receptors.
- A hormone may increase the number or affinity of receptors for itself or for another hormone. This is "up-regulation" of receptors.

Feedback regulation of the hormone secretion:

- Hormone secretions are regulated predominantly by "negative feedback" loops. (Some exceptions- LH-estrogen positive feedback before ovulation; oxytocin release during parturition)

31 ENDOCRINE SYSTEM PART - 1

ADRENAL GLAND

- Hybrid gland ,has an outer part cortex and inner medulla
  - Derived from both neuronal and epithelial tissue
- The gland secretes catecholamines ,adrenaline and NE
- Cortex
  - Zona Glomerulosa : Mineralo corticoids (Aldosterone)
  - Zona Fasciculata : Gluco corticoids
  - Zona Reticularis : Sex Steroids
- Medulla
  - Contain chromaffin cells(pheochromocytes),functional analogues of sympathetic post ganglion fibres of ANS
  - It is an enlarged and specialized sympathetic ganglion ,neural signal to this organ evokes hormonal secretion
  - Adrenal medulla >80% is epinephrine ; <20 % is NE

AA (Tyrosine)
↓
L-dopa
↓
Nor adrenaline
↓
(Only in adrenal medulla)Adrenaline

- The cells of the adrenal medulla are exposed to high local concentrations of cortisol from the cortex.
- Cortisol inhibits neuronal differentiation of the medullary cells so that they fail to form dendrites and axons
- Cortisol induces the expression of the enzyme phenyethenolamines -n-methyl transferase (PNMT)in the catecholamine biosynthetic pathway.
- This enzyme adds a methyl group to NE ,forming the hormone epinephrine.
- Thus most of the circulating epinephrine in blood comes from the adrenal medulla . and about 30% of the circulating NE from the medulla :the remaining 70% is released from postganglionic.

SYMPATHETIC ALARM REACTION 00:07:20

- Adrenal medulla releases the adrenaline during states of emergency. This response to stress is called flight fight reaction.
- In stressful situation, there widespread stimulation of the sympathetic nervous system. Sympathetic nerves to the adrenal medulla will also cause release of adrenaline (and nor adrenaline) from the gland .thus there would be a sympathetic mass discharge.
- Mental or physical stress can thus excite the sympathetic nervous system. States of anxiety, angers, active aggressive states are particularly responsible for such stimulation
- It will have the following effects :
  - Dilatation of pupils
  - Increased heart rate ,cardiac output and blood pressure
  - Vasodilation in skeletal muscles (to increase its blood flow)
  - Bronchodilatation
  - Glycogenolysis;increase in blood glucose (so that the fuel is ready for the muscles and organs)
  - Increased cerebration /mental activity
  - Thus the body is prepared for a vigorous muscular activity ,so as to face the stressful situation
- Applied physiology
  - Pheochromocytoma is the tumour of the chromaffin cells in adrenal medulla
  - There is hypersecretion of catecholamines
  - Patients have sustained hypertension ,also other clinical manifestations

ADRENAL CORTEX GLAND 00:09:57

- Secretion of steroids
- Adrenal cortex gland is the gland is larger in fetus and newborn, compared to adults. The fetal adrenal cortex has an outer "neocortex", about 15% of the total volume of the gland, and inner "fetal zone" which is about 85%. After birth, in about 3 to 12 months, the "fetal zone" undergoes involution and it disappears completely. Only the "neocortex" remains, and functions as the adult adrenal cortex gland. The other gland that is larger in infants than in adult is : pineal gland.
- Adrenal cortex gland secretes steroid hormones. These hormones are synthesized from common precursor cholesterol, and they have CPPP ring.
- The (adult) adrenal cortex gland has 3 zones
  - Zona glomerulosa: It synthesizes and secretes aldosterone. Aldosterone is a mineralocorticoid; it is a steroid that affects the mineral levels of the blood.
  - Zona Fasciculata: It synthesizes and secretes glucocorticoids. Cortisol is the prototype example of the glucocorticoids. They are called glucocorticoids as they increase the blood glucose levels, apart from

the other effects exerted by them.
  - Zona reticularis: It secretes sex steroids.
- Many authors argue that the inner two zones- zona glomerulosa and reticularis should be considered single functional unit. This unit secretes glucocorticoids and sex steroids (androgens and very small amounts of estrogen)}

STEROIDOGENESIS IN THE ADRENAL CORTEX

- All the adrenal steroids are synthesized from cholesterol; cholesterol conversion to pregnenolone is the common step in the synthesis of all steroids.
  - Zona glomerulosa
    → Cholesterol → pregnenolone → progesterone → 11- deoxycorticosterone → corticosterone → 18(OH) → corticosterone → aldosterone.
  - Zona fasciculate:
    → Cholesterol → pregnenolone → progesterone → 17(OH) - progesterone → 11-deoxycortisol → cortisol.
  - Zona reticularis:
    → Cholesterol → pregnenolone → 17(OH) - Pregnenolone DHEA* DHEA sulfate; DHEA → androstenedione.
  - [*DHEA= dehydroepiandrosterone]
- The rate – limiting step in steroidogenesis is the transfer of cholesterol from the outer mitochondrial membrane to the inner mitochondrial membrane. The Steroidogenic Acute Regulatory Protein (StAR protein) is indispensible for this transport.
- The adrenal steroid synthesis involves enzymes that belong to the cytochrome p450 mono-oxidase gene family, commonly referred to as CYPs.

ALDOSTERONE

00:18:05

- It is a mineralocorticoid synthesized by the zona glomerulosa.
- Principal action of aldosterone is: it increases Na^+ retention into the blood.
  - It increases Na+ reabsorption from the principal cells of the late distal tubule and collecting duct.
  - It increases K+ secretion by the principal cells of the late distal tubule and collecting duct.
  - It increases H+ secretion by the intercalated cells of the late distal tubule and collecting duct. (PRINCIPAL CELL Na^+ reabsorption & K^+ secretion; and then INTERCALATED CELL reabsorbs the K^+ and secretes H^+)
- Mechanism of action: {it may be recalled that Na^+ reabsorption by renal tubules occurs in two steps- Na^+ - K^+ pump located at the basolateral membrane removes Na^+ from the tubular cell into the blood. And, Na^+ in tubular lumen moves into the tubular cell via the epithelial Na+ channels (ENaCs) located at the apical membrane}
- Aldosterone increases the expression of the -subunit of the ENaCs; it also increases the stability of the ENaCs in the apical membrane. This action is mediated by the aldosterone- inducible serine / threonine kinase SGK-1 (Nedd 4-2 is a protein that targets ENaCs for degradation; SGK-1) prevent this degradation. Liddle's syndrome- Mutation in ENaCs; Nedd 4-2cm cannot target them for degradation. ENaCs reside in the apical membrane for longer and result in more Na+ retention)
- Aldosterone also promotes Na^+ reabsorption by increasing the activity of Na^+ - K^+ pump in the basolateral membrane.
- The excretion of K+ is linked to the reabsorption of Na+ ; ENaCs and Na+ - K+ pump establish the electrochemical gradients for apical secretion of K+. Aldosterone also increases gene expression of the renal outer medullary K+ channel (ROMK channel). Thus, aldosterone promotes K+ secretion into the distal nephron and its excretion.
- Stimulation of aldosterone secretion- angiotensin II, extracellular K+ acute rise in ACTH
- Inhibitors of aldosterone secretion – ANP, chronic rise in ACTH.
- Renin-angiotensin system regulates the aldosterone secretion. Juxtaglomerular (JG) cells in the kidney releases renin in response to a decrease in blood pressure in the afferent arteriole. Also, decreased volume and decreased delivery of Na^+ to the macula densa cells cause these cells to set up a single for JG cells to release renin. Renin acts enzymatically on angiotensinogen in blood, to form angiotensin I. angiotensin I is then converted to angiotensin II by the action of angiotensin converting enzyme (ACE) in the lungs.
- Release of aldosterone : Angiotensin II binds to the Gq-coupled AT1 receptor on the zona glomerulosa cells to cause release of aldosterone.
- Synthesis of aldosterone: Angiotensin II increases expression of StAR steroidogenic acute regulatory protein) and CYP11B2 (aldosterone synthase) (increased ECF K^+ and acute rise in ACTH are the other two stimuli for aldosterone secretion)
- Increased extracellular K^+ → depolarization of the membranes of zona glomerulosa cells opening of voltage – sensitive Ca^{++} channels → Ca++ influx causes aldosterone to be secreted

Applied physiology

- Hypokalemia : Excess aldosterone secretion will lead to

excess secretion of K+ by renal tubules; excess excretion of K+ results in hypokalemia.

- Alkalosis: Hyperaldosteronism will cause excess secretion of H^+ into renal tubules, Excess elimination of H+ will result in alkalosis.

GLUCOCORTICOIDS

00:32:12

- Raise blood glucose; suppress inflammation, fight stress

Introduction

- They are the steroids that raise blood glucose
- Cortisol is the principal / prototype glucorcorticoid.

Transport of cortisol

- Circulating cortisol is bound to corticosteroid – binding globulin (CBG), also called transcortin (90%), and albumin (5% to 7%)

Physiologic effects of cortisol:

- Metabolic effects: (Hyperglycemia; glucose derived from non- carbohydrate sources, thus breakdown of proteins and fats.)
- On carbohydrate metabolism: GLUCONEOGENESIS
  - Cortisol is an anti-insulin hormone. It causes hyperglycemia and insulin assistance.
  - The principle hyperglycemic action of cortisol is by gluconeogenesis. This occurs by protein catabolism / breakdown and mobilization of amino acids- to form glucose.
  - It also causes glucose intolerance; blocking glucose transport in muscle and adipose tissue. It cause insulin exhaustion and eventual "disteroid / adrenal diabetes".

- On protein metabolism: (breakdown, for gluconeogenesis)
  - For gluconeogenesis, proteins are broken down from skeletal muscle. Amino acids are released into the blood. Most important glucogenic amino acid is alamine.
  - Also, protein synthesis is inhibited – antianabolic effect.

- On fat metabolism: (lipolysis, mobilization of fats)
  - Gluconeogenesis from fats; fats are broken down and glycerol provides substrate for glucose formation.
  - Mobilization of fats from adipose tissue. This leads to characteristic distribution of fat in the central axis of the body- "centripetal"
    - → Deposition of fat on the face- "moon face"
    - → In the supracapsular region – "buffalo hump"
    - → Protuberant belly

Non – metabolic effects

- Cortisol is Anti-Inflammatory, Anti-Allergic, Immunosuppressive, and Anti- Stress.
- Ani-inflammatory effects:

{Inflammation is the response of tissues to any type of injury. There is increased capillary permeability, migration of WBCs, release of proteolytic enzymes, etc. It interferes with healing}

  - Cortisol stabilizes lysosomal membranes, thereby inhibiting the release of proteolytic enzymes.
  - Prevent migration of fluid and WBCs out of capillaries
- Immunosuppressive and anti- allergic action:
  - Cortisol reduces the actions of lymphocytes, and decreases the number of circulating T-lymphocytes.
  - By immunosuppression, it also exerts anti – allergic action. It decreases the release of histamine.
  - It also reduces the number of circulating eosinbophism

Action on connective tissue

- Cortisol inhibits fibroblast proliferation and collagen formation
- Stress adaptation:
  - Cortisol allows the human to adapt to various types of stress (trauma, infection, etc). It is known to stimulate sympathetic activity. It enhances catecholamine synthesis.
- Cardiovascular effects:
  - Cortisol increases the blood pressure. It enhances the vasopressor effect of norepinephrine.
- CNS effects
  - Cortisol may cause euphoria, restlessness, and psychosis.
- Gastric effects
  - Cortisol increases the acid flow in the stomach, and it decreases the mucosal cell proliferation. This may result in peptic ulcers in stomach.
- During fetal development
  - Cortisol is required for normal development of CNS, skin, G.I. tract, and lungs. Differentiation and maturation of type II pneumocytes in lungs will promote surfactant production during late gestation.

REGULATION OF SECRETION OF CORTISOL / GLUCOCORTICOIDS

00:43:50

- The most important regulator of the cortisol secretion is the ACTH (corticotropin).
- Most important action of ACTH is to stimulate conversion of cholesterol to pregnenolone.
- ACTH secretion is controlled by the corticotrophin releasing hormone (CRH) from the hypothalamus.
- ACTH secretion is increased when body faces stress.

- ACTH secretion shows a circadian rhythm; highest levels in blood at 5 A.M. and lowest level at 5 P.M. Hence, even the cortisol levels are highest in the early morning and lowest in the evening.
- Negative feedback inhibition: Circulating cortisol inhibits further secretion of ACTH and CRF.

DISORDERS OF THE CORTISOL SECRETION

00:47:04

- Hypersecretion- Cushing's syndrome
- Hyposecretion- Addison's disease
- Cushing's Syndrome:
  - Prolonged excessive production of cortisol; may result from an adrenal tumor or adrenal hyperplasia.
  - Features are mainly those of protein breakdown and fat mobilization and deposition.
  - Acne and hirsuitism (excessive hairness). Acne are due to increased activity of the sebaceous glands.
  - Centripetal redistribution of fat leads to
    → "Moon face" (face becomes rounded due to fat deposition)
    → "Buffalo hump" (fat deposition in the supracapsular region)
    → Protuberant belly (fat over the abdomen)
  - Protein breakdown leads to:
    → Purple striae (striations) over the abdomen, thighs; due to tendency to Cushing (easy breakdown of the vascular connective tissue)
    → Thinning of bones
  - The patient will have hyperglycemia and eventual diabetes.
  - The patient will be hypertensive
- Addison's disease
  - It is chronic adrenal cortex insufficiency; there is hyposecretion of the cortisol.
  - It may result from bilateral destruction of the adrenal cortex, or failure of the anterior pituitary.
  - The outstanding clinical features are: muscular weakness and easy fatiguability; pigmentation of the skin and buccal mucosa
  - Loss of weight, dehydration
  - Hypotension
  - Hypoglycemia
  - Anorexia, nausea and vomiting
  - Decreased ability to withstand trauma, infections, hemorrhage, and other "stress"
  - Reason of pigmentation: cortisol secretion is abolished in Addison's disease. Then, by negative feedback, ACTH secretion by pituitary is increased. Since ACTH has MSH- like activity, it stimulates melanin production, resulting in pigmentation.

ENDOCRINE PANCREAS: (THE REGULATION OF BLOOD GLUCOSE)

00:52:32

- Pancreas is a mixed gland. It serves exocrine function of secreting enzymes for digestion of all the major nutrients. The endocrine function of the pancreas is regulation of blood sugar.
- The endocrine pancreas (2% of total pancreatic mass) comprises of a cluster of specialized endocrine cells – the islets of Langerhans. These islets have 3 cells types:

• Alpha (α) cell (10%)	• Outer rim of islet	• Glucagon
• Beta (β) cell (75.3%)	• Center of islet	• Insulin
• Delta (δ) cell (5%)	• Dispersed, mostly near periphery of islet	• Somatostatin
• F cell	• Posterior portion of the head of pancreas	• Pancreatic polypeptide

- Functional islets appear at the beginning of 3rd trimester of gestation.
- Blood flow through the islets passes from β cells to cells and cells . Hence, the first cells affected by circulating insulin are the cells, in which insulin inhibits glucagon secretion.

INSULIN -THE ANABOLIC HORMONE

00:56:09

- Insulin is the primary anabolic hormone; it promotes glucose uptake and utilization by muscle and adipose tissue. It promotes glycogen formation from glucose, and glycogen storage in liver and muscle. It also promotes protein and TG synthesis, and inhibits lipolysis and protein degradation.
- Insulin is the primary anabolic hormone; it promotes glucose uptake and utilization by muscle and adipose tissue. It promotes glycogen formation from glucose, and glycogen storage in liver and muscle. It also promotes protein and TG synthesis, and inhibits lipolysis and protein degradation. Absolute or relative lack of insulin, or resistance to insulin action result in diabetes mellitus.

Structure, synthesis, secretion

- Insulin is a protein hormone; it belongs to a gene family

that also includes IGF-I and IGF-II, and relaxin.

- Synthesized as a precursor preproinsulin; cleaved to form proinsulin. Proinsulin = insulin + C peptide (connecting peptide; 31 amino acids). It is cleaved to form insulin. Proinsulin has 7-8% of the biological activity of insulin; C peptide has no known biological activity.
- Insulin = 1 a chain + 1 B chain; chains connected by a disulfide bridge. Insulin is stored in secretory granules in zinc-bound crystals. Granules release equimolar amounts of insulin and C peptide into the blood. Measurement of C peptide in the blood can be used to quantify
- Half-life of insulin ~ 5-8 min
- The primary stimulus for insulin secretion is glucose. Glucose enters the B cells of islets by the facilitated diffusion via GLUT-2 transporter. Within the B cell, glucose is phosphorylated to glucose-6-phosphate by the enzyme glucokinase. Glucokinase is said to be the "glucose sensor" of the B cell, because rate of glucose entry is correlated to the rate of glucose phosphorylation, which in turn, is directly related to insulin secretion.
- Glucose-6-phosphate is metabolized by B cells; it increases the intracellular ATP. This causes closure of an ATP-sensitive k channel. This results in depolarization of the B cell membrane, which opens voltage gated Cat channels. Cal entry via these channels into B cell leads to insulin release from the secretory granules by exocytosis.
- The ATP-sensitive K' channel is a protein complex. It contains a subunit called SUR which is activated by sulfonylurea drugs. These drugs are used as hypoglycemic agents in impaired B-cell function.

Insulin secretion stimulated by:	Insulin secretion stimulated by:
• Hyperglycemia	• ↓blood glucose
• ↑amino acids	• ↓amino acids
• ↑FFAs	• ↓FFAs
• GIP	• Somatostatin
• CCK	• Leptin
• Secretin	• Epinephrine(via alpha receptor)
• VIP	
• Gastrin	
• GLP-1	
• Epinephrine(via beta receptor)	
• Parasympathetic stimulation	

Insulin receptor

- It belongs to the receptor tyrosine kinase (RTK) family. (Other members of the family are receptors for IGFs, and some other growth factors.} The receptor is present in the cell membrane; it has two subunits - a and B. The a subunit is on the external aspect of the membrane and has hormone-binding sites. The B subunit spans the membrane and has tyrosine kinase on the cytoplasmic aspect of the membrane. Binding of insulin to the a-subunit leads to autophosphorylation; Beta subunits cross-phosphorylate each other on 3 tyrosine residues in the intracellular portion of the receptor; forming phosphotyrosine residues).
- The phosphotyrosine residues then cause phosphorylation of tyrosine of a host of proteins such as: (i) Insulin receptor substrates (IRS) family, (ii) Gab-1, (iii) Shc, (iii) p62dok, (iv) C-Cbl, (v) SIRP signal regulatory protein} family members, and (vi) APS {adaptor protein containing a pleckstrin homology [PH] and Src-homology-2 [SH2] domain}
- Termination of insulin receptor activity - Internalization and dephosphorylation by protein tyrosine phosphatases terminates the activity of the insulin receptor. Protein tyrosine phosphatase 1B (PTP and leucocyte antigen-related (LAR) phosphatases have been shown attenuate insulin receptor activity. Another possible mechanism is th activation of the "suppressor of cytokine signaling" (SOCS) family of proteins, which reduces activity and/or levels of the insulin receptor insulin receptor substrate proteins.
- In type 2 diabetes mellitus, insulin resistance has been reported to due to elevated levels of both PTP1B and LAR.

Metabolic actions of insulin:

- Ingestion of a mixed meal stimulates release of insulin from the B cells. Insulin then inhibits glucagon release from the adjacent a cel Insulin: glucagon ratio increases in hepatic portal vein as it enters liver.
- In the liver:
  - Promotes glucose uptake and glucose utilization by the liver
  - promotes conversion of glucose into its storage form (glycogen) -glycogenesis, decreases breakdown of glycogen (glycogenolysis).
  - Promotes glycolysis, decreases gluconeogenesis
- In adipose tissue:
  - Promotes glucose uptake in fat cells by increasing GLUT-4 availability.
  - Lipogenesis & anti-lipolysis: Insulin stimulates expression of lipoprotein lipase enzyme. There is increased fatty acid synthesis and formation of very low density lipoproteins (VLDLs). Fatty acids enter

adiocytes where they are stored as triglycerides (TG).
  - Decreases lipolysis
- In skeletal muscle:
  - Insulin increases glucose intake hy increasing the availability of GLUT.4 transporter. creases glucose utilization, increases glycogenesis, decreases glycogenolysis Increases amino acid uptake and protein synthesis; decreases protein breakdown. Insulin exerts its actions by increasing expression of the enzymes.
  - For instance glucokinase for glucose uptake and utilization, glycogen synthase for conversion of glucose into glycogen, etc. As glucose and potassium are cotransported simultaneously into the cells, insulin also promotes potassium entry into the cells. This action may be utilized to push the K' from blood into cells and reduce its levels in hyperkalemia.

DIABETES MELLITUS (DM)

01:23:06

- It is a disease in which there is absolute or relative deficiency of insulin or pladdersemce to the insulin action (or both). -
- The most characteristic feature of DM is hyperglycemia (raised blood glucose. It may also result in glycosuria (presence of glucose in urine).
- Type IDM, also called insulin-dependent diabetes mellitus (IDDM), is characterized by destruction of B cells (mostly due to an autoimmune mechanism). The classic triad of symptoms may be seen - "polyuria, polydipsia, and polyphagia",
  - Hyperglycemia leads to increased glucose load to renal tubules; tubular glucose may cause "osmotic diuresis" - polyuria. The diuresis with loss of body fluids activates thirst mechanism - polydipsia (excessive thirst). In the absence of the anabolic hormone insulin, there is a catabolic state characterized by weight loss and muscle wasting. It causes an increase in appetite - polyphagia.
  - Absolute lack of insulin results in diabetic ketoacidosis (DKA). Fatty acid metabolism, in the presence of very low intracellular glucose, would result in the formation of the ketone bodies. Many of these ketone bodies are acids; they decrease the plasma pH (acidosis).
- Type II DM, also called non-insulin-dependent diabetes mellitus (NIDDM), is characterized by abnormal insulin resistance of the target tissues. The resistance to insulin action is particularly common in obese individuals.
  - As a consequence of insulin resistance, initially there is reactive hyperinsulinemia. Ultimately, there is relative hypoinsulinemia inadequate release of insulin to compensate for the end-organ resistance). It may be a result of 6 cell dysfunction, due to pancreatic exhaustion, amylin deposition, or other reasons.

GLUCAGON

01:29:12

- 29-amino acid
- Member of the secretin gene family.
- It is secreted by the a cells of the pancreatic islets; it is involved in the regulation of blood glucose homeostasis
- Glucagon increases the blood glucose levels; thus its effects are opposite to those of insulin.
- Glucagon acts on the liver and adipose tissue; its actions are mediated by the second messenger CAMP. (short half-life 6 minutes) Hypoglycemia stimulates the glucagon secretion; glucagon increases blood glucose. It has following actions:
  - Increases glycogenolysis (glycogen breakdown) and gluconeogenesis(glucose formation from non-carbohydrate sources).
  - Stimulates lipolysis in adipose tissue; increases free fatty acids in blood.Glucagon causes inhibition of glucose utilization by peripheral tissues.
  - Glucagon is ketogenic; it forms ketoacids from acetyl CoA. (ketones are an important source of fuel for muscle cells and heart cells during times of starvation, sparing blood glucose for other tissues that are obligate glucose users.)
  - Insulin: glucagon ratio (1/G) determines metabolic status. Since most of the effects of insulin and glucagon are opposite to each other, 1/6 ratio determines the net physiological response.
    - → In the fed state: Molar 1/6 ratio is approximately 30.
    - → After overnight fast: 1/6 ratio falls to about 2.
    - → In prolonged fasting: 1/6 ratio may be as low as 0.5.

SOMATOSTATIN

01:34:31

- Secreted by the 6 cells of pancreatic islets. (also secreted by hypothalamus)
- "D" cells or 6 cells are also present in the pyloric antrum of stomach; they secrete somatostatin which acts in a paracrine fashion. When the antral pH falls below 3, somatostatin is secreted by "D" cells. It then acts on neighbouring "G" cells and inhibits gastrin secretion.) "D" cells in the oxyntic region of stomach directly inhibit parietal cell (HCl) secretion. It inhibits insulin and glucagon secretion. It also inhibits secretion of GH, gastrin, VIP, and TSH.

CALCIUM HOMEOSTASIS

01:36:10

- Regulation of Cat in the body{Parathyroid hormone,

calcitonin, and vitamin D

- Cal 2+ distribution: More than 99% of the total body Cal is stored in the skeleton. The skeleton of a 70-kg adult contains about 1000 gm of Cal; and about 1 gm in the extracellular pool.
- Plasma Cal = about 10 mg%
- Cal in plasma:
  - Ionized or free (45%)
  - Non-ionized or bound (55%): {Of this bound form - 45% is bound to protein (mainly albumin), and 10% is complexed with ions (citrates, HPO4", etc) The sum of the free/ionized and complexed Cal+ (55%) forms the diffusible fraction of calcium; the protein-bound form (45%) ca constitutes the non-diffusible fraction.
    - → PTH, calcitonin, and vitamin D regulate the ionized Cal in the serum.
    - → About 1% of the body's calcium pool consists of young (labile) bone. It is readily exchangeable. That is, it provides an immediate reserve for calcium, in case there is a sudden decrease in blood Ca. Remaining 99% calcium of the Ca pool is not readily exchangeable. It is stable (mature) bone.
    - → Bone Ca is found in the form of hydroxyapatite crystals.
    - → A large surface area is provided by the microcrystalline structure of bone.
    - → Calcium: phosphorus ratio in bone is about 1.7:1.
- Calcium regulation in blood
  - It involves three tissues: bone, kidney, and intestine. It involves three hormones: PTH, calcitonin, and Vitamin D.
  - It involves three cell types: osteoblasts, osteoclasts, and osteocytes. Osteoblasts: cause deposition of new bone, thus they are bone forming cells. They would deposit the calcium from blood onto the bones.
  - Osteoclasts: cause resorption of bone, thus they remove bone constituents. They would move bone calcium into blood.
- Hormonal control of Ca metabolism:
  - There is no role played by the pituitary gland in calcium homeostasis.
    - → Parathyroid hormone (PTH): (increases blood calcium)There are four parathyroid glands located on the posterior aspect of thenThyroid gland. They secrete the parathyroid hormone (PTH) or aftormone. PTH is essential for life; its absence will lead to severe hypocalcemia. The resulting laryngeal spasm will be fatal.
    - → The PTH is released by the gland when the blood calcium falls. It then increases the blood calcium.
- Mechanism:
  - The PTH receptor: It belongs to GPCR superfamily; spans the membrane 7 times. Because it also binds PTH-related peptide (PTHP)", the receptor is called PTH/PTHTP receptor.
  - The PTH/PTHTP receptor is expressed on osteoblasts in bone and in the renal tubules.
  - Binding of PTH to its receptor increases CAMP. - PTH directly stimulates osteoblastic activity and stimulates osteoclastic activity indirectly through osteoblast-derived paracrine factors.
  - Osteoclasts cause bone resorption; thus Ca from the bone is removed, and is released into blood.
  - PTH exerts its effects on the bone, kidneys, and intestine. a. On the bone:
  - PTH causes increased mobilization of Ca from the bone. This is bone resorption or bone dissolution. Calcium from the bone will be released into the blood, thus increasing blood calcium.Regulation of bone remodeling by PTH requires normal levels ofvit.D.
  - On the kidney: (calcium reabsorbed from tubules into blood) - PTH acts on renal tubules, to cause reabsorption of Ca" from the tubulesinto the blood. This occurs from the distal nephron. Mechanism: It is by active transport. PTH increases tubular maximum (Tm) for calcium.
  - PTH also inhibits phosphate reabsorption from the proximal tubules, by inhibiting the activity of the sodium-dependent phosphate transporter (NPT-2). This leads to phosphate excretion in the urine-phosphaturia. -
  - The decrease in blood phosphate is important in the context of calcium homeostasis. At normal plasma concentrations, calcium and phosphate are at or near chemical saturation levels. If PTH were to increase both calcium and phosphate levels, they would crystallize in bone and soft tissues (as calcium phosphate), and the required increase in plasma calcium concentration would not occur.
- On the intestine: (Ca++ absorption from the gut)
  - Calcium and phosphate absorption from the intestine is increased by the PTH. This occurs mainly by facilitated diffusion.
  - Ca absorption increased by PTH is an indirect effect. PTH promotes synthesis of vitamin D, by stimulating 1a-hydroxylase (CYP1a) expression in the proximal renal tubule. Vitamin D, in turn, increases Ca absorption from the gut, and also amplifies the effect of PTH.
  - PTHrP - The PTH-related peptide is synthesized by a variety of normal and malignant tissues. The PTH receptor on bone and kidney recognizes peptide; PTHrP mimics the actions of PTH on these tissues. Normal physiologic function of PTHTP is not defined. Many tumors are capable of manufacturing and

secreting PTHIP. Patients with such tumors exhibit severe hypercalcemia.

- Hypoparathyroidism: This may occur due to removal of or damage to parathyroid glands during a surgery (such as thyroidectomy). The symptoms are due to reduction of serum Ca; and there are increased phosphate levels.
- Tetany: (decreased serum calcium) - It exhibits increased neuromuscular excitability.Low serum Catt results in decreased neuromuscular threshold. A single stimulus may produce repetitive responses; there is also spontaneous neuromuscular discharge. The common manifestation of tetany is "carpopedal spasm". The flexion at the wrist, fingers are extended, thumb is drawn on to the palm. ("obstetrician's hand")
- Tousseau's sign: When a BP cuff is applied to the arm, and pressure is- raised, the capopedal spasm is manifested.
- Chvostek's sign: Even a faint tap over the angle of mandible causes facial muscles go into spasm; it is due to stimulation of hyperirritable facial nerve.
- Symptoms of tetany may begin to appear when the serum Ca falls upto 7 mg%.
- Death may occur when the serum Cat* falls below 6 mg%. - Reason of death in tetany: It causes spasm of laryngeal muscles, and spasm of thoracic/respiratory muscles.
- Apart from parathyroid deficiency, the other cause of clinical tetany is ALKALOSIS. For instance, hyperventilation washes out CO2 and H + from blood. It results in alkalosis. Increased alkalis then increase plasma protein jonization, which in turn reduce the free Ca in plasma.
- Hypomagnesemia can also cause hypoparathyroidism.

- Calcitonin: (decreases blood calcium)
  - In the thyroid gland, out of the follicles, there are parafollcells..These "C" cells secrete calcitonin or thyrocalcitonin.
  - It reduces blood calcium. Calcitonin secretion is stimulated when the blood calcium is increased.
  - Calcitonin exerts its effect on 3 tissues: bone, intestine, and kidney
  - On the bone -calcitonin receptor is present on the osteoclasts.Calcitonin inhibits osteoclastic activity :this will inhibit bone resorption.it slows the rate of bone turnover
    - → Calcium from blood will be deposited on the bone
  - On the intestine
    - → Calcium inhibits the intestinal (jejunal) absorption of dietary ca and phosphate
  - On the kidney
    - → Calcitonin promotes urinary excretion of calcium ,phosphate and sodium .
    - → It also decreases the enzyme which forms vitamin d at the final step in the kidney(less vitamin D, less intestinal absorption of calcium)
    - → There are no definitive complications from calcitonin deficiency or excess in humans . Calcitonin doesnt seem to have an important.

Paget's disease:

- Excessive bone turnover that is driven by large, bizarre osteoclasts.
- Vitamin D: (although it is called vitamin, it is a steroid hormone.}
  - Steroid with 27 carbon atoms; it is the largest steroid hormone. - The active metabolites of vitamin D are calcidiol and calcitriol; they exert the effects of vitamin D.
- Synthesis of active vitamin D3: (calcitriol)
  - In the epidermis (skin), there is a previtamin: "7 - dehydrocholesterol". When sun's u.v. rays fall on the skin, this 7-dehydrocholesterol is converted into "cholecalciferol".
  - Cholecalciferol goes to liver. Here, a hydroxyl (OH) group is attached to 25th carbon atom. This forms 25-OH) cholecalciferol.
  - Actions of vitamin D: (increases blood calcium, but also causes bone deposition)
  - Vitamin D acts together with the PTH. Thus, their actions are mostly synergistic. It is to increase the blood calcium. -
  - On the bone: along with PTH, it causes mobilization of Calcium from bone into the blood. However, this action also fosters bone deposition (paradoxically)
  - On the intestine: increased calcium absorption from the intestine. PTH enhances this action; and this is the principal action of vitamin D.
  - On the kidney: It causes reabsorption of Cat* from the distal tubules. But unlike PTH, it does not cause phospahturia. It causes phosphates also to be reabsorbed.
- Applied physiology:
  - Vitamin D deficiency in childhood causes rickets; and in adults its deficiency causes osteomalacia. There is demineralization and softening of bones.

CLINICAL QUESTIONS

Q. Laron syndrome (LS) is an autosomal recessive disorder. Affected individuals classically present with short stature between -4 to -10 standard deviations below median height, obesity, craniofacial abnormalities, micropenis, low blood sugar, and low serum IGF-1 despite elevated basal serum GH. True about Laron dwarfism is?

A. Growth hormone deficiency
B. Growth hormone insensitivity
C. Plasma IGF-1 is markedly increased
D. Plasma IGF-BP3 at normal levels

Answer: B

Solution:
Laron dwarfism:

- Plasma GH is normal or elevated.
- **GH receptors** are **unresponsive** as a result of loss-of-function mutations of the gene for the receptors.
- **Results** in **growth hormone insensitivity.**
- Plasma **IGF-I** is **markedly reduced**, along with **IGFBP-3** (IGF-binding protein-3).

Rx: With the availability of recombinant IGF-1, it is possible that effective treatment of these children will restore growth.
Reference: Medical Physiology, A Cellular and Molecular Approach, UPDATED SECOND EDITION. Walter F. Boron, Emile L. Boulpaep. Section VIII, The Endocrine System. Chapter 48, Endocrine Regulation of Growth and Body Mass. Pg. 1037.

32 ENDOCRINE SYSTEM PART- 2

PITUITARY GLAND

00:00:30

- Physiologically, the pituitary gland is divisible into two distinct portions: the anterior pituitary, also known as the adenohypophysis, and the posterior pituitary, also known as the neurohypophysis.
- Hormones secreted by the anterior pituitary:
  - Growth hormone (GH): promotes growth
  - Prolactin: promotes mammary gland development and milk production
  - Adrenocorticotropic hormone (ACTH): controls the secretion of the hormones of adrenal cortex gland
  - Thyroid stimulating hormone (TSH): controls the secretion of thyroxine by the thyroid gland
  - Follicle- stimulating hormone (FSH) and
  - leutinizing hormone (LH) :FSH and LH are gonadotropins; control growth of the gonads as well as their reproductive activities
- Hormones secreted by the posterior pituitary
  - Anti diuretic hormone (ADH) :also called vasopressin ; controls the rate of water excretion into the urine
  - Oxytocin :helps in milk ejection during breast feeding and probably helps in delivery of the baby at the end of gestation

CONTROL OF PITUITARY SECRETION BY THE HYPOTHALAMUS

00:01:44

- Posterior pituitary: Secretion from the posterior pituitary is controlled by nerve fibers originating in the hypothalamus and terminating in the posterior pituitary. This is called neuroendocrine control. Examples of hypothalamic "releasing hormones" (RH) that control anterior pituitary hormone secretions GH-RH for growth hormone, GnRH for Gonadotropins, CRH for Corticotropin (ACTH), TRH for Thyrotropin (TSH).
- There are inhibiting hormones for the pituitary hormones, for instance, GH-IH or somatostatin for GH,Prolactin -prolactin inhibitory factor (PIF)

CELL TYPES OF THE ANTERIOR PITUITARY

00:09:17

- Main types of cells:
  - Chromophobe cells, which do not have Stanable granules, and
  - Chromophil cells; contain cytoplasmic granules which take up stain readily
  - Chromophil cells are further divided into:
    - → Acidophil or alpha cells - produce GH and prolactin
    - → (b)Basophil or beta cells - produce FSH, LH, ACTH, and TSH.
- Usually, there is one cell type for each major hormone formed in the anterior pituitary gland.
  - Somatotropes: human growth hormone (hGH or GH)
  - Corticotropes: adrenocorticotropic hormone (ACTH)
  - Thyrotropes: thyroid-stimulating hormone (TSH)
  - Gonadotropes: gonadotropins FSH & LH
  - Lactotropes: prolactin (PRL)
- About 30 to 40% of the anterior pituitary cells are somatotropes, about 20% cells are corticotropes, and remaining cells 3 to 5 % each.

HORMONES OF THE POSTERIOR PITUITARY

00:12:45

- ADH and oxytocin are nonapeptides (nine amino acids).
- These hormones are synthesized as precursor preprohormones by the hypothalamic neurons, in the cell bodies that are located in the supraoptic nuclei and paraventricular nuclei of the hypothalamus.
- The axons of these neurons project to posterior pituitary.
- The hormones, when synthesized or bound to the peptides called neurophysins (ADH + neurophysin I+ oxytocin + neurophysin II). As they are transported down the axon, they are proteolytically cleaved from the neurophysins.
- Free hormones and neurophysins are released from the axon terminals into the circulation. The swollen axonal endings have been termed Herring bodies.
  - "Anti-diuretic hormone (ADH): (also called "vasopressin")
  - Functions/actions:1.The primary function of the ADH is to maintain the normal osmolality of body fluids, by conserving water from the renal tubules. Since it conserves water, it also helps in the regulation of blood volume.2. ADH acts on the blood vessels; it causes vasoconstriction. For this effect,it is also called "vasopressin."
  - Mechanism of ADH action:There are two types of ADH/vasopressin receptors: V1 and V2.
  - V1 receptors are present in the blood vessel walls and they mediate vasoconstriction . V2 receptors are present in the distal tubule and the principal cells of the collecting ducts in the kidneys.

- When ADH acts on these receptors, there is insertion of channel proteins called "aquaporins". Aquaporin II channels allow water reabsorption from distal collecting tubules and the collecting ducts of renal nephron.
- V2 receptor is a GPCR linked to GS-CAMP-PKA pathway.
- It is located o the basal side of the renal tubular cells.
- Signaling via V2 receptor causes insertion of Aquaporin II channels into the apical membrane of the principle cells.
- Aquaporins III and IV are constitutively expressed on the basolateral side of the target cells. Thus, transepithelial flow of water is enhanced via these channels. Water reabsorption decreases the urine flow (antidiuresis); Urine osmolality increases and plasma osmolality decreases by ADH action.
- Physiological stimulus for the release of ADH: o Increased ECF osmolality (most important stimulus), o decreased blood volume and pressure (this stimulus evokes the renin angiotensin-aldosterone axis mainly)
- The osmosensitive neurons in the hypothalamus or circumventricular organs respond to changes in ECF osmolality by shrinkage or swelling Response to the hyperosmolality depends on the nature of the solutes. Solutes such as Na ,sucrose and mannitol do not readily enter osmosensitive cells; they are effective osmoles that would cause water to hove out of the cells by osmosis and cause cellular shrinkage. These cells are more permeable to urea ;hence urea is an effective osmole.
- Another stimulus for ADH release is: large decrease in blood volume. When there is more than 10% decrease in the total circulating blood volume, ADH will be released. Thus, in the second stage of circulatory shock it becomes an important tool in blood volume restoration. ADH action of vasoconstriction may be of consequence in vasodilatory shock
- The regulators of ADH secretion during shock ~ low-pressure "volume receptors" in atria.

- NOTE: Under the conditions of shock, ADH will restore the blood volume at the expense of plasma osmolality. Plasma will become hypotonic due to ADH action. However, this hypotonicity is tolerated so that restoration of blood volume takes precedence.
- Other factors influencing ADH release:
  - Stimulators: Nausea; drugs such as barbiturates, nicotine, opiates.
  - Inhibitors: Alcohol, hormones such as ANP & cortisol.
- Diabetes insipidus: Results from ADH deficiency; it causes excretion of large amounts of hypotonic urine.
- Central diabetes insipidus : lack of ADH
- Nephrogenic diabetes insipidus
  - Plasma ADH normal (or high); resistance to ADH action on renal tubule Psychogenic D.I. (psychogenic polydipsia) compulsive water drinkers; i water is withheld, the ADH secretion increases and urinary flow.

Refer Table 32.1

SIADH (SYNDROME OF INAPPROPRIATE ADH SECRETION)

00:38:04

- In certain kinds of stress (e.g. surgery), there is an excessive release of ADH It results in excretion of hypertonic urine. Pulmonary TB is associated with SIADH. Seen Also in trauma, anaesthesia, pain

Oxytocin

- It is a small peptide hormone. It is synthesized by the paraventricular nucleus of the hypothalamus. And is released from the posterior pituitary gland
- The principal action site of oxytocin is the female breast. Oxytocin stimulates contraction of specialized smooth muscle cells (myoepithelial cells) in the breast.
- This results in transfer of milk from the alveoli of breast glands into the ducts.Milk ejection reflex / milk let down reflex: (An example of "neuroendocrine reflex", in which the afferent limb of the reflex is neural and the efferent limb is hormonal)
- When the baby starts suckling at the nipple, afferent signals from the breasts are sent, via the nerves, to the pituitary gland. The oxytocin released then reaches the breasts and causes ejection of milk. Among all hormones, this reflex has the shortest latency (for the onset of action), a few seconds.
- Oxytocin has another action. It can also stimulate contraction of smooth muscle in the uterus. A non-pregnant uterus does not respond to the oxytocin. However, near the end of pregnancy, the delivery of the baby may be initiated by oxytocin action on the uterus. The process of parturition/delivery occurs by positive feedback mechanism.

HORMONES OF THE ANTERIOR PITUITARY

00:44:40

Prolactin

- It is synthesized by the acidophil cells (lactotropes) in the anterior pituitary gland.
- It has the function of milk synthesis in breast glands in females.
- Prolactin secretion is predominantly under inhibitory control by prolactin inhibiting factor (PIF) from

hypothalamus. Thus, disruption of the pituitary stalk would result in an increase in prolactin level (due to interruption of PIF), but decrease the ACTH, TSH, FSH & LH, and GH (due to interruption of the corresponding hypothalamic releasing hormones for these hormones)

- TRH and hormones of the secretin family have been shown to act as prolactin releasing factors.
- Prolactin secretion is inhibited by dopamine. Thus, dopamine agonists(such as bromocriptine) may be used to inhibit prolactin secretion. Dopamine antagonists (such as tricyclic antidepressant drugs) will increase prolactin secretion.
- Prolactin release also increases in response to stimulation of the mother's nipple by a suckling infant.
- Lactational amenorrhea (absence of menses during lactation and breast feeding) is due to suppression of GnRH by prolactin.

Adrenocorticotropic hormone: (corticotrophin)

- The primary effect of ACTH is to promote the synthesis and secretion of the steroid hormone cortisol from the adrenal cortex gland.
- The secretion of ACTH is controlled by corticotrophin-releasing hormone(CRH) from hypothalamus. It is released mainly in response to body stress.
- ACTH is actually synthesized from a large precursor protein - called pro opio melanocortin (POMC). This protein is cleaved to form ACTH, and beta lipotropin (B-LPH). {During fetal life and pregnancy, the intermediate lobe of the pituitary - a small wedge of tissue between the anterior and posterior lobes - processes the same POMC to yield y-melanocyte stimulating hormone (gamma-MSH), alpha-MSH, corticotropin-like intermediate lobe peptide (CLIP), gamma-LPH, and beta-endorphin.}
- It should be noted that ACTH has 39 amino acids. Alpha-MSH (amino acids 1-13) is cleaved from ACTH. The remaining fragment (amino acids 18-39 will form CLIP. ACTH has MSH-like activity. Keratinocytes in the skin express POMC gene, and they secrete a-MSH normally. Keratinocytes secrete a-MSH in response to U.V. light; this a-MSH then acts via the melanocortin receptor on neighboring melanocytes to darken the skin (melanin is the pigment that is responsible for the dark color of the skin At high levels, ACTH can also cross-react with the melanocortin receptor to cause darkening of the skin.

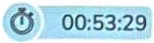
TSH / Thyroid stimulating hormone: (thyrotropin)

- Belongs to the family of glycoprotein hormones; the other members are FSH, LH, and hCG.
- The action of TSH is to cause synthesis and secretion of thyroid hormone from the thyroid gland.
- TSH secretion is under the control of hypothalamic hormone TRH (thyrotropin releasing hormone). Its secretion is inhibited by negative feedback exerted by thyroid hormones.

Gonadotropins: FSH and LH

- Follicle stimulating hormone (FSH) and Luteinizing hormone (LH) are T own as gonadotropins.
- In general, they have two primary effects:
  - To promote the development and maturation of sperm and ovum; and
  - To stimulate production of sex steroid hormones by the gonads. The principal sex steroids are: testosterone (males), and estrogen and progesterone (females).

GROWTH HORMONE (GH)/ SOMATOTROPIN



- GH is synthesized by the somatotropes of the anterior pituitary. It is a 191-amino acid protein that is similar to prolactin and human placental lactogen (HPL). There is some overlap of actions among these hormones GH exerts anabolic actions that promote body growth.
- Actions of GH: Keeps blood glucose high so as to make it available for growing tissues; prevents protein breakdown and promotes protein synthesis as a framework for growth; breakdown of lipids allows cells to use fatty acids as the fuel for energy.
- Metabolic Actions:
  - On Carbohydrate Metabolism:
    - → It decreases the peripheral utilization of glucose. Reduced uptake and utilization of glucose by cells leads to increased blood glucose hyperglycemia. In the conditions of fasting or starvation, this glucose is made available for obligate glucose users such as brain.
    - → High blood glucose will cause insulin release from the pancreas.
    - → Excessive GH secretion may lead to sustained hyperglycemia; it will Cause excess insulin secretion. Eventually, insulin may be exhausted. This leads to diabetes mellitus. It is called "pituitary diabetes". Thus, GH is a diabetogenic hormone
  - On protein metabolism
    - → GH stimulates synthesis of proteins. All aspects of protein synthesis are increased by the GH, particularly in the muscle.
    - → Thus, GH promotes amino acid transport into cells, increased DNA transcription and mRNA translation. All these effects will increase protein Synthesis.
    - → Proteins are "spared", that is not utilized for energy. Their breakdown is prevented. This is

called "protein sparing effect of GH.
- On fat metabolism:
  - → GH causes increased breakdown/mobilization of fats for the use of energy. Triglycerides are broken down, forming free fatty acids (FFA).
  - → Thus, GH increases the FFA levels in plasma.
  - → In the event of less glucose available in cells, fat oxidation may lead to formation of ketone bodies - the ketogenic effect of GH.

- Other Physiologic (Non-Metabolic) Actions:
  - Somatic growth: growth of bone, cartilage, and connective tissue
    - → Growth hormone stimulates increased deposition of protein and increased growth in almost all tissues of the body. The most obvious effect is to increase growth of the skeletal frame.
    - → Long bones grow in length at the epiphyseal cartilages. New cartilage is first deposited, due to proliferation of chondrocytes. Then the cartilage is converted into new bone.
    - → Growth hormone strongly stimulates osteoblasts. These are bone forming cells. After a certain age (puberty), epiphyses fuse with the shaft and bones cannot increase in length thereafter. However, bones can increase in thickness throughout life, under the influence of GH. This is due to periosteal growth.
    - → Increased tissue growth and increased organ size also occurs under the influence of GH.This is because of increased protein synthesis.
- Mechanism of action:
  - GH receptor
    - → It belongs to the cytokine receptor family. The GH-receptor is a tyrosine-kinase-associated receptor. By itself, it does not possess tyrosine kinase activity. Instead, its cytoplasmic domain is associated with the Janus family of protein tyrosine kinases. (Janus family is called JAK; originally named "just another kinase".) Binding of GH to the receptor activates a member of the JAK family. JAKs then phosphorylate another family of proteins in the cytoplasm, called STATS (signal transducers and activators of transcription). STAT proteins, when phosphorylated on tyrosine residues, enter the nucleus and regulate gene expression.
    - → The effects of GH on skeletal growth are mediated by a family of polypeptides called insulin-like growth factors (IGFs) {Previously known as somatomedins, as they mediate the effects of somatotropin (GH).} There are two types: IGF-I and IGF-II. They are primarily produced by the liver; other tissues also synthesize these factors. {They are called insulin-like growth factors because they are structurally similar to proinsulin - the insulin precursor. And, their metabolic actions are similar to metabolic actions of insulin.}
    - → The linear growth of the skeleton, caused by the GH, is actually effected by the IGF-I {GH has a very short half-life in circulation; IGFs have a very long half-life in circulation).

REGULATION OF SECRETION OF GH

01:11:06

- Stimulators of GH release
  - Exercise, emotional stress
  - Sleep (especially first 2 hours of sleep)
  - Hypoglycemia
  - Increased plasma amino acids (especially arginine)
  - GH-RH (released by hypothalamus)
- Inhibitors of GH release
  - Growth hormone itself; inhibits GH release by negative feedback loop
  - FFAs (negative feedback)
  - GH-IH or somatostatin released by hypothalamus
  - Glucocorticoids
  - GHRH is a member of VIP/secretin/glucagon family; it promotes GH secretion and GH gene expression
  - Somatostatin (GH-IH) is released by many sites: hypothalamus,pancreas.(Somatostatin from pancreas acts locally; it inhibits secretion of insulin & glucagon.)
  - Ghrelin: primarily produced by the stomach but also expressed in the hypothalamus; it increases appetite so as to increase nutrient intake on one hand, and GH release so as to promote growth by utilizing the nutrients.

DISORDERS OF GH SECRETION

01:14:15

- Deficiency of GH:
  - In childhood: dwarfism
  - In adults: acromicria
- Excess GH secretion:
  - Before puberty: gigantism or giantism
  - After puberty: acromegaly
- Gigantism or giantism: It is the disorder of excess GH secretion before puberty
- Acromegaly: It is the disorder of excess GH secretion after puberty.
  - However, bone deposition will continue to occur due to excess GH action. Hence, the bones increase in thickness.
  - Enlargement of the hands and feet (acral parts). The hands are broadened with thickening of the fingers. The terminal phalanges are tufted.
  - Enlargement of facial bones. Protrusion of the lower

jaw - called "prognathism"; enlargement of nasal bones and supraorbital ridges.
  - The subcutaneous tissues of the hands, feet, scalp, nose, lips, and forehead are thickened. This causes appearance of deep furrows over the scalp, resembling "bulldog scalp". The tongue is thickened.
  - Kyphosis of the spine causes bowing of the person, looking "gorilla type".
  - The viscera, heart, lungs, liver, spleen, and tongue are all enlarged. This enlargement is collectively called "splanchnomegaly."
- **Dwarfism:** (short-statured individual)
  - Stunted but proportionate growth; 3 to 4 ft height due to arrest of skeletal growth
  - Intelligence may be normal and proportionate to age in some types of
  - dwarfism (Levy-Lorain type).
  - The gonads are underdeveloped and secondary sexual characters do not develop. The sexual functions are depressed.
  - Some other variants of dwarfism have been described:
    - → Levi-Loram dwarfism: rate of GH secretion is normal or high, but there is hereditary inability to form somatomedin C (IGF-1). African Pygmies may have this abnormality.
    - → Laron type dwarfism: GH hormone secretion is normal, but there is growth hormone insensitivity due to GH receptor abnormality.
- **Acromicria**
  - Hypopituitarism in adults; hypo-functioning of the acidophil cells of the anterior pituitary. Deficiency of GH in adults.
  - Retarded development of bones, hands, feet, and face.
  - Other conditions of the hyposecretion of GH:
    - → Simmond's disease
    - → Sheehan's syndrome

THE THYROID HORMONES

01:22:41

Introduction

- Thyroid gland secretes two hormones: T3 and T4 (and a small amount of reverse T3 (rT3).
- The thyroid hormones control body's basal metabolic rate (BMR). However, these hormones are not absolutely essential for life.

Structure

- The thyroid gland is made up of acini or follicles. Each follicle contains a viscid, homogenous mass called thyroglobulin. It is commonly called colloid.
- Thyroglobulin is the storage protein of the thyroid gland. Thyroid hormones are bound to it. Thyroid hormones are synthesized in the colloid.

SYNTHESIS OF THE THYROID HORMONES:(FROM IODINE)

01:27:30

- Thyroid hormones are synthesized from the iodine in the diet.
  - Iodine in the diet: The iodine of food is converted into iodides in the digestive tract and in this form it is absorbed into the blood. Via, circulation, it reaches the thyroid gland.
  - Trapping of iodides by the thyroid gland: Circulating iodides are trapped by the thyroid gland. Inorganic iodide is transported into the thyroid gland by the so-called "iodide pump"; it is an active transport mechanism. The effectiveness of iodide trapping can be assessed by the thyroid/serum (T/S) ratio. The normal T/S iodine concentration is approximately 30.
  - Oxidation of inorganic iodide to free iodine: Once the inorganic iodide is transported within the gland, within a few seconds it is converted to free iodine. This oxidation is catalyzed by the enzyme PEROXIDASE.
  - Iodination of the tyrosine residue ("organification"): Active iodine now reacts with tyrosine residue of protein chain of he thyroglobulin. This forms mono-iodo-tyrosine (MIT).
  - Further **iodination of MIT:** One more iodine combines with MIT, to form di-iodo-tyrosine (DIT)
- Coupling and condensation: formation of thyroid hormones
  - 1 MIT+ 1 DITtri iodo-thyronine (called T3))
  - 1 DIT+1DIT tetra-iodo-thyronine (called T4 or thyroxine)
  - T3 and T4 are stored in the colloid material; attached to the thyroglobulin. Thus thyroid hormones are the only hormones that are stored extracellularly.
- Wolff Chaikoff effect: Excess iodine given to person with a normal thyroid gland status will inhibit organification and hormone synthesis.This blockage is temporary.
- Release of the thyroid hormones:
  - → The thyroid gland releases thyroid hormones in the following ratio: 90% secretion is T4; 9% secretion is T3 (ratio of about 10 :1); reverse T3 (rT3) secreted less than 1%. (rT3 is biologically inactive).

Transport of thyroid hormones in blood:

- Thyroid hormones are bound with 3 plasma proteins and then transported in blood.
  - Thyroxine binding globulin (TBG): It has high affinity for thyroid hormones. However, its capacity (quantity available) to bind thyroid hormones is low.
  - Thyroxine binding prealbumin (TBPA); also called transthyretin: Compared to TBG, it has lower affinity but higher capacity to bind thyroid hormones.

- Albumin Compared to TBG & TBPA, albumin has higher capacity for binding circulating thyroid hormones; however its affinity for thyroid hormones is relatively low. Hence, it binds a small portion of thyroid hormones in blood.

- 99.15 % of T3 is loosely bound with plasma proteins. 99.5 % of thyroxine is bound to plasma proteins.

METABOLISM OF THYROID HORMONES

01:40:42

- T4 is converted peripherally into TB by the action of enzyme deiodinase present in the cells; it removes one iodine from the outer ring of T4. The effects of the thyroid hormones are exerted by the T3. Some of the T4 entering the cells deiodinated to reverse T3 (rT3), when T4 is deiodinated in the inner rng
- There are 3 types of the deiodinase enzyme: D1, D2, and D3.
  - Type 1 deiodinase D1)Located in the cell membrane, it converts T4 to T3 before it enters the cells. It is found mainly in the liver and kidney.
  - Type 2 deiodinase (D2): Found primarily in pituitary, brain, and brown fat: it is present in the endoplasmic reticulum.
  - Type 3 deiodinase (D3): Found primarily in the membranes of the cells in placenta, brain, and skin. It forms rT3 from T4.
- Note that: majority of secretion of the thyroid gland is T4. The gland can Synthesize T3. But it does so in small amounts. And, then T4 is peripherally converted into T3 and then T3 exerts the effects. If it is the T3 that is going to exert the actions, and thyroid gland can synthesize it too, then Why the gland first secretes T4 and then in tissues it is converted into T3?
  - T4 is bound more extensively with the plasma protein carriers.
  - T4 has a long life (7-8 days) compared to T3 (1 day).

FUNCTIONS OF THE THYROID HORMONES

01:42:44

- Maturation, differentiation, and growth:
  - Thyroid hormones play an important role in normal human maturation.
    Bone maturation gets delayed in hypothyroid children. Perinatal lung maturation s influenced by thyroid hormones.
  - Adequate thyroid hormones are necessary for normal growth.
- Metabolic functions:
  - General metabolism: O2 consumption, heat production:
    → The outstanding action of thyroxine is to stimulate metabolism in the
    tissues generally. It will have two effects: increased Oxygen consumption and increased heat production.
    → The basal metabolic rate (B.M.R.) or the rate of basal energy expenditure is controlled by the thyroxine
    → As the metabolism increases, there is increased oxygen consumption. A correlate of this is an increase in the size and number of mitochondria, and increase in the enzymes that regulate oxidative phosphorylation.
    → The increase in B.M.R. is also associated with an increase in Na-K
    → ATPase (pump) activity, It is an active transport process; it is estimated to spend about 40% of the total energy expenditure by the cells.
  - As the metabolism increases, heat production also increases in the body.
    → Hypothyroid individuals are obese (due to decreased energy expenditure) and are intolerant to cold (due to reduced heat production).
    → Hyperthyroid individuals are thin and are intolerant to hot weather.
    → In general, all aspects of nutrient metabolism (anabolic & catabolic pathways) are stimulated by thyroid hormones. In many instances, the net effect is dose- dependent.
  - **Effect on carbohydrate metabolism**
    → Increased carbohydrate metabolism may result in hyperglycemia. It will result from Increased breakdown of glycogen(glycogenolysis), and gluconeogenesis.
  - **Effect on protein metabolism**
    → All aspects of protein metabolism increase. Protein synthesis is promoted
    by thyroid hormones, thus a crucial role in growth is played by them along with GH.
    → High levels can cause net protein breakdown and increased urinary
    nitrogen excretion
  - **Effect on fat metabolism**
    → All aspects of fat metabolism(synthesis, mobilization, degradation) are increased.
    → In general degradation is affected more than synthesis. Hypothyroid persons suffer from atherosclerosis. Low thyroid- reduced lipolysis cholesterol deposited in blood vessels- atherósclerosis.
  - **Relative vitamin deficiency:** By stimulating metabolic processes, thyroid hormones increase the demands for vitamins (co-factors in various pathways) There may be a relative deficiency of water-soluble vitamins in hyperthyroidism.

Other systemic actions: (non metabolic)

- On cardiovascular system: (stimulated metabolism, stimulates cardiorespiratory functions)
  - Increased myocardial contractility may result from direct actions on myocardium, such as actin & myosin concentration, 1 Na K-pump activity and myosin ATPase activity. In addition, thyroid hormones also increase sympathetic nervous system activity.
  - Hyperthyroidism produces myocardial hypertrophy. (In contrast, it causes atrophy of skeletal muscle)
  - Positive chronotropic and inotropic effect.
- ECG changes:
  - Hyperthyroid persons: changes indicative of LVH. (2)
  - Hypothyroid individuals: Inverted T waves (particularly in lead II); low amplitude of all waves.
  - Hyperthyroid individuals show:
    - → increased stroke volume & heart rate: thus increased cardiac output.
    - → Systolic BP increases, but diastolic BP decreases.Thus, pulse pressure widens. (Mechanism of decreased diastolic BP: decreased peripheral resistance due to vasodilation a) thyroid hormones directly act on, and cause relaxation of, vascular smooth muscle. increased metabolism/heat production causes cutaneous vasodilation.
- On the nervous system:
  - Myelinogenesis, neuronal outgrowth, and Synapse formation during the fetal and neonatal period require thyroid hormones.
  - The critical period of brain development begins early in the intrauterine life, and continues upto 2 years of age. The process requires normal levels of thyroid hormones.
  - Lack of thyroid hormones during this period wil cause impairment of CNS development resulting in severe and irreversible brain damage. It wil manifest in the form of mental retardation.
  - Even after the development period, thyroid hormones affect CNS functions. Hypothyroid individuals have reduced neuronal and synaptic excitability. They have prolonged reflex times, they are dull and lethargic, excessively sleepy. Hypothyroidism can produce psychological disturbances,leading to myxedema madness. Opposite effects (insomnia, decreased reflex time, etc) are observed in hyperthyroidism.
  - Sympathetic nervous system: Its activity is increased by thyroid hormones. The effects are mediated via ß-adrenergic receptor stimulation. It results in increased heart rate, tremors, and excessive sweating
  - On GIT:
    - → Appetite is increased due to increased activity of thyroid; and weight loss occurs due to increased metabolism. Thus, weight loss even in the presence of voracious appetite is a hallmark of hyperthyroidism.
  - On reproductive system:
    - → Gonads function normally only when the thyroid secretion is normal.
    - → In hypothyroid, gonadal growth is impaired; secondary sexual characters do not develop.

DISORDERS OF THE THYROID HORMONES OR THYROID GLAND

01:56:19

- Goiter: Generalized enlargement of the thyroid gland is called "goiter". It may occur in euthyroid, hypo- or hyperthyroid individuals.
- Hypothyroidism:
  - In infants and children, this disorder results in "cretinism"; in adults, it leads to "myxedema".
  - Cretinism:
    - → hypothyroidism in infants and children
    - → Dietary iodine deficiency during pregnancy or iodine deficiency in the postnatal period would cause deficient synthesis of thyroid hormones.
    - → The child's milestones of growth are delayed:

(i) The child fails to grow in height and weight;
(ii) dentition is delayed;
(iii) holding up of head, sitting, standing, walking, and speech - all these milestones are delayed.

- → The child is dwarfish (short statured)
- → Due to impaired CNS development, mental retardation is an important feature
- → Under development of gonads, absence of sexual functions and secondary sexual characters.

  - Hypothyroidism in adults:
    - → Thyroid deficiency in adults; usually it occurs in adult females below the age of 35 years.
    - → The term "myxedema" is used to describe the non-pitting type of edema.
    - → Accumulation of mucopolysaccharides in the interstitial space results in retention of fluid. It has a greater viscosity (semisolid; jelly-like) due to which the edema is non-pitting.
    - → Other features: swollen, puffy face,
    - → Yellowish appearance of the skin. (carotene - to - vitamin A conversion requires thyroxine. In hypothyroidism, carotene accumulation in skin gives yellowish appearance.)
    - → Changes in hair texture (because thyroid hormones regulate protein metabolism): thin & brittle hair, loss of the lateral 1/3rd of the eyebrows is common.
    - → Due to slowed metabolism, person will be obese and intolerant to cold

→ Polymenorrhea or menorrhagea are common in females.

- Hyperthyroidism
  - Excess thyroid secretion is hyperthyroidism; the most prevalent form is Grave's disease.
  - Thyrotoxicosis / Grave's disease:
    → Excess thyroid secretion;
    → There is generalized moderate enlargement of the thyroid gland.
    → Hyperthyroidism with toxic symptoms is thyrotoxicosis.
    → Grave's disease is thought to be due to an autoimmune process. T lymphocytes become sensitized to antigens within the thyroid gland. T cells then stimulate B-lymphocytes to produce antibodies which may serve as TSH agonists. That is, the antibodies mimic the action of TSH on the thyroid gland. This results in excessive thyroid hormone synthesis. (The antibody is sometimes referred to as "thyroid stimulating immunoglobulin" (TSI). It is directed against thyroglobulin, thyroid peroxidase, and the TSH receptor on the gland.)
    → Exophthalmos: It means protrusion of the eyeball. The eye changes commonly seen in Graves' disease - lid lag, upper lid retraction, extraocular muscle weakness, diplopia, periorbital edema, and proptosis. Proptosis occurs due to increased retro-orbital contents. There is fibroblastic proliferation and mucopolysaccharides accumulate in the retro-orbital tissues. The retro-orbital fibroblasts and adipocytes are targets of the autoimmune attack.
    → Dermopathy/pretibial myxedema: (myxedema is the feature of hypothyroidism as well. In both instances, edema is due to accumulation of glycosaminoglycans (GAGs).) In the pretibial regions, the skin thickens and forms "pig-like" plaques.
    → Other features: BMR will be high. Hence, the person will be thin, and intolerant to heat. Also, there are palpitations; skin is warm and moist.
    → Oligomenorrhea and amenorrhea in women.
    → Muscle weakness is a common occurrence.
    → Tremors, tachycardia(sleeping, pulse rate>90) are the toxic symptoms.

Regulation of secretion of thyroid hormones

- There are two main factors which influence the secretion of TSH:
  - the release of TRH from the hypothalamus, and
  - the blood level of thyroid hormones.
- Other regulators of thyroid hormone release:
  - Temperature
  - Stress: it increases thyroid activity.
  - High concentrations of iodides: although iodine is necessary for the synthesis of thyroid hormones, high concentrations of organic iodide lead to decrease in iodide uptake. Thyroid synthesis and release will decrease.
  - Dietary goitrogens: certain foods can produce goiter. For example, cabbage is known to be anti-thyroid.

Table 32.1

	Central DI	Nephrogenic DI	Psychogenic DI
Plasma Osmolality	Increased	Increased	Increased
Urine Osmolality	Decreased	Decreased	Decreased
Plasma ADH	Low	Normal to high	Low
Urine osmolality after mild water deprivation	No change	No change	Increases
Plasma ADH after water deprivation	No change	Increases	Increases
Urine osmolality after administration of ADH	Increased	No change	Increases

CLINICAL QUESTIONS

Q. Molecular mimicry is defined as the theoretical possibility that sequence similarities between foreign and self-peptides are sufficient to result in the cross-activation of autoreactive T or B cells by pathogen-derived peptides. Which of the following endocrine disorder is a result of molecular mimicry?

A. Addisons disease
B. Diabetes Mellitus
C. Hashimoto's thyroiditis
D. Hypoparathyroidism

Answer: C

Solution:
The cause of autoimmune thyroid disease is not completely known by medical science. However, a combination of genetic and environmental factors is thought to play a role.
Hashimoto thyroiditis is caused by an **abnormal immune** response that includes the production of antithyroid antibodies against the thyroid follicular cells, microsomes, and TSH receptors.

Molecular Mimicry

- A new theory explains how an immune system can be "tricked" into attacking the thyroid cells.
- ***Yersinia*** resides in intestinal bacteria has been found to share identical amino acid sequences when compared to the **TSH** receptor, **thyroglobulin**, **thyroperoxidase** [TPO], and **Sodium Iodide symporter** [NIS].
- ***Borrelia burgdorferi*** has also been implicated
- This explains the increased antibodies found on lab panels in Hashimoto's patients.
- These are the antibodies to thyroglobulin and thyroperoxidase (TPO) commonly used by the doctor to confirm a diagnosis of Hashimotos Thyroiditis.

TSH Receptor Antibodies
Comes in 2 varieties.

1. The first type, the TSH receptor is **stimulated** → **Grave's Disease** and **hyperthyroidism**.
2. The second variety, the TSH receptor is **blocked** → **Hashimotos's** disease.

- Although both Graves and Hashimotos have a common origin in the molecular mimicry theory
- Grave's causes a **hyperthyroid** state, and Hashimoto's causes a **hypothyroid** state.
- Both Graves and Hashimotos antibodies can coexist in the same patient and one can transform into another.

Reference: Medical Physiology, A Cellular and Molecular Approach, UPDATED SECOND EDITION. Walter F. Boron, Emile L. Boulpaep. Section VIII, the Endocrine System. Chapter 49, The Thyroid Gland. Pg. 1055.

33 MALE REPRODUCTIVE SYSTEM

SUMMARY

1. Male reproductive physiology
2. Blood test is barrier
3. Spermatogenesis
4. Difference between male and female spermatogenesis
5. Effect of temperature
6. Semen
7. Sertoli cells

MALE PRODUCTIVE PHYSIOLOGY

00:00:37

- The major male reproductive function are:
  - Secretion of sex hormones,
  - Production of sperm, and
  - Transport of sperm form the male to the female

STRUCTURE:

- The testes are made up of loops of convoluted seminiferous tubules, in the walls of which the spermatozoa are formed from the primitive germ (spermatogenesis). Both ends of each loop drain into a network of ducts in the head of the epididymis. From there, spermatozoa pass through the tail of the epididymis into the vas deferens. They enter through the ejaculatory ducts into the urethra in the body of the prostrate at the time of ejaculation.
- Between the tubules in the testes are nests of cell containing lipid granules, the interstitial cells of Leydig, which secrete testosterone into the bloodstream
- The spermatic arteries to the testes are tortuous, and blood in them runs parallel but in the opposite direction to blood in the pampiniform plexus of spermatic veins. This anatomic arrangement my permit contercurrent exchange of heat and testosterone

Blood – Testis Barrier

00:04:54

The walls of the seminiferous tubules are lined by

1. Primitive germ cells and
2. Sertoli cells
   - Sertoli cells are large glycogen-contining cells that stretch from the basal lamina of the tubule to the lumen.
   - Germ cells must stay in contact with Sertoli cells to survive, and this contact is maintained by bridges of carbohydrate molecules. Tight junctions between adjacent Sertoli cells near the basal lamina form the interstitial tissue to the adluminal compartments and lumen. However steroid peneterates this barrier with ease.
   - The fluid in the lumen of seminiferous tubules is quite different fom plasma- as it contain very little protein and glucose but is rich in androgens, estrogen, K^+, inositol, and glutamic and aspartic acids. Maintenance of its composition depends on the blood –testis barrier.
   - The barrier also protects the germ cells from blood-borne noxious agents, prevents antigenic products of germ cell division and maturation from entering the circulation and generating an autoimmune response and may help establish an osmotic gradient that facilities movement of fluid into the tubular lumen.

THE FORMATION OF SPERM TAKES PLACE IN THE SEMINIFEROUS TUBULES OF THE TESTES

Spermatogenesis

00:07:18

- It occurs in three distinct phases:
  - Stem cell renewal and production of spermatogonia,
  - Germ cell proliferation, and
  - Spermiogenesis
- The first phase:- The spermatogonia, the primitive germ cells, divide by mitosis to form primary spermatocytes. This process begins during adolescence
- The second phase:- Primary spermatocytes undergo meiotic division, reducing the number of chromosomes. In this two – stage process, they divide into secondary spermatocytes and then into spermatids, which contain the haploid number of 23 chromosomes.
- The third phase: The spermatids mature into spermatozoa (sperms). This final stage is referred to as spermiogenesis; it is characterized by the absence of cell division.
- The latter two phase occur in the adluminal compartment, where the consecutive processes of meiosis, genetic recombination, haploid gene expression, formation of the sperm acrosome and

flagellum, remodeling and condensing of chromatin. and finally extrusion of cytoplasm tak . place. Cylins and cyclin – dependent kinases are essential mediators of mitosis and meiosis

- As a single spermatogonium divides and matures, its descendants remain tied together by cytoplasmic bridges until the late spermatid stage. This appe\arently ensure synchrony of the differentiation of each clone of germ cells. All stage of sperm development are present in the seminiferous tubules at any given time.
- The whole sequence of spermatogenesis is under intrinsic regulation by a preprogrammed temporal pattern of germ cell expression that directs differentiation and morphogenesis.

Each spermatogonium can give rise to 64 spermatozoa

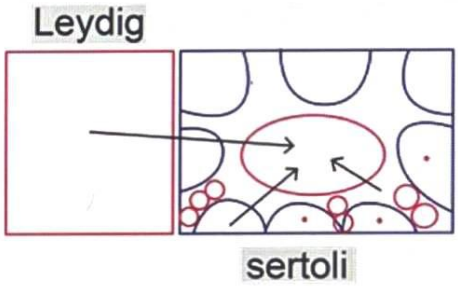
- The first two mitotic divisions of a spermatogonium give rise to four cells (type A): a single resting dark cell (Ad), that will eventually serve as the ancestor of a later generation of sperm, and three active pale cells (Ap). The Ap cells divide by further mitoses to yield type B spermatogonia, which then give rise to many primary spermatocytes. Some Ap cells may also transdifferentiate to Ad cells and form a reservoir.

In humans, it takes an average of 74 days to form a mature sperm from a primitive germ cell

- The most reliable expression of the sperm – production rate is the daily number of sperm cells produced per gram of testicular parenchyma. In 20-year of old men, the production rate is approximately 6.5 million sperm per gram per day. The rate falls progressively with age and averages around 3.8 million sperm per gram per day in men 50 to 90 years old. This decrease is probably related to the high rate of degeneration of germ cells during meiotic prophase.
- Spermatogenesis in the male differs from oogenesis in the female in 3 important aspects 00:13:12

1. In the female,, the mitotic proliferation of germ cells takes place entirely before birth. In the male, spermatogonia proliferate only after puberty then throughout life.
2. The meiotic divisions of a primary occyte in the female produce only one mature ovum. In the male, the meiotic divisions of a primary spermatocyte produce four mature spermatozoa
3. In the female, the second meiotic division is completed only upon fertilization. Thus, not further development of the cell takes place after the completion of meiosis. In the male, the products of meiosis (the spermatids) undergo substantial further differentiation to produce mature spermatozoa.

- Each sperm is an intricate motile cell, rich in DNA, with a head that is made up mostly of chromosomal material. Covering the head like a cap is the acrosome, a lysosome – like organelle rich in enzymes involved in sperm penetration of the ovum and other events involved in sperm penetration of the ovum and other events involved in fertilization. The motile tail of the sperm is wrapped in its proximal portion by a sheath holding numberous mitochondria. The membranes of late spermatids and spermatozoa contain a special small form of angiotensin – converting enzyme called germinal angiotensin II converting enzyme. (The function of this enzyme in the sperms is unknown, although male mice in which the function of the angiotensin – converting enzyme gene has been disrupted have reduced fertility.)
- The spermatids mature into spermatozoa in deep folds of the cytoplasm of the Sertoli cells. Mature spermatozoa are released from the Sertoli cells and become free in the lumens of the tubules. The Sertoli cells secrete androgen – binding protein (ABP), inhibi, and mullerian inhibiting substance (MIS). They do not synthesize androgens, but they contain aromatase (CYP19), the enzyme responsible for conversion of androgens to estrogens, and they can produce estrogens.
- ABP maintains a high, stable supply of androgen in the tubular fluid.
- Inhibit inhibits FSH secretion.



- MIS causes regression of the mullerian ducts in males during fetal life.
- FSH and androgen maintain the gametogenic function of the testis.
- The maturation from spermatids to spermatozoa depends on androgen acting on the Sertoli cells.
- FSH acts on the Sertoli cells to facilitiate the last stages of spermatid maturation.
- For optimal spermatogenesis to occur, following factors are necessary – two testicular cell types – Leydig cells and Sertoli cells, two gonadotropins – LH and FSH, and one androgen- testosterone. LH and Leydig cells are

required to produce testosterone. LH (LH or rather its substitute hCG, may be used therapeutically to initiate spermatogenesis in azoospermic or oligospermic men.) FSH and Sertoli cells are important for the nursing of developing sperm cells and for the production of inhibin and growth factors, which affect the Leydig cells.

Further development of spermatozoa:

- Spermatozoa leaving the testes are not fully mobile. Their maturation continues and they acquire motility during their passage through the epididymis.
- The ability to move forward (progressive motility), which is acquired in the epididymis, involves activation of a unique protein called Cat Sper, which is localized to the principal piece of the spterm tail. This protein appears to be a Ca^{++} ion channel that permits cAMP- generalized Ca^{++} influx.
- The fertilizing power of sperms from the distal end of the epididymis is twice as high as that of sperms from the proximal ends. It seems therefore, that the secretion of the epididymis normally exerts a 'spermatotrophi' action
- Ejaculation of the spermatozoan involves contractions of the vas defect.....in part by P2X receptors for ATP, and fertility is reduced in mice in which these receptors are knocked out.
- Sperms form hyaluronidase, an enzyme which liquefies the hyaluronic acid found in mucus and in the zona pelllucida of the ovum. In this way, the sperms can penetrate the normal plus of mucus in the cervix uteri and get through the zona pellucida which forms a tough lining surrounding the ovum.
- Once ejaculated into the female, the spermatozoa move up the uterus to the isthmus of the uterine tubes, where they slow down and undergo capacitation. This further maturation process involves two components: increasing the motility of the spermatozoa and facilitating their preparation for the acrosome reaction. However, the role of capacitation appears to be facilitatory rather than obligatory, because fertilization is readily produces in vitro. From the isthmuses the capacitated spermatozoa move rapidly to the tubal ampullas, where fertilization takes place.

Effects of temperature

00:26:21

- Spermatogenesis requires a temperature considerably lower than the internal body temperature. The testes are normally maintained at a temperature of about 32C. They are kept cool by air circulating around the scrotum and probably by heat exchange in a countercurrent fashion between the spermatic arteries and veins.

SEMEN

00:26:42

- The fluid that is ejaculated at the time of orgasm, the semen, contains sperms and the secretions of the seminal vesicles, prostate, Cowper's glands, and probably, the urethral glands.
- An average volume per ejaculate is 2.5-3.5mL after several days of continence. The volume of semen and the sperm count decrease rapidly with repeated ejaculation. Even through it takes only one sperm to fertilize the ovum, there are normally about 100 million sperms per mL of semen.
- 50% of men with counts of 20-40 million / mL and essentially all those with counts under 20 million /mL are sterile. The presence of many morphologically abnormal or immotile spermatozoa also correlates with infertility. The PGs are in high concentration in semen.
- Human sperms move at a speed of about 3 mm/ min through the female genital tract. Sperms reach the uterine tubes 30-60 minutes after copulation

SERTOLI CELLS

00:28:05

1. Nursing of the developing spermatozoa
2. Blood testicular barrier
3. Secretin of inhibin

34 FEMALE REPRODUCTIVE SYSTEM

SUMMARY

1. The Ovaries
2. The biology of oogenesis: (the formation of ova)
3. Folliculogenesis
4. The Menstrual Cycle

THE FEMALE REPRODUCTIVE SYSTEM

- Reproductive function in the human female is inherently cyclic.

THE OVARIES

00:02:56

- As a hormone – secreting organ, the ovary functions in two ways:
  i. The ovarian sex steroids and protein hormones function locally to modulate the complex events in the development and extrusion of the ova (the process is called ovulation).
  ii. Ovarian hormones are secreted into the circulation and they act on diverse target organs, including the uterus, fallopian tubes, vagina, breast, hypothalamus, pituitary gland, adipose tissue, bones, kidney, liver, and vascular system. Many, but not all, of these distant effects are closely related to the reproductive sequence.
- The fundamental reproductive unit in the female is the single ovarian follicle, which is composed of one germ cell completely surrounded by a cluster of endocrine cells.
- When fully developed and functional, the follicle:
  i. Maintains and nurtures the resident oocyte,
  ii. Matures the oocyte and releases it at the right time,
  iii. Prepares the vagina and fallopian tubes to assist in fertilization
  iv. Prepares the lining of the uterus to accept and implant a zygote, and
  v. Maintains hormonal support for the fetus until the placenta can take over this function.
- Formation of oval and development of follicles occurs as described

A. THE BIOLOGY OF OOGENESIS: (THE FORMATION OF OVA)

00:06:05

- The primary germ cells in the female are termed as oogonia.
- During the 2nd and 3rd months of embryonic development, meiosis begins meiosis oogonia, converting them to primary oocytes. The primary oocyte is surrounded by granulosa cells. The primary oocyte is surrounded by granulosa cells; the entire structure is called a primary follicle, or primordial follicle.
- In humans, no new ova are formed after birth.
- During fetal development, the ovaries contain over 7 million primordial follicles. However, many undergo atresia (involution) before birth and few are lost after birth.
- At the time of birth, there are 2 million ova, but 50% of these are atretic. The other 50% (1 million) that are normal undergo the first part of the first meiotic division at about this time and enter a stage of arrest in prophase in which those that survive persist until adulthood.
- There is continuing atresia during development, and the number of ova in both of the ovaries at the time of puberty is less than 300,000.
- The process of oocyte attrition occurs by apoptosis.
- Transforming growth factor (TGF-β and FAS ligand and their receptors stimulate oocyte apoptosis).
- Various survival factors, including fibroblast growth factor, leucocyte inhibitory factor (LIF), and kit ligand (released by follicle cells), oppose apoptosis.
  (Thus, in contrast to the male, who continuously produces spermatogonia and primary spermatocytes, the adult female cannot produce new oogonia.)
- Only one ovum per cycle normally reaches maturity. Just before ovulation, the first meiotic division is completed. One of the daughter cells, the secondary oocyte, receives most of the cytoplasm, while the other, the first polar body, fragments and disappears.
- The secondary oocyte immediately begins the second meiotic division, but this division stops at metaphase and is completed only when a sperm penetrates the oocyte. At that time, the second polar body is cast off and the fertilized ovum proceeds to form a new individual.

B. FOLLICULOGENESIS

00:12:60

- From the time of birth, there are many primordial follicles under the ovarian capsule. Each contains an immature ovum.
- The primary oocyte is surrounded by granulosa cells; the entire structure is called a primary follicle, or primordial follicle.

(The granulosa cells secrete mucopolysaccharides that form a protective halo or membrane, called the zona pellucida. The granulosa cells form a barrier around the developing follicle that prevents the entrance of substances such as proteins, ions, and drugs, which could destroy the developing germ cell)

- As granulosa cells proliferate, they form a multi-layered epithelium around the oocyte. At this stage, the follicle is referred to as a secondary follicle.
- Once a secondary follicle acquires 3 to 6 of granulosa cells, it secretes paracrine factors that induce nearby stromal cells to differentiate into epitheloid thecal cells. Once a thecal layer is formed around the follicle, the follicle is referred to as the mature preantral follicle. It takes several months for a primary follicle to reach the mature preantral stage.

THE MENSTRUAL CYCLE

00:14:31

I. The ovarian cycle:

- At the start of each cycle, several of these follicles enlarge, and a cavity forms around the ovum (antrum formation). This cavity is filled with follicular fluid. The fluid in the antrum contains mucopolysaccharides, gonadal steroid hormones, FSH, LH, inhibin, activin, follistatin, several growth factors {IGF-1, IGF-2, IGFBP1-5, TGF-β, and epidermal growth factor (EGF)}, oxytocin, ADH, corticotrophin-releasing hormones (CRH) proopiomelanocortin products, the renin-angiotensin system and various cytokines (IL-1, TNF-). The steroid hormones reach the antrum.
- In humans, one of the follicles in one ovary starts to grow rapidly on about the sixth day of the cycle and becomes the dominant follicle, while the other regress, forming atretic follicles. The atretic process involves apoptosis.
- How one follicle is selected to be the dominant follicle seems to be related to the ability of the follicle to secrete the estrogen inside it that is needed for final maturation. A high index of its granulosa cells is a key characteristic of this selected dominant follicle.
- In a maturing ovarian (graafian) follicle, the cells of the theca interna are the primary source of circulating estrogens. However, the follicular fluid has high estrogen content, and much of this (local) estrogen comes from the granulosa cells.

  At about 14th day of the cycle, the distended follicle ruptures, and the oocyte, with its surrounding granulosa cell layer (the "cumulus oophorus"), is extruded into the abdominal cavity. This is the process of ovulation. The ovum is picked up by the fimbriated ends of the uterine tubes. It is transported to the uterus and, unless fertilization occurs, is extruded out through the vagina.

- Rise in basal body temperature occurs at the time of ovulation (since progesterone is thermogenic). It is considered an indicator of ovulation. The follicle that ruptures at the time of ovulation promptly fills with blood, forming corpus hemorrhagicum. Minor bleeding from the follicle into the abdominal cavity may cause peritoneal irritation and fleeting lower abdominal pain ("mittelschmerz").
- The granulosa and theca cells of the follicle lining promptly begin to proliferate, and the clotted blood is rapidly replaced with yellowish, lipid-rich luteal cells, forming the corpus luteum. This initiates the luteal phase of the menstrual cycle. The theca and granulosa cells are now called theca lutein and granulosa lutein cells respectively. These luteal cells secrete estrogens and progesterone. Growth of the corpus luteum depends on its developing and adequate blood supply, and there is evidence that vascular endothelial growth factor (VEGF) is essential for this process. The corpus luteum is the new endocrine unit that provides the necessary balance of gonadal steroids, to optimize conditions for implantation of a fertilized ovum, and for subsequent maintenance of the zygote until the placenta can assume this function.
- If pregnancy occurs, the corpus luteum persistent and there are usually no more periods until after delivery. If there is no pregnancy, the corpus luteum begins to degenerate ("luteolysis") about 4 days before the next menses (24th day of the cycle) and is eventually replaced by scar tissue, forming a corpus albicans.

II. The uterine cycle / endometrial cycle

- The ovarian steroids- estrogens and progestin – control the cyclic monthly growth and breakdown of the endometrium. The three major phases in the endometrial

cycle:

1. Menstrual phase
2. Proliferative phase
3. Secretory phase

The Menstrual Phase

- If the oocyte was not fertilized and pregnancy did not occur in the previous cycle, a sudden diminution in estrogen and progesterone secretion signals demise of the corpus luteum. As hormonal support of the endometrium is withdrawn, the vascular and glandular integrity of the endometrium degenerates, the tissue breaks down, and menstrual bleeding ensues, which is defined as day 1 of the menstrual cycle. After menstruation, all that remains on the inner surface of most of the uterus is a thin layer of nonepithelial stromal cells and some remnant glands.

The Proliferative Phase

- Under the influence of estrogen from the developing follicle, the endometrium increases rapidly in thickness from the 5th to the 14th days of the menstrual cycle. As the thickness increases, the uterine glands are drawn out so that they lengthen, but they do not become convoluted or secrete to any degree. These endometrial changes are called proliferative, and this phase of the menstrual cycle is called the proliferative phase. It is also called the preovulatory or follicular phase.

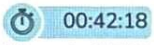
  {During the proliferative phase, the telomeres at the end of each chromosome, which are shortened during each mitosis leading to apoptosis of the cells, are repaired by the enzyme telomerase. Eastradol induces high levels of telomerase during the proliferative phase and thereby prevents apoptosis in the endometrium}

The Secretory Phase:

- After ovulation, the endometrium becomes more highly vascularized and slightly edematous under the influence of estrogen and progesterone from the corpus luteum.

  {In contrast to estradiol, progesterone suppresses telomerase, telomers are lost, and apoptosis of endometrial cells is facilitated}
- The glands become coiled and tortuous, and the begin to secrete a clear fluid. Consequently, this phase of the cycle is called secretory or luteal phase.
- The endometrium is supplied by two types of arteries. The superficial two – thirds of the endometrium that is shed during menstruation, the stratum funcitonale, is supplied by long, coiled spiral arteries, whereas the deep layer that is not shed, the stratum basale, is supplied by short, straight basilar arteries.
- When the corpus luteum regresses, hormonal support for the endometrium is withdrawan. The endometrium becomes thinner, which adds to the coiling of the spiral arteries. Foci of necrosis in the endometrium and these coalesce. In addition there is necrosis of the walls of the spiral arteries, leading to spotty hemorrhages that becomes confluent and produce the menstrual flow.
- The vasospasm is probably by locally released psotaglandins. There are large quantities of prostaglandins in the secretory endometrium and in menstrual blood.
- From the point of view of endometrial function, the proliferative phase represents restoration of the epithelium from the preceding menstruation, and the secretory phase represents preparation of the uterus of implantation of the fertilized ovum.
- The length of the secretory phase is remarkably constant to about 14 days, and the variations seen in the length of the menstrual cycle are due to variations in the length of the proliferative phase. When fertilization does not occur, the endometrium is shed and a new cycle starts.

NORMAL MENSTRUATION



- Menstrual blood is predominantly arterial, with only 25% of the blood being of venous origin. It contains tissue debris, PGs, and relatively large amounts of fibrinolysin from endometrial tissue (due to which menstrual blood does not normally contains clots). The average amount of blood loss is about 30mL.
  - Cyclic changes in the uterine cervix.
- Estrogen makes the cervical mucus thinner and more alkaline, changes that promote the survival and transport of sperms. (After ovulation) progesterone makes it thick, tenacious, and cellular. The mucus is thinnest at the time of ovulation, and its elasticity, or spiinnbarkeit, increases so that by midcycle, a drop can be stretched into a long, thin thread that may be 8-12 cm or more in length. Also, it dries in an arborizing, fern- like pattern when a thin layer is spread on a slide. After ovulation and during pregnancy, it becomes thick and fails to form the fern pattern.
- Vaginal cycle

- Under the influence of estrogens, the vaginal epithelium becomes cornified. Under the influence of progesterone, a thick mucus is secreted, and the epithelium proliferates and becomes infiltrated with leucocytes

- Cyclic changes in the breasts:
  - Estrogens cause proliferation of mammary ducts, whereas progesterone causes growth of lobules and alveoli.

OVARIAN STEROIDOGENESIS 00:47:04

- Before ovulation, the LH and FSH act on the cells of the developing follicle. The theca cells have LH receptors, whereas granulosa cells have born FSH and LH receptors.

Two cells two-enzymes hypothesis

- The theca cells and theca- lutein cells can take up cholesterol and produce testerone from it, under the influence of LH. But these cells do not have the aromatase enzyme necessary for estrogen production from testosterone.
- Granulosa cells and granulosa-lutein cells have the aromatase. The convert testosterone to estrogen, under the influence of FSH
- After ovulation, there is "luteinisation" of the follicle. The theca and granulosa cells of the follicle differentiate into the theca-lutein and granulosa –lutein cells, under the LH. The leuteinzing action of LH thus converts the follicle into the corpus luteum.
- Although the corpus luteum produces both estrogen and progesterone, the luteal phase is primarily dominated by progesterone secretion.
- Estrogen production by is largely a function of the theca – lutein cells (which also produce testosterone). Progesterone production of the corpus luteum is primarily a function of the granulosa-lutein cells (which also produce estrogens).

HORMONAL PATTERNS DURING THE MENSTRUAL CYCLE 00:52:25

- Toward the end of the luteal phase, plasma FSH and LH level are at their lowest levels; LH/FSH ratio is slightly greater than 1, 1to 2 days before the onset of menses FSH levels begins to rise.
- During the second half of the follicular phase, FSH levels fall modestly, and LH levels continue to rise; the LH / FSH ratio increases to about 2.
- The ovulatory phase is characterized by very sharp spike in plasma gonadotropin levels. LH / FSH ratio arises to about 5, this is due to the LH surge.
- After ovulation, LH and FSH continue to decline, and they reach their lower points toward the end of the cycle.

HORMONAL REGULATION OF OOGENESIS AND THE STAGES OF FOLLICULAR DEVELOPMENT 00:57:39

Stage 1: (Mostly local phenomenon)

- The initial growth of the primordial follicle appears to be a local phenomenon (independent of gonadotropins). Factors from the oocyte stimulate early granulosa cell development. The cross-signalling between the oocyte and its surrounding granulosa cells may be mediated by TGF- and epidermal growth factor (EGF). In addition, a growth differentiating factor, called GDF-9, is secreted by oocytes and affects granulosa cells.

Stage 2: (FSH absolutely necessary)

- The initial action of FSH on primary follicles is to stimulate growth of the granulosa cells. Aromatase activity and estrogen production increases. Local synthesis of IGF-1 and IGF-2 in response to FSH, further amplifies the primary FSH signals for proliferation of granulosa cells and steroidogenesis.
  - The local gonadal protein hormones also contributes paracrine effects of estradiol production. Inhibin B from granulosa cells, together with IGF-1 stimulated by GH action and locally produced IGF-2, augments androgen production by theca cells. Aromatase then produces estrogen from androgen precursors. GH also has a role in development of the follicle and oocyte FSH also stimulates granulosa cell metabolism and provides lactic acid and 2 ketoisocaprosis acid as energy sources for the oocytes

Stage 3: (LH has the central role)

- There is only one dominant follicle by days 5 to 7 of the follicular phase. Its key characteristic aromatase activity, and therefore synthesis of estradiol is more efficient.
  - The sharply increasing estradiol release from the dominant follicle triggers the ovulatory surge of gonadotropins. A critical plasma estradiol level of at least 200 pg/ml, sustained for at least 2 days, is required to elicit this positive feedback effect on LH.
  - The surge of LH with FSH then triggers ovulation by multicomponent mechanism.

i. Stimulation of progesterone levels enahcne proteolytic

enzyme activity and increases the distensibility of the follicle. As a result, follicular fluid volume rapidly increases.

ii. The LH surge also induces the enzyme prostaglandin endoperoxidase synthase in granulosa cells. This enzyme increases the synthesis of PGs, thromboxones, and leukotrienes, and thereby causes a pseudoinflammatory response that leads to follicular rupture.

iii. Mucification of the cumulus oophorus, and possibility contraction of the follicular wall stimulated by oxytocin, contributes to extrusion of the

iv. Plasminogen activator, stimulated by FSH, generates plasmin which catalyzes breakdown of the follicular wall.

- LH surge also induces type 1 11-hydroxysteroid dehydrogenease. This increases the synthesis of cortisol from cortisone, and thereby provides the postovulation- suppressing effect of cortisol on inflammation; inflammatory response thus subsides and corpus luteum is formed.

The post ovulatory luteal phase

- LH is essential for luteinzation of the granulosa cells; they start producing progesterone at high concentrations.
- The levels of LH and FSH gradually decline
- If the declining LH levels of the late luteal phase are not replaced by the equivalent placental hormone, hCG, the corpus luteum regressesh.
- Apoptosis of luteral cells is stimulated by interactions between essential transcription products of the tumor suppressor genes, p53 and Wilm's tumor-1 (LH and HCG inhibit expression of the oncogenic p53 gene). Secretion of progesterone and estradiol ceases completely in 14 days.
- In the no pregnant female, luteolysis begins by the 8th day after ovulation. Estradiol stimulates oxytocin secretion from posterior pituitary; plus oxytocin is produced locally secretion from posterior pituitary; plus oxytocin is produced locally in the corpus luteum. Oxytocin stimulates production of PGF_{2a} which in turn inhibits the actions of LH on luteal cells. This inhibition leads to loss of steroid production and apoptosis. Macrophages and T luymphocytes secrete TNF- and interferon-y, which augment PGF_2 synthesis and accelerate the process of luteolysis. Prolactin also stimulates particular lymphocytes to increase expression of fas-ligand, which mediates luteal cell death by apoptosis.

CLINICAL QUESTIONS

Q. Gonadotropin-releasing hormone(GnRH) is a releasing hormone responsible for the release of FSH and LH from the anterior pituitary. GnRH is a tropic peptide hormone synthesized and released from GnRH neurons within the hypothalamus. It constitutes the initial step in the hypothalamic–pituitary–gonadal axis. Before the onset of puberty, the GnRH neurons are under the inhibitory control of?

A. Glycine
B. Glutamate
C. Gamma amino butyric acid (GABA)
D. Beta-endorphin

Answer: C

Solution:

- The transition to a reproductive state (during puberty) requires maturation of the entire hypothalamic-pituitary-gonadal axis.
- Before this maturation occurs, plasma LH and FSH levels are diminished despite low concentrations of gonadal steroids and inhibin.
- **GnRH neurons** are said to be under the **inhibitory influence of *GABAergic neurons*.**
- Additional inhibition comes from NPY, endorphins, and nocturnal melatonin secretion. Hence, **[option - C]** is more appropriate.

Reference: Guyton and Hall Textbook of Medical Physiology 13th Edition, Page No: 1033.

LEARNING OBJECTIVES

UNIT 9 THE NERVOUS SYSTEM

INTRODUCTION TO CENTRAL NERVOUS SYSTEM

- Major Sections of the CNS
- Introduction
- Macroglia
- Microglia
- Classification of the Neurotransmitters
- Synapse
- Structure of Synapse
- Transmission at the Synapse
- Synaptic Potentials
- Basic Terminology
- Properties of Synapse
- Fate of the Neurotransmitter at the Synapse
- Neurotransmitters
- Reflex (Introduction)
- Classification of the Reflexes

SENSORY SYSTE

- Senses, 3 Neuron path, Laws for encoding
- Receptor
- Ascending tracts
- Cortex
- Physiology of pain

MOTOR SYSTEM PART-1

- Introduction
- 2 Neuron Path
- Organization of Motor Cortex
- Organization of Motor System
- Corticospinal Tract
- Functions of Pyramidal Tract
- Effects of Lesions of Pyramidal Tract
- Cerebellum (Introduction)
- Connections of Cerebellum
- Efferents
- Circuit of Cerebellum
- Functions of Cerebellum
- Function Tests

MOTOR SYSTEM PART 2

- Basal ganglia

- Circuits
- Parkinsonism
- Huntintons disease
- Lower motor neuron
- Muscle spindle
- Golgi Tendon
- Hypertonias

PHYSIOLOGY OF PAIN

- Speech (introduction)
- Central Speech Apparatus
- Execution of Speech
- APHASIA
- Cortex
- Limbic System
- Hypothalamus(introduction)
- Hypothalamic Nuclie And Lesions
- Learning And Memory (introduction)
- Conditioning
- Types Of Memory
- EEG (Introduction)
- Types of Waves on EEG
- Sleep(Introduction)
- Types of Sleep

AUTONOMIC NERVOUS SYSTEM

- Classification of ANS
- Location of Sympathetic & Parasympathetic System
- Pre-ganglionic and Post-ganglionic Fibres of Sympathetic & Parasympathetic System
- Neurotransmitters in ANS
- Receptors of Ach
- Adrenergic Receptors
- Effects of Sympathetic & Parasympathetic System on various Organs
- MCQ on CSF Pressure

37 INTRODUCTION TO CENTRAL NERVOUS SYSTEM

BRAIN AND SPINAL CORD CONSTITUTE THE CENTRAL NERVOUS SYSTEM

Four major Sections of the CNS are:

1. Introduction, Synapse, Neurotransmitters
2. Sensory System (how sensations are carried from peripheral system to cerebral cortex)
3. Motor System
4. Higher functions Hypothalamus, limbic system

Introduction:

- There are two types of cells in CNS:
  - Neurons
  - Glia
- Neurons are basic structural and functional unit of CNS and glia are the supporting cells of CNS. If you look at the numbers ratio there are almost ten times more glial cells as compared to the neurons in the CNS.
- No new neurons are formed after birth as neurons are terminally differentiated tissue. However what increases after the birth is number of new synapses i.e. how the brain develops and how the learning occurs, is due to the synapses and the neurotransmitters. The number of neurons would not increase beyond a certain age.

Exception:

- Olfactory neurons, continue to divide throughout life because of the superficial location of their nerve cell bodies and their capacity to undergo damage and regenerate in response to air entry and exit.

Glial Cells: 2 Types

- Macroglia
- Microglia

Macroglia

1. Astrocytes

Functions:

a. Reinforce the blood brain barrier
b. neuronal microenvironment I.e., regulation of k+, H+, Neurotransmitters reuptake and redistribution

Question: Which cell is primarily involved in the Blood brain barrier?

Ans: Tight endothelial junctions (not astrocytes)

2. **Oligodendrocytes:**

- Myelination of nerves in the CNS, one oligodendrocyte myelinates multiple neurons (1:20)

(Schwann cells- myelination of nerves in the PNS, multiple Schwann cells myelinates single neuron, 20:1)

Microglia

- Borns out of the CNS and then migrates inside the CNS.
- Functions as a phagocytic cell/Scavenger cell

Question: Which part of the brain contains highest no. Of neurons?

Ans: Cerebellum

Important Information

- Nucleus Raphe Magnus: greatest density of serotonergic neurons
- Locus Coeruleus: greatest density of noradrenergic neurons
- Nucleus Accumbens: greatest density of dopaminergic neurons

Classification of Neurotransmitters (NTS)

Functional:

- Excitatory
  - Glutamate
  - Aspartate
- Inhibitory
  - GABA mc in brain
  - Glycine mc in spinal cord

Important Information

- Excitatory NTS- opens Na^+/Ca^{+2} channels in the postsynaptic membrane
- Inhibitory NTS- opens Cl^-/k^+ channels in the postsynaptic membrane

Structural:

- **LMW transmitters:** Acetylcholine, Catecholamine, Glutamate, GABA etc.

- **HMW neuropeptides:** Opioids, Endo-cannabinoids, Orexin

Synaptic vesicle: synthesize inside the neuron cell body and then travels down the axon to its terminal end.

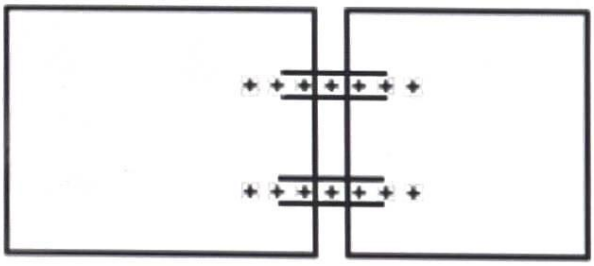
LMW NTS are synthesize locally in the axonal terminal whereas HMW NTS are synthesize as precursors inside the cell body and are then migrates down to axonal terminal

SYNAPSE

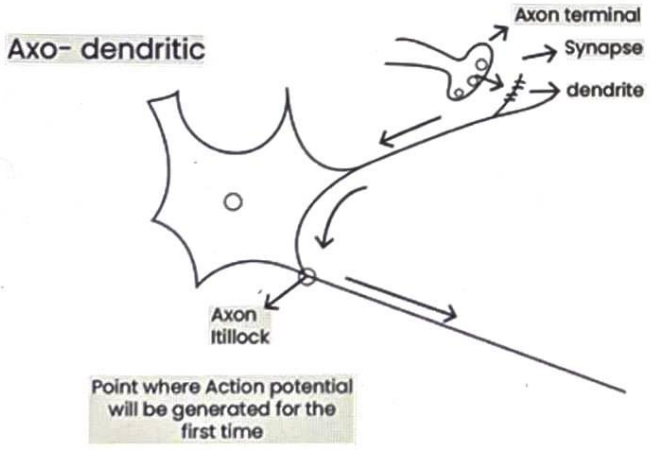
- **A junctional region between the two neurons where impulse from the one neuron is passed on to another neuron.**
- Electrical impulse at presynaptic membrane cause release of neurotransmitter at synaptic junction and then neurotransmitter cause excitation of the post synaptic membrane.

Types of Synapses:

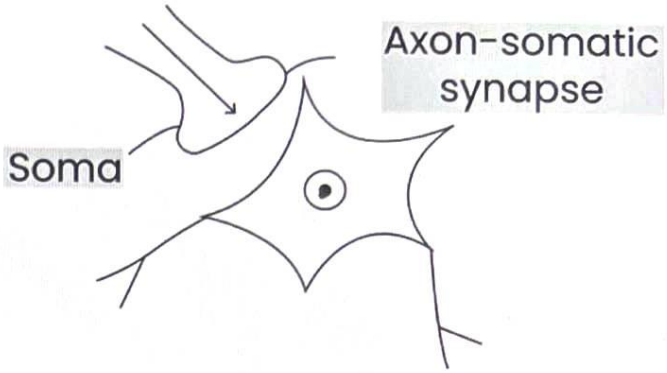
- Electrical Synapse
  - Gap junctions



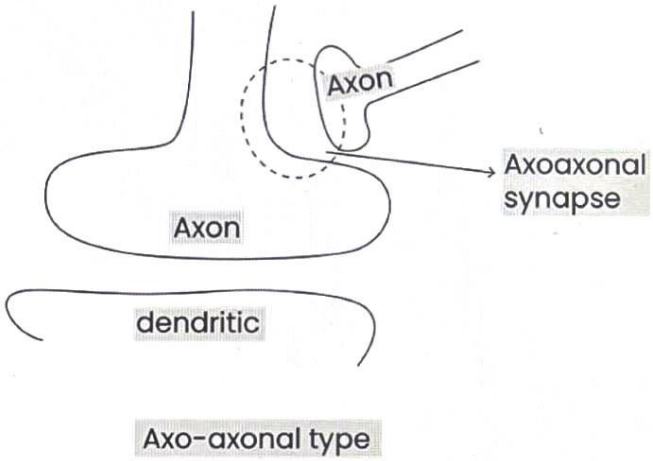
  - Locations
    - → Retina
    - → Inferior olivary nucleus
    - → Heart
- Chemical Synapse
  - Axo-dendritic type (excitatory synapse) : More than 95% of Synapses in the CNS



  - Axo-somatic type (Inhibitory synapse) : 3-6% of Synapses in the brain

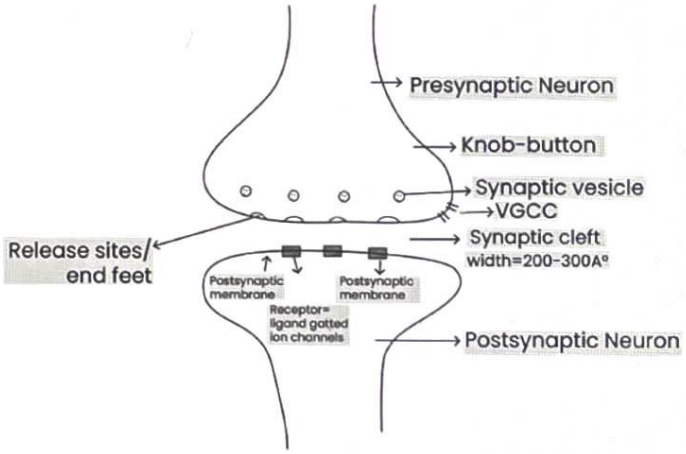


    - → e.g.
      - Renshaw cells on anterior motor neuron
      - Endogenous analgesia system
      - Purkinje cell system in the Cerebellum
- Axo-axonal type= for presynaptic inhibition



Axo-axonal type

Structure and transmission at Synapse:



- SNAP proteins : Synaptobrevin and Syntaxin are proteins present in presynaptic membrane and helps in neurotransmitter release.

- Synap-25 : protein present in postsynaptic membrane
- **Receptor:**
  - Aka Target molecule/Ligand gated ion channel.
  - Is present on post synaptic membrane.
  - Consist of two parts:
    → Receptor portion
    → Channel gates

Note:
- Clostridium tetani and Clostridium Botulinum interferes with SNAP proteins present at presynaptic membrane and interrupt the neuronal transmission at synapse

TRANSMISSION AT SYNAPSE:

Arrival of impulse at the Presynaptic terminal
↓
Change in voltage at the presynaptic terminal leads to opening of calcium channels and calcium influx occurs
↓
Migration and fusion of synaptic vesicle with release site present at presynaptic membrane
↓
Release of neurotransmitter by exocytosis
↓
Neurotransmitter traverses the synaptic cleft and Binds to Receptor molecule present on post synaptic membrane.
↓
In case of excitatory neuron, binding of neurotransmitter with the receptor part leads to release of Na+ or Ca++ and causes depolarization. And in case of inhibitory neuron, it leads to opening of K+ or Cl- channels and causes hyperpolarization.

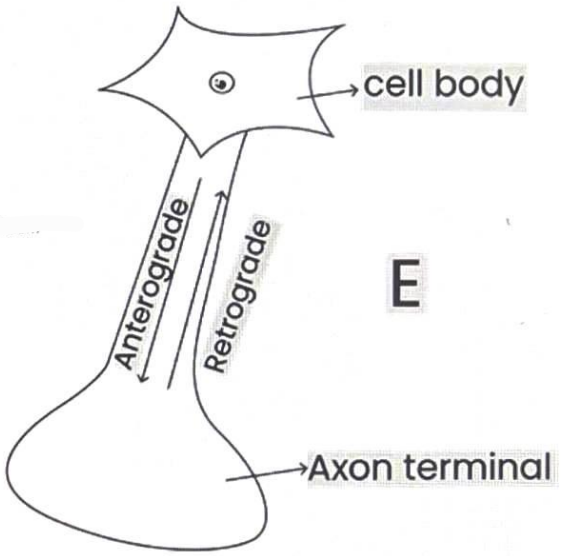
Synaptic Potentials:

- EPSP (excitatory postsynaptic potential): occurs due to opening of Na+/Ca++ channels at postsynaptic membrane.
- IPSP (inhibitory postsynaptic potential): occurs due to opening of k+/Cl- channels at postsynaptic membrane.

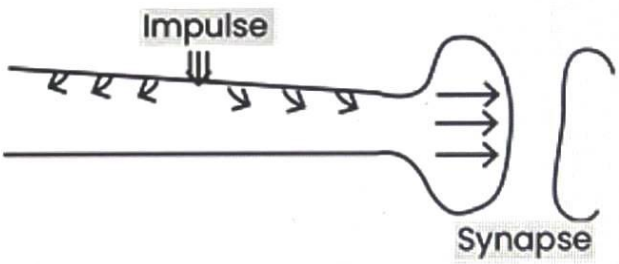
Note:
- EPP is an end plate potential and has an amplitude of approx. 40 mV. Because of its large amplitude, 1 EPP leads to generation of 1 Action potential. On the other side, EPSP is an excitatory postsynaptic potential and has an amplitude of approx. 2-4 mV. Because of its small amplitude multiple EPSP add up to generate 1 Action potential.

EPSP	Acion Potential
1. Localized	1. Propagated
2. 2-5 mv	2. 105 mv
3. Graded	3. Obeys All or none Principle
4. Monophasic	4. Biphasic

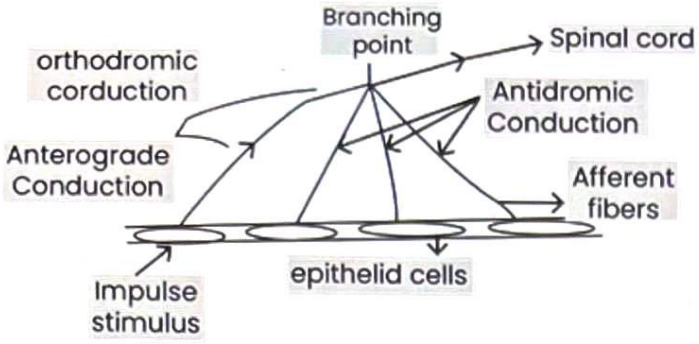
Terminology:
- Anterograde Transmission: transmission of axonal materials from the cell body to the direction of the axonal terminal
- Retrograde Transmission: transmission of axonal materials from the synapse to the direction of cell body.



- Unidirectional transmission: At Synapse impulse only travels in one way I.e., towards the synaptic cleft.
- Bidirectional transmission: On stimulation of nerve axon membrane, impulse can travel to both directions I.e., towards and away from the synapse.



- Orthodromic: Conduction of impulse in the anterograde fashion.
- Antidromic: Conduction of impulse opposite of the normal direction of conduction I.e, opposite to anterograde direction.

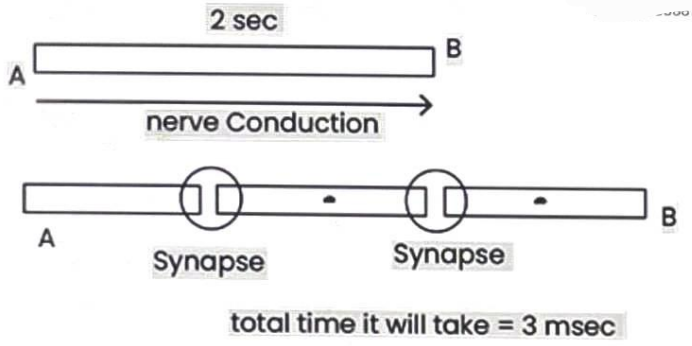


Properties of Synapse:

1. One Way Conduction
2. Delay: 0.5 msec of delay occurs at each and every synapse.

Example:

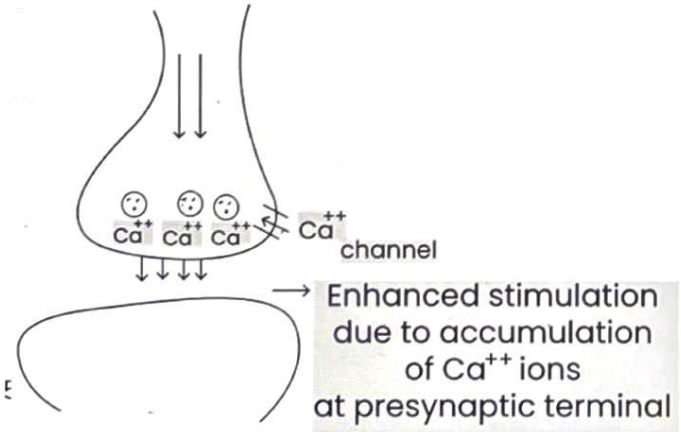
- It takes 2msec to travel from point A to point B on a particular pathway which contains no synapses. And if that pathway contains 2 synapses it will take 3mses in total to travel from point A to point B (delay time at synapse = 0.5msec)



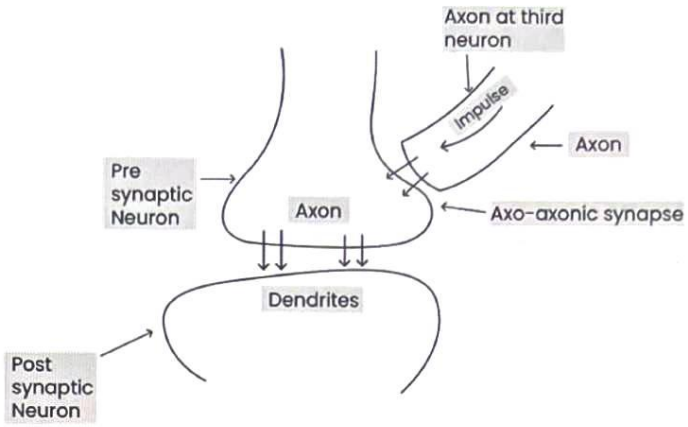
total time it will take = 3 msec

3. Synaptic fatigue: Repeated stimulation of synapse causes exhaustion of neurotransmitter and no impulse conduction occurs for some time.
4. Post tetanic potentiation:

- High frequency stimulation of synapse for some time leads to enhanced transmission. It occurs in response to accumulation of calcium at presynaptic terminal.



- An increase in the effect of a presynaptic neuron on a postsynaptic neuron caused by a third neuron that makes an axoaxonic synapse with the presynaptic neuron near its terminal button.

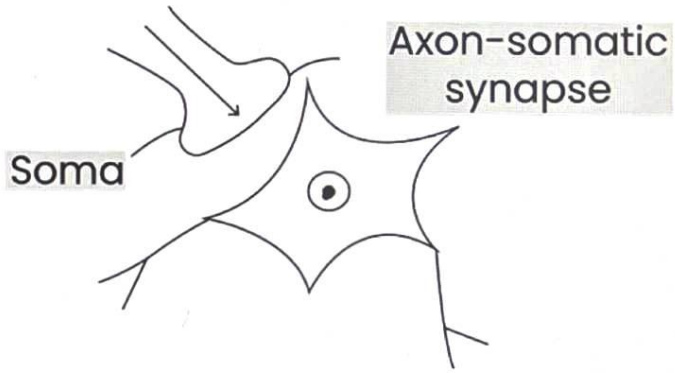


Note:

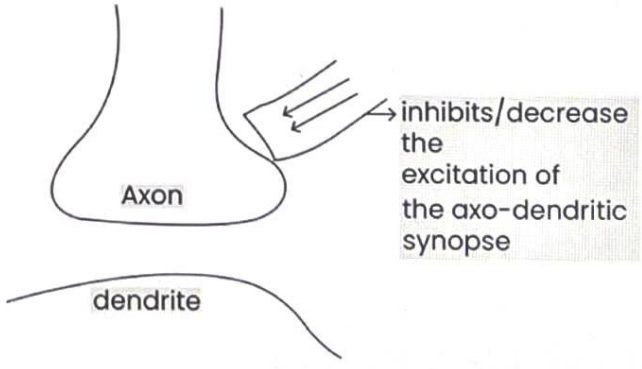
- Release of neurotransmitter is proportional to amount of calcium present at presynaptic terminal.

6. Inhibition: inhibitory neurons open K+/Cl- channels and generates IPSP

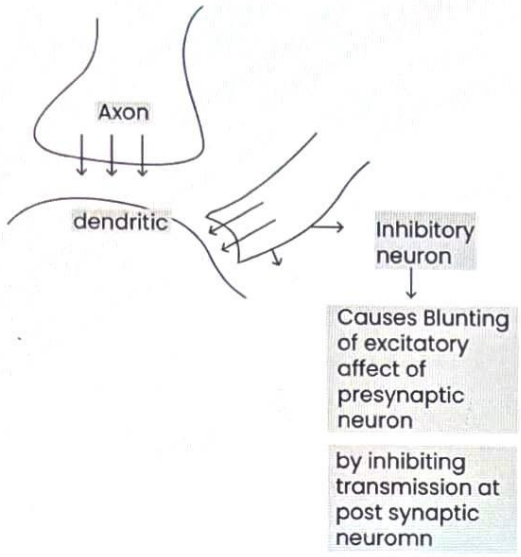
- Types of inhibition: # Direct = occurs in case of axo-somatic synapse



- #Presynaptic = occurs in the axo-axonal synapse via decrease release of neurotransmitter at axo-dendritic synapse



- #Postsynaptic: occurs because of hyperpolarization of postsynaptic membrane.

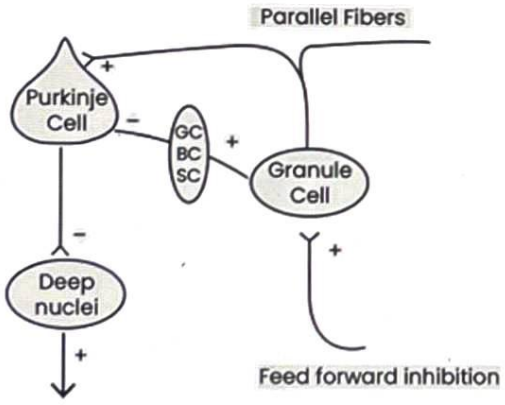


Important Information

- Other special types of inhibition: #. Renshaw cell inhibition- Renshaw cell is a short inhibitory interneuron in a spinal cord. These cells prevent the motor neuron from getting fatigued by inhibiting/decreasing continues stimulation from various areas of brain. Therefore, it decreases the excitability of the motor neuron.

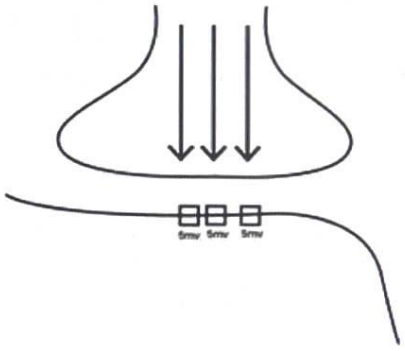
Question: Renshaw cell inhibition is what type of inhibition?
Ans: Recurrent type of inhibition

- Apart from anterior motor neuron, Renshaw cells also gives axons to other neurons present at that level. By doing this, it helps in sharpening the signal from anterior motor neuron
- Feed-forward inhibition: common in cerebellum



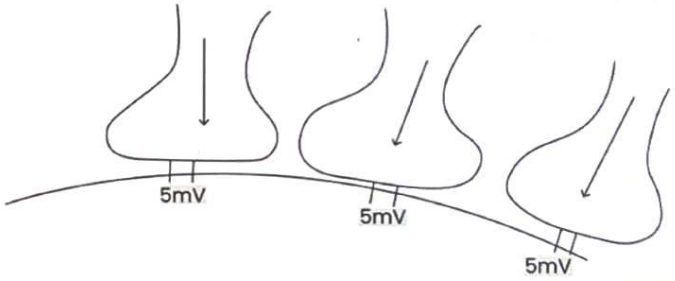
Feed forward inhibition

7. Summation of the EPSP's: A necessity to generate an Action potential.
- It occurs in two ways Temporal and Spatial summation
- Temporal summation:
  - Occurs when series of subthreshold EPSP's in an excitatory nerve fiber produces an action potential in the post synaptic neuron.
  - A prerequisite for this is the time (15 msec). EPSP is a decremental potential, so if second impulse does not come within 15 msec, the EPSP generated by first impulse will go in vain and will not lead to any action potential generation. To reach or cross the threshold potential of post synaptic membrane which is 70mV, it will take summation of 3 or more than three EPSP's to generate an action potential.



Temporal Sumation

- Spatial summation: Cumulative effect of different EPSP's generated at different synapses at the same time upon the membrane action potential.



Spatial summation of these EPSP's

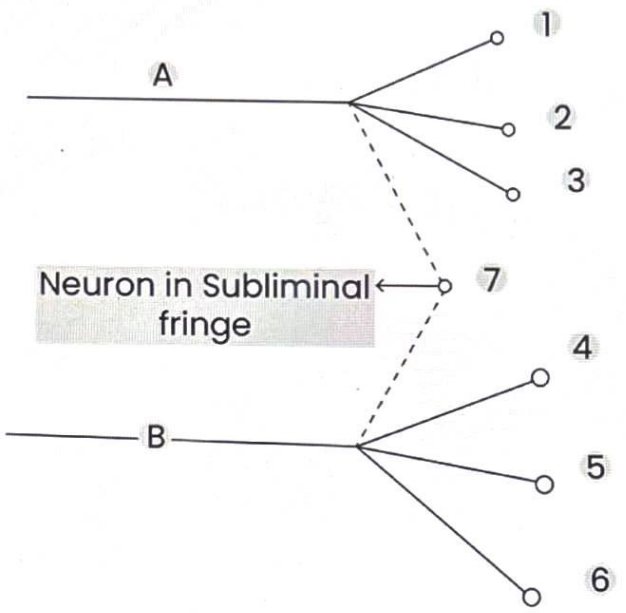
5mV + 5mV + 5mV = 15mV

Note:
- For the spatial summation to occur over the space, it requires the next impulses to come within 15 msec of each other.

8. Subliminal fringe: The simultaneous firing of two presynaptic neurons gives more than anticipated response because some neurons are said to be in subliminal fringe.

Example:

- Neuron A and neuron B are firing 3 neurons each individually, but the simultaneous stimulation of both A and B neuron will produce effect more than their individual effect as the simultaneous stimulation will excite one more neuron as shown in the image with dotted line:



9. Occlusion: Simultaneous stimulation of A and B results in activation of 5 postsynaptic neurons instead of 6. this is called occlusion.

Fate of Neurotransmitter at the Synapse

- Enzymatic destruction
  e.g. : Acetylcholinesterase degrades acetylcholine into acetyl part and choline part
- Reuptake and repackaging
- Diffuses out of synaptic cleft

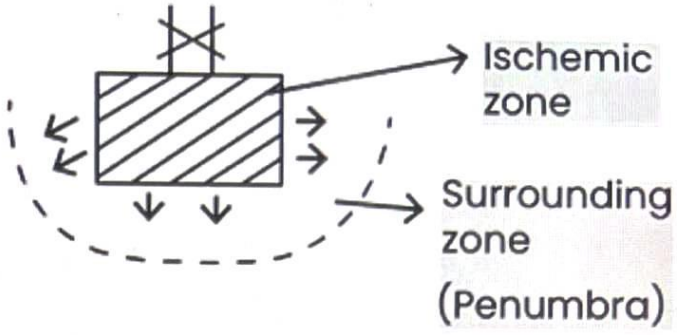
NEUROTRANSMITTERS (NT's)

Glutamate:

- Plays role in more than 90% of excitatory transmission occurs in the CNS (retinal rods, cortex, Hippocampus etc.)
- Types of Glutamate receptors
  - Kainate
  - AMPA
  - NMDA= N- Methyl-D-Aspartate receptor
    → Major role in long term potentiation in Hippocampus

**** Penumbra in CNS, process where Glutamate plays major role.**

- Penumbra means extension of ischemic damage to area surrounding the original area supplied by blocked artery. Or extension of ischemic damage beyond the original ischemic area



Flow chart

GABA:

- Most common inhibitory neurotransmitter. More than 905 of inhibitory transmission occures through this neurotransmitter.
- Applied: Stiff Man Syndrome
  - Is an autoimmune disease, characterized by presence of Anti- GAD antibodies which inhibits the conversion of Glutamate into GABA. Therefore, no GABA formation occurs and it leads to excessive facilitation of stretch reflex and excessive tone in muscles

Execessive facillitation of stretch fibers/reflex

↓ ↓

Excessive tone in muscles

Note:

- Anti-GAD antibodies are also seen in T1DM. Because of that, T1DM may also be seen in patients with Stiff man syndrome.

Glycine:

- Commonest inhibitory NT in the Spinal cord.
- Applied: Strychnine poisoning
  - Strychnine acts as an antagonist of glycine in the spinal cord. Therefore, it leads to excessive muscle contraction and spasms.

Neurotransmitters in the Analgesia System

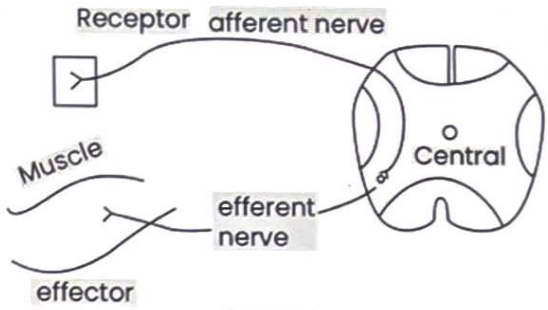
- Endogenous opioids: Endorphins, encephalin, Dynorphin
- Endogenous cannabinoids:
  - 2-AG (2-arachinoid glycerol), Anandamide
  - Acts via CB1 and CB2 receptors
  - CB1 mediates the Euphoria effects
  - CB2 mediates the Analgesic effects

REFLEX

- Definition: Involuntary response to a sudden and adequate stimulus

Or

- Reflex is a physiologic process by which a sensory stimulus is automatically converted into amktor response without the involvement of the higher centers.
- Components: There are 5 components of reflex are:
  - Sensory receptor
  - Afferent nerve
  - Center
  - Efferent nerve
  - Effector organ



Reflex Arc

Classification of Reflexes

- Anatomical
  - Spinal :Tendon jerk reflex
  - Supra-spinal
    - → Pupillary light reflex
    - → Corneal reflex
    - → Conjunctival reflex
- Physiological
  - Flexor/ withdrawal type: Protective, Pain reflex
  - Extensor reflex : Postural reflexes
  - Based upon no of synapses
    - → Monosynaptic: Tendon jerk reflex
    - → Oligosynaptic: Initiated by the Golgi tendon organ
    - → Polysynaptic: Pain reflexes

Clinical

- Superficial
  - Corneal reflex
  - Abdominal reflex
  - Plantar reflex
- Deep reflexes
  - Tendon jerk reflexes
- Visceral reflexes
  - Gastro-colic reflex,
  - Baroreceptor reflexes

Innate vs Acquired reflexes

- Unconditioned reflexes
- Conditioned reflexes
- e.g., Pavlov's experiment of classical conditioning

Properties of reflexes are same as of the properties of synapse

36 SENSORY SYSTEM

SUMMARY

1. Senses, 3 Neuron path, Laws for encoding
2. Receptor
3. Ascending tracts
4. Cortex
5. Physiology of pain

SENSES

00:01:19

GENERAL	SPECIAL
1. Touch	1. Vision
2. Pain	2. Hearing
3. Pressure	3. Taste
4. Proprioception	4. Smell
5. Vibration	5. Equilibrium

SPECIAL SENSES

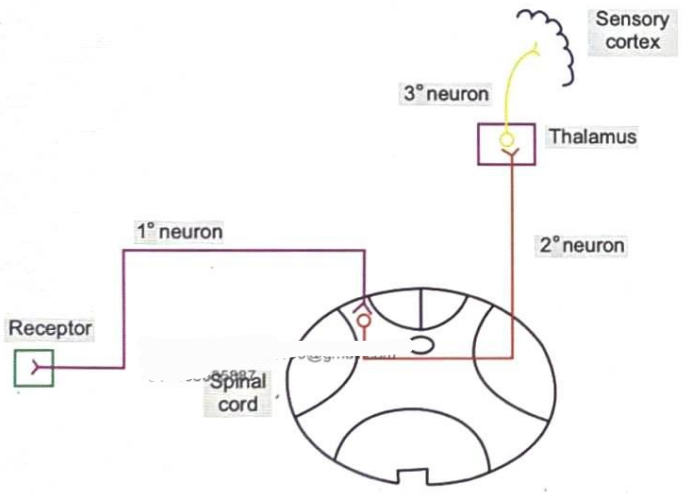
- Contains specialized end organ
- Carried by cranial Nerve

GENERAL SENSES (Based on stimulus)

3 Neuron Path

00:03:20

- 1° neuron → starts from receptor & enters the spinal cord
- 2° neuron → starts from spinal cord, crosses midline & ends on thalamus
- 3° neuron → starts from thalamus to the sensory cortex



THALAMUS is the OBLIGATE RELAY STATION for all general and special sense Except OLFACTION.

THALAMUS

- OBLIGATE RELAY STATION for all senses

Q. Which of the following thalamic nuclei is involved in motor function?

a) VPL nucleus
b) Venterolateral nucleus
c) Ventro basal complex
d) Intralaminar nucleus

- Thalamic nuclei involving in motor functions
  - Ventro Anterior
  - Ventro Lateral
  - Centro Median

  } connected with cerebrum & Basal ganglia
- Sensory system has sensory stimuli which are a form of energy and are converted into electrical energy via receptors.
- Encoding of sensry system.

LAWS

00:12:30

DALE'S PRINCIPLE

- Applicable for entire nervous system
- Same neuro transmitter is released from all the branches of a neuron

MULLER'S DOCTRINE OF SPECIFIC NERVE ENERGIES

00:14:50

- No matter what form of energy is applied, each sensory pathway conveys the same form of energy that it is supposed to convey

LABELLED LINE PRINCIPLE

00:17:29

- Encodes modality, location (to some extent)
- Each sensory modality is carried by a specific tract in CNS located in a specific part of CNS
- Ex: Fine touch carried by dorsal columns

LAW OF PROJECTION

00:18:31

- Phantom limb
- No matter where you apply a stimulus, cortex projects the sensation onto the receptor from where the pathway starts
- Phantom pain sensation may disappear after 6 months

INTENSITY DISCRIMINATION

00:28:52

Q. Intensity discrimination in CNS occurs by changing what?

a) AP amplitude
b) AP duration
c) AP frequency
d) AP velocity

WEBER FECHNER LAW

00:32:36

- S = K X log (I)
  - S → magnitude of sensation Felt
  - K → proportionality constant
  - I → actual Intensity applied

- Ex: K = 1 } S = 1x1 → If the perception felt is doubled,
- I = 10 } S = 1 actual intensity at the periphery is ↑ by 10 times
- I = 100 → S = 1x2 = 2

STEVEN'S POWER LAW

00:25:22

- $S = KX(I)^n$

BELL MEGENDIE LAW

00:36:28

- DORSAL ROOTS ARE SENSORY & VENTRAL ROOTS ARE MOTOR

RECEPTORS

00:37:21

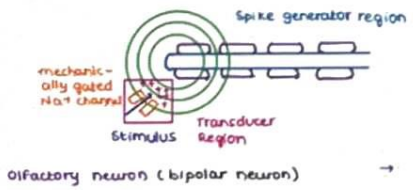
- Specialised end organs
- Biological transducers → converts any form of energy into electrical energy

Q. For which sensation is both transducer and spike generator regions are on the same cell?

a) Vision
b) Olfaction
c) Propriception
d) Vibration

PACINIAN CORPUSCLE

00:40:46

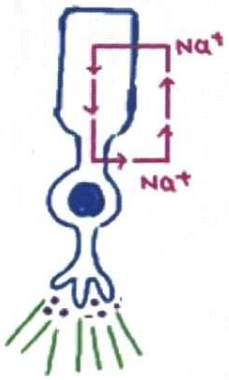


- 1st AP generated at 1st Node of Ranvier in sensory neurons (EXCEPTION)
- Receptor potential should be > 10mV, to generate a spike potential

Receptor Potential	AP
• Localized • Graded (10-100 mv) • Monophasic	• Self-propagated • All or none • Biphasic

- Localized depolarising potential except vision (by rods & cones)
- Red receptor potential is a hyperpolarising potential.

- In neurons 1st AP is at axon hillock but for cutaneous nerves, it is at 1st Node of Ranvier
  - For most of sensations, receptor potential is depolarising potential, but
- In case of visual sense, rod receptor potential is hyper polarizing potenial



- When light strikes, Na^+ goes out but can't come back in
- ROD is HYPERPOLARIZED
- ↓ Glutamate at Synapse
- Light is perceived
- Reason → Evolution development

CLASSIFICATION

01:00:07

TELE RECEPTORS

- Source of stimulus is at a certain distance from the body

EXTEROCEPTIVE SENSES

- Source of stimulus is on external aspect of body
- INTEROCEPTIVE SENSE → Source of stimulus is deep inside the body
  E.g. Proprioception

1. MECHANO RECEPTORS
   - Meissner's corpuscle
   - Merkel disc
   - Pacinian corpuscle
   - Ruffini's corpuscle
   - Iggo dome

2. THERMO RECEPTORS
   - Belong to TRP (Transient Receptor Potential) Superfamily
   - CMR (Cold & Menthol Sensitive Receptor)

3. CHEMO RECEPTORS
   - Olfactory ®
   - Taste ®
   - Glomus cell

4. ELECTRO MAGNETIC RECEPTORS→ Rods & Cones
5. NOCICEPTORS
   - Belongs to TRP Super Family
   - Vanilloid Receptor (TRP-V_1)
   - NOT FREE NERVE ENDINGS

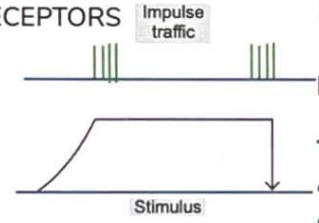
PROPERTIES

01:08:23

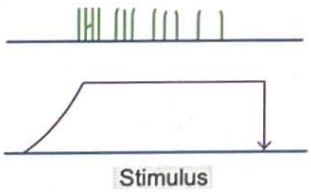
1. Specificity
2. Receptor potential
3. Adaptation
   - Receptor responds to stimulus briefly but with continued stimulus, receptor stops responding
   - When continuous stimulus is removed, receptor responds briefly
     → ↓ the unnecessary sensory iformation is stoppped at the periphery (burden tocerebral cortex)
     → Only change in the environment detected

TYPES

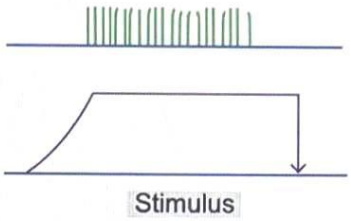
1. RAPIDLY ADAPTING / PHASIC RECEPTORS
   - PACINIAN CORPUSCLE
     → Phasic receptor
     → Mechano receptor
     → Best suited for vibration



2. SLOWLY ADAPTING RECEPTOR
   - MERKEL RECEPTOR
     → Ruffini's corpuscle
     → Helps in continuously sending the important sensory information



3. NON ADAPTING / TONIC RECEPTOR
   → Do not adapt
   → Helps to carry the very important sensory information
   → Ex: PAIN RECEPTOR



MECHANO RECEPTORS

01:23:40

RECEPTOR	LOCATION	SPEED OF ADAPTATION	SENSATION ENCODED
Merkel's Disc	(Most superficial) Epidermis	Slowly	Location of touch
Meissner corpuscle	Dermis	Rapidly	Speed of application of touch → Flutter along the skin
Pacinian corpuscle	Dermis & Deeper tissues	Very rapidly	Vibration
Ruffini's corpuscle	Ligaments, Muscles & Tendons	Slowly	Deep pressure (massage)

BRAILLE → meissner corpuscle > ruffini's corpuscle

TEMPERATURE RECEPTOR'S

01:29:30

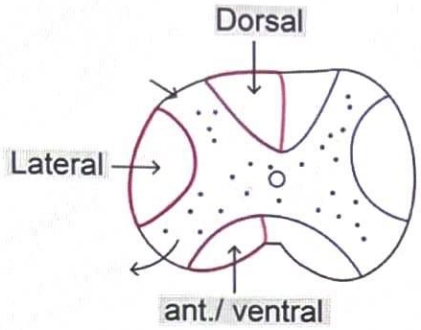
- Tonic + Phasic receptors
- For every 1° C steady ambient temperature , tonic discharge occurs
- From 10° C - 30° C
  - For each 1°C, tonic discharge occurs by Cold receptors
- From 32° C - 38° C
  - For each 1° C, tonic discharge occurs by Warm receptors
- > 45° C → PARADOXICAL COLD
- 30° C - 32° C→ THERMO NEUTRAL ZONE
- 20°C - 24°C→ Maximum firing frequency of cold receptors (Thermogenic shivering can be intiated)

- For sudden change to temperature, Phasic discharge occurs
- ↓ temperature, cold receptors fired physically
- ↑ temperature, warm receptor fired physically
  - Indicates the change in direction of temperature

ASCENDING TRACTS

01:37:15

SPINAL CORD CROSS SECTION



- Central H Shaped grey area
- Anterior white column
- Posterior white column
- Lateral white column

1. DORSAL COLUMN SYSTEM
   - Carries Fine touch (2 point discrimination)
     - → Pressure
     - → Vibration
     - → Proprioception (Conscious)

2. ANTERO LATERAL SYSTEM
   - Carries Crude touch
     - → Pain
     - → Temperature
     - → Tickle, Itch
     - → Sexual sensations

by lateral white column

DORSAL COLUMN	ANTERO LATERAL COLUMN
Faster	Relatively slow
• Aα, Aβ	• A, C
• 70 - 120 m/sec	• 5 - 30 m/sec
• Spatial organisation	• No spatial organisation

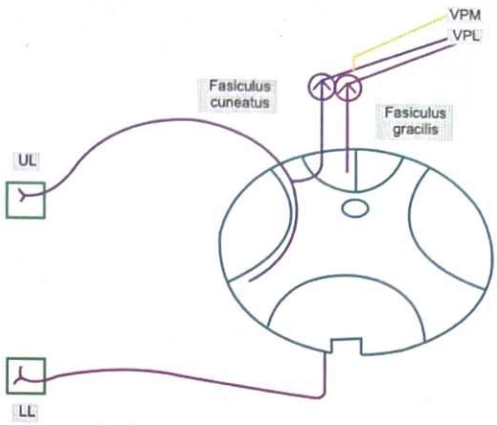
DORSAL COLUMN

01:53:49

- Stereognosis is lost in the lesion of fasciculus cuneatus
- Faciculus gracilis

Tract of GOLL & BURDACH (old name)

- Fasciculus cuneatus



- 1°neurons ends in upper medulla, In nucleus gracilis & nucleus cuneatus
- 2°neuron
- starts in upper medulla & crosses midline & runs in medial leniscus & joined by trigeminal nerve & ends in thalamus
- 2° neuron of dorsal column ends in ventro lateral nucleus
- Trigeminal nerve ends in ventro posterior medial nucleus of thalamus

ANTERO LATERAL COLUMN

02:05:02

PAIN FROM UL

- 1° neuron enters the spinal cord & ends there
- 2° neuron starts from dorsal horn & crosses midline in anterior commissure & ascends up as LATERAL SPINO THALAMIC TRACT to Thalamus

PAIN FROM LL

- 1°neurons enter spinal cord and ends there
- 2°neurons starts & crosses midline & runs upwards in lateral white column
- UL fiber joins lower limb & LL fiber pushed laterally

Arrangement of fibers in lateral white column (from lateral to medial)

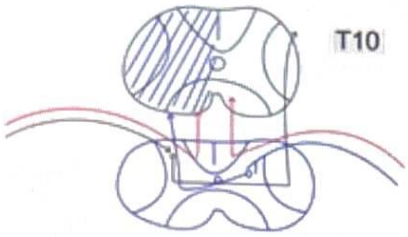
1. LL
2. Abdomen
3. UL
   - in the tumor of lateral column, 1st sensation affected is →pain from opposite side of LL
   - VPL NUCLEUS → Relay nucleus for all the sensations
   - Ventro basal complex
   - SYRINGOMYELIA

   } for pain sensation

     - → Cyst filled lesion in central canal (Syrinx)
     - → Grows anteriorly & damage pain & temperature fibres first

BROWN SEQUARD SYNDROME

02:19:20

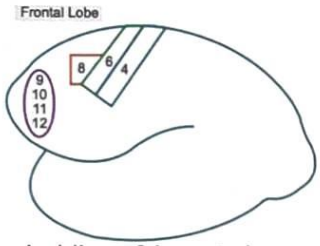


- Hemisection of spinal cord
- Loss of sensation
- Below the level of lesion, fine touch is affected but opposite side fine touch is intact
- Pain and temperature of the opposite side below the lesion is affected while the same side is unaffected
- At the level of lesion, there is hyperesthesia, lower motor neuron type of lesion
- Below the level of lesion, upper motor neuron type of lesion

SENSORY CORTEX

02:26:11

- Area 3,1,2→S I (Somato sensory Area I)
- Area 5,7 →S II (Secondary sensory cortex)
- S I → Concerned in perception of sensation
  - S II→ Concerned in analysis & interpretation of sensations [Stereognosis]



- Body representation is contra lateral, oblique & inverted (upper body in lower end of cortex & vice versa)
- Largest representation- Lips> Face> fingertips (2 point discrimination is best on fingertips)

PHYSIOLOGY OF PAIN (and Analgesia)

02:35:34

Definition- Unpleasant sensory sensation assciated with negative emotion

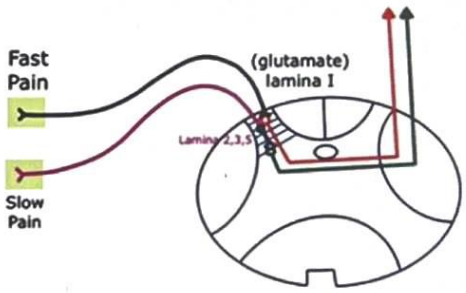
PAIN INSENSITIVE STRUCTURES	PAIN SENSITIVE STRUCTURES
Brain	Vessels, Meninges
Eye-Cornea	
Thorax- Lung parenchyma	Pleura, Airways
	Heart, Pericardium
Abdomen- Liver parenchyma o Intestines →Not sensitive to sharp cutting pain →Sensitive to torsional pain	Liver capsule
	Gall Bladder, Bile duct
GU tract- Kidney	Ureter, Bladder, Urethra

TYPES OF PAIN

1. Fast pain/ 1st /sharp/ acute/ pricking pain (Aδ)
2. Slow pain/ 2nd/ dull/ chronic/ aching pain (C type)

Receptors for pain (Nociceptors)- TRP superfamily (Vanilloid)

- Neospinothalamic tract carries Fast pain (Glutamate)
- Paleospinothalamic tract carries Slow pain (Substannce P)
- Pain carried by Lateral Spinothalamic tract



VARIETIES OF PAIN

02:54:16

- Physiologic → Starts from receptor & conveyed to cortex

1. ALLODYNIA
   - Non noxious stimulus gives pain sensation
   - Ex: Trigeminal neuralgia
2. NOCICEPTIVE → Noxious stimulus giving corresponding degree of pain
3. HYPERALGESIA → Noxious stimulus giving exaggerated pain

- Types- Primary (Stimulus applied at the site of injury) & Secondary (Painful stimulus applied away from the site of pain)

- Pathologic → Does not start from receptor
  Neuropathic pain (nerve injury)
  - Causalgia
  - Phantom pain

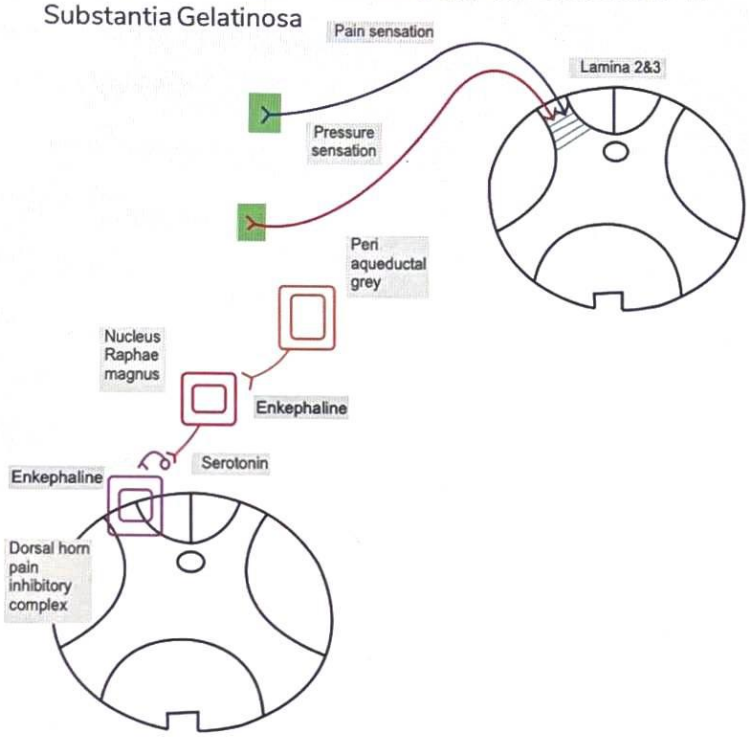
ANALGESIA SYSTEMS

02:00:53

- Gate control theory of pain
- Descending analgesia system
- Opioids / endogenous cannabinoids

GATE CONTROL THEORY OF PAIN

- Accupressure Therapy is based on this
- Gate is Substantia Gelatinosa of Rolando (Lamina 2 & 3)
- Pressure sensation inhibits pain via collaterals in Substantia Gelatinosa



DESCENDING ANALGESIA SYSTEM

- 3 COMPONENTS

1. PERI AQUI DUCTAL GRAY

- Projects on nucleus raphae magnus
- Has enkephalic neurons
- NT → Enkephalin

2. NUCLEUS RAPHAE MAGNUS

- Projects serotinergic neurons & ends on inter neurons
- NT → Serotonin
- Inter neurons forms Dorsal Pain inhibitory complex

3. DORSAL PAIN INHIBITORY COMPLEX

- Inter neurons NT → Enkephalin
- Pre synaptic & post synaptic pain inhibition occurs
- Enkephalin has inhibitory effect on pre & post pain carrying afferents

ENDOGENOUS OPIOIDS / ENDOGENOUS CANNABINOIDS

ENDOGENOUS CANNABINOIDS

1. 2-AG
2. Anandamide
   - act via CB Receptors
   - CB_1 → a/w Euphoria
   - CB_2 → a/w Control of pain

ENDOGENOUS OPIOIDS

1. Endorphins
2. Enkephalins
3. Dynorphin
   - POMC (basophil cells of intermediate pituitary)
   - Corticotrophins — βLPH ↓ ENDORPHINS
   - MSH

RECEPTORS

03:17:51

- Endorphins → μ
- Enkephalins → κ
- Dynorphins → δ

Endorphin predominant Actions

1. Meiosis
2. Constipation

Tolerance does not develop

μ	κ	δ
• Analgesia • Meiosis • Sedation • Euphoria • Constipation • Respiratory depression ↑ GH secretion ↑ Prolactin Secretion	• Analgesia • Meiosis • Sedation • Dysphoria • Diuresis	Analgesia

CLINICAL QUESTIONS

Q. An Aesthesiometer is a device for measuring the tactile sensitivity of the skin (or mouth, or eye, etc.). The distance by which 2 touch stimuli must be separated to be perceived as 2 separate stimuli is greatest on?

A. The lips
B. The palm of the hand
C. The back of scapula
D. The dorsum of the hand

Answer: C

Solution:

Two-point discrimination:

- It is the **ability to distinguish between two adjacent mechanical stimuli** applied to the skin.
- It depends on the **receptor density** and **receptive field sizes** of the sensory neurons.
- The area of the skin, when stimulated, causes an activity in the sensory neuron is called the **receptive field** of the neuron.
- **Receptive field sizes are small over finger tips, lips and face area**. Hence, two-point discrimination ability is greater in these parts.
- On the **back, the large receptive field sizes cause this distance to be 50-60 mm.**
- **Aesthesiometer:**
  - **Weber's compass aesthesiometer** is used for testing two-point discrimination.
  - **Von frey's hair aesthesiometer** is used to measure touch threshold.

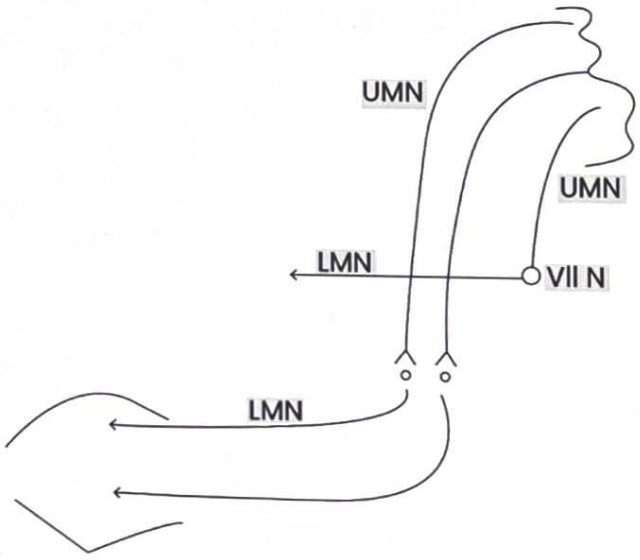
Reference: Guyton and Hall Textbook of Medical Physiology 13th Edition, Page No. 614

37 MOTOR SYSTEM PART-1

- THE Motor System is a system that controls the body's voluntary movements.
- The UMN and LMN neuron pathways are responsible for its operation.
- UMNs are found in the motor cortex, and their fibres descend down the spinal cord, terminating on LMNs at various levels of the spinal cord, as well as at the level of the brain stem in some cases. The LMNs take the impulse from the spinal cord and convey it to various parts of the body via their fibres. Muscles are one example.

TWO NEURON PATH

00:01:38



Important Information

- The inhibitory effect of UMN on LMN is primarily inhibitory.

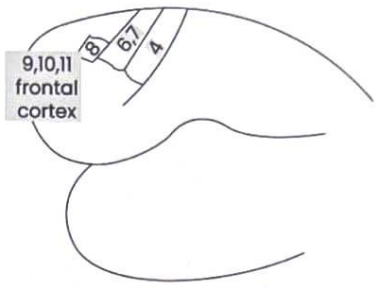
- **Applied:** If the UMN is damaged, there will be no inhibitory effect on the LMN, and the LMN response will be amplified. In the case of an LMN lesion, however, there will be no reaction and no movement.

ORGANIZATION OF MOTOR CORTEX

00:09:41

- The motor cortex is a part of the brain that

Area-4,6,7,8



- Primary motor cortex (Area 4)
- Areas 6 and 7 are the premotor and supplementary motor areas.
- Frontal eye field (area 8)
- Areas 9,10,11,12 of the frontal lobe are concerned in a person's social and intellectual activity.

Important Information

Q. When a man decides to make a voluntary movement, the first impulse is recorded on which portion of the motor system?

Ans: The premotor cortex, also known as region 6 of the motor cortex.

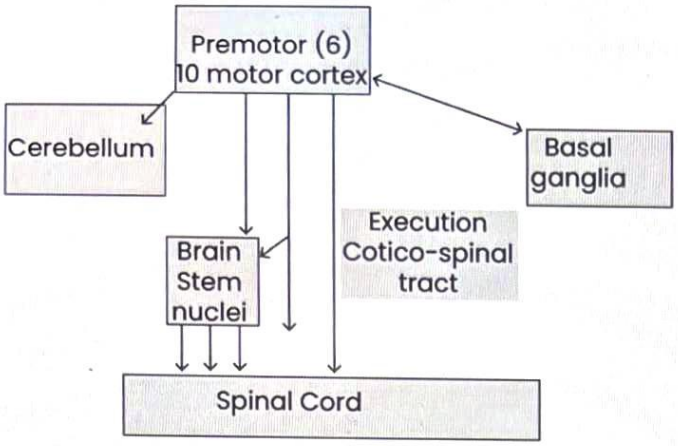
- Along the precentral gyrus of the frontal lobe, the Motor Homunculus is a topographic representation of the human body parts and their correspondents. There's a contralateral, roughly inverted, and oblique representation there.

Important Information

Q. In the moto cortex, which motor regions have the most representation?

Ans: The muscles of mastication and the thumb muscles, which are used in highly skilled actions.

ORGANIZATION OF MOTOR SYSTEM 00:16:53



- The Basal Ganglia's function is to turn abstract cognition into movement.
  - To choose the desired motion
  - To put a stop to the other movement
  - To give movement a sense of spontaneity.
- If the basal ganglia is damaged, it will take longer for the brain to respond to the abstract idea of movement.
  - Gives the movement a sense of direction.
  - Gives a sense of scale
- Cerebellum: Controls the timing of motor contractions.
- The primary motor area is responsible for commanding motor movements.
- The descending tracts deliver a signal to the spinal cord from the primary motor region, which results in movement execution/initiation.
- Cortico-spinal tracts, also known as Pyramidal tracts, are a type of cortico-spinal tract.
- The signal is sent down the descending pathways from the primary motor cortex to the brain stem nuclei, and then to the spinal cord.
- Plays a key role in the movement's inception.
  - Distal muscular control, which aids in skilful movements such as thumb and foot muscles

Extrapyramidal tracts are a type of extrapyramidal tract.

- Vestibulospinal tract: Assists in maintaining body balance and posture.
- Reticulospinal tract: regulates the body's central axial muscles.
- The rubrospinal tract connects the red nucleus to the spinal cord.
- The tectospinal tract is in charge of controlling movement in response to visual and auditory stimuli.
- Quadrigemina corpora
  - Two superior and two inferior colliculi make up this structure in the tectum.
  - Vision is linked to superior colliculi.
  - Hearing is associated with inferior colliculi.
  - Extrapyramidal tracts are a type of extrapyramidal tract that exists outside
  - Areas of the cortex responsible for motor function
  - The ganglia at the base of the spine

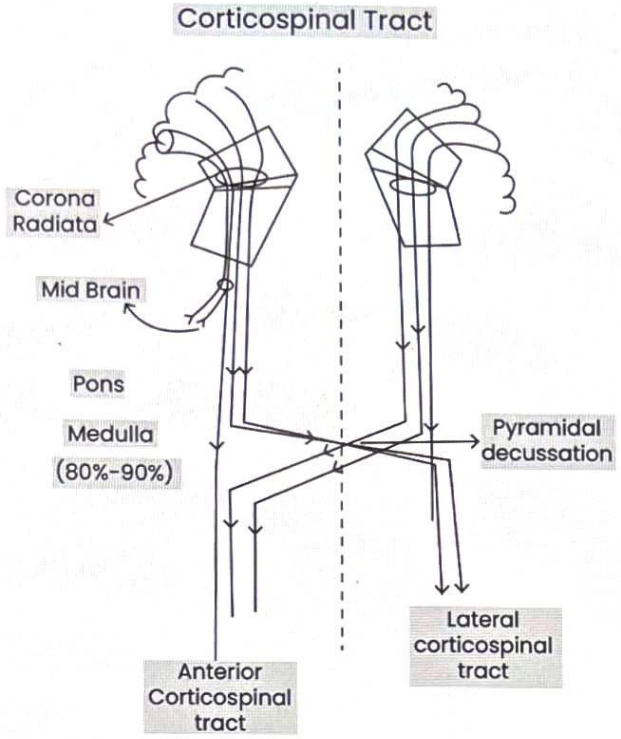
Cerebellum

- Constant changes in muscle posture (unconscious proprioception).
- By way of the LMN, it sends data to the spinal cord.
- The output of the cerebellum is sent to the LMN via the spinal cord, and muscle actions are fine-tuned.

CORTICOSPINAL TRACT 00:42:17

- 30 percent of fibres originate in the corticospinal tract, which is located in the motor cortex's area 4.
- Area 6 of the motor cortex contains 30% of fibres.
- 40% of fibres originate straight from the postcentral gyrus/sensory cortex.
- The Giant Betz cell, also known as the Pyramidal cell, produces 3% of all fibres.
- Betz cell with a massive size
  - The cell body is big
  - Fibres that are extensively myelinated
- The remaining 97 percent of fibres come from neuronal cells of typical size.
- The Corona radiata is formed when fibres from these distinct locations converge.
- Then pass through the anterior 2/3rd of the internal capsule's posterior limb.
- A corticobulbar/cortico-nuclear tract is formed when 10-15% of fibres terminate on brain stem nuclei.
- The remaining fibres descend further down the brain stem. 85-90 percent of these fibres travel down to the opposite side of the medulla and enter the lateral portion of the spinal cord, forming the lateral corticospinal tract.
- The opposing side's fibres likewise cross at the same level.
- Medullary decussation or Motor decussation refers to the crossing of these fibres.
- The fibres in the remaining 10-15% of the body do not cross and continue along the same side. An anterior corticospinal tract is formed by these fibres running over the anterior side of the spinal cord.

- All of these fibres eventually come to an end on the anterior LMN of the spinal cord.



FUNCTIONS OF THE PYRAMIDAL TRACT

00:57:16

- Initiates voluntary movements
- Controls distal muscle groups
- Controls thumb and skilled muscle movements
- Controls stance and gait

EFFECT OF THE LESION OF THE PYRAMIDAL TRACT

00:58:15

- UMN lesion
  - Increased muscle tone/Spastic paralysis of muscles
  - Clasp-knife reflex
  - Increased tendon reflexes
- +Ve Babinski sign- extensor plantar reflex

Important Information

- Normally +Ve Babinski sign is present in the children from birth to the age of 12-18 months
- -Ve Babinski sign or absent Babinski sign means Flexor plantar response which normally start occurring after the age 12-18 months

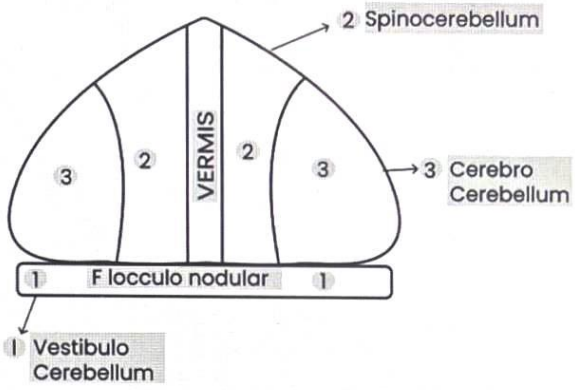
CEREBELLUM

01:07:39

- The master coordinator for the voluntary movements
- Aka small brain
- Cerebellar peduncles
  - Are bundles by which connect it to the

Functional divisions of the cerebellum

- Vestibulocerebellum
  - A function region, in the flocculonodular lobe of cerebellum
  - Controls equilibrium and posture
  - Controls eye movements in response to head movements



- Spinocerebellum
  - A function region in the paravermal area of cerebellum
  - Aka paleocerebellum
  - Responsible for coordination between muscles during movement
  - Responsible of precision and smoothness of movements
  - Damping of movements
  - Controls alternating rapid movements and tone of muscles
- Cerebrocerebellum
  - Aka as neocerebellum
  - Helps in planning and programming of movements

CONNECTIONS OF CEREBELLUM

01:21:25

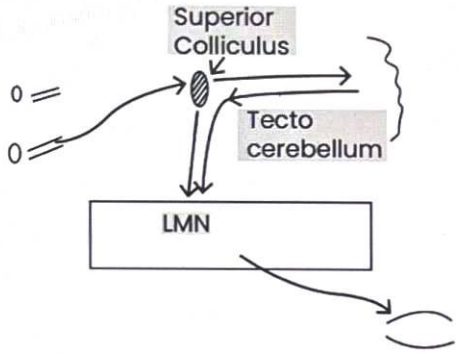
Afferent	Function
• Vestibulo cerebellar tracts	• Head orientation, Head rotation
• Spino cerebellar tracts	
• Dorsal spinocerebellar tracts	• unconscious Proprioceptive impulses from lower Parts of the body
• Ventral spinocerebellar trats	• unconscious Proprioceptive impulses from upper Parts of the body

• Cunio cerebellar tracts	• Unconscious proprioceptive impulses from arm and neck region
• Tecto cerebellar tracts	• Carry visual and auditory impulses

Important Information

Q. The structure responsible for eye hand coordination?
Ans: Superior colliculus

Superior colliculus: Visual impulses 2nd CN



- Fastest ascending tract in the CNS
  - Ventral spinocerebellar tract
- Fastest descending tract in the CNS
  - Corticospinal tract
- Longest tract in the CNS
  - Cortico Ponto cerebellar tract
- Cortico Ponto cerebellar tract
  - Responsible for intention of the cortex regarding movement
- Olivocerebellar tract
  - Converge inputs from multiple sources

EFFERENT CONNECTIONS 01:37:35

Refer Flow Chart 37.1

- Stars from the Deep nuclei of the cerebellum
- Nucleus fastigius: Deep nuclei of Vestibulo cerebellum region
- Nucleus interpositus: Deep nuclei of Spino cerebellum region
- Globose and emboliform are parts of the nucleus interpositus
- Dentate Nucleus: Deep nuclei of Cerebro cerebellum region

CIRCUIT OF THE CEREBELLUM 01:44:47

Refer Flow Chart 37.2

Inhibitory interneurons of cerebellum are

- Golgi cell
- Basket cell
- Stellate cell
- These inhibitory neurons are responsible for the feed forward inhibition of purkinje cell
- Before the purkinje cells can receive the excitatory input from the granule cell via parallel fibers, they got inhibited by these interneurons

FUNCTIONS OF CEREBELLUM 01:54:30

- To maintain and Equilibrium and posture
- To control coordination of muscle
- To control smoothness and precision of muscle
- To control alternating rapid movements
- Damping function
- Regulation of tone of the muscles

LESIONS

- Ataxia: Loss of coordination
- Dysmetria: Loss of smoothness and precision
- Adiadochokinesia/Dysdiadochokinesia: Loss of rapid alternating movements
- Past pointing: Loss of damping function
- Hypotonia: Loss of muscle tone

Intentional tremors

- At rest- no tremors occur
- During movement- tremors occur

Resting tremors

- As seen in parkinsonism
- At rest- tremors present
- During movements/any action- no tremors occur

CEREBELLUM FUNCTION TESTS 02:01:21

- Perform these tests first with eyes open and then eyes closed
- For upper limbs
- Finger nose test
- Finger to finger test

For lower limbs

- Knee heel test
- Tandem walking test
- Rhomberg's test

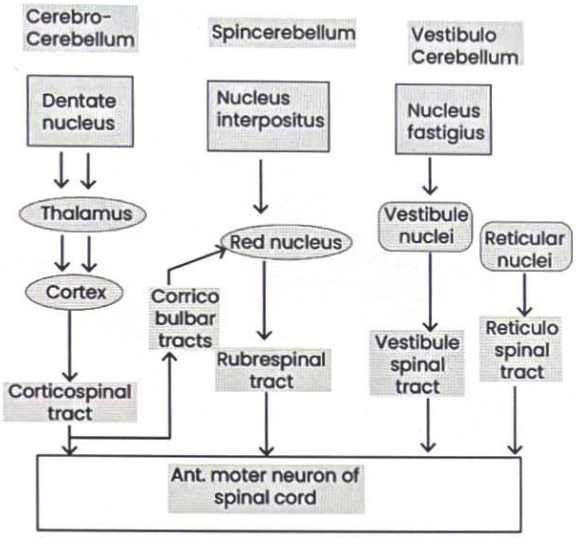
Ataxia

- Sensory ataxia

- No information is coming from the spinal cord to the cerebellum
- While performing function test with eyes open, patient will be able to perform the test because of visual sensory inputs but with eyes closed, the patient will falter

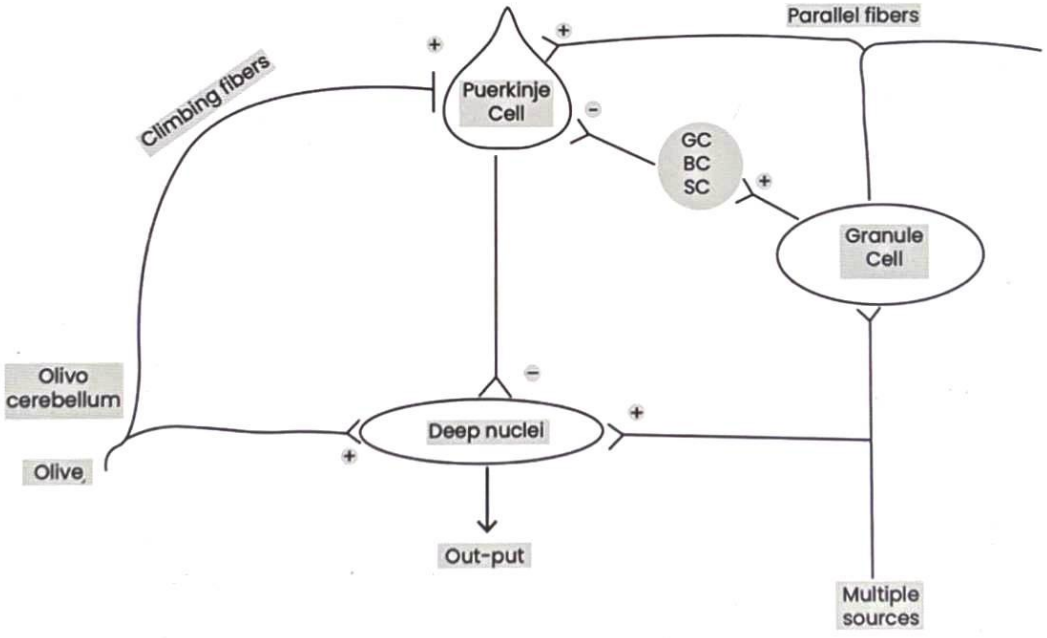
Flow Chart 37.1

Output of cerebellum



Flow Chart 37.2

CIRCUIT OF CEREBELLUM



38 MOTOR SYSTEM -2 BASAL GANGLIA

- Ganglia – collection of nerves in peripheral system counterpart in brain called nucleus
- Sub cortical matter of grey matter

Cerebellum	Basal ganglia
• Directly connected to spinal /cord that connected to muscles arise the movement • Blindly execute only	• Directly connected to motor cortex • Giving a purpose to movement based on past memory

Sub cortical masses of Grey mater

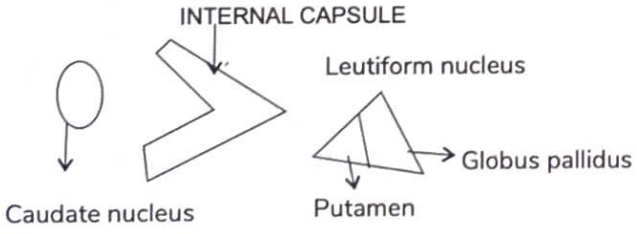
1. Caudate nucleus
2. Putamen
3. Globus pallidus /pallidum
   - GP Externa
   - GP Interna
4. Substantia nigra
   - Pars compacta
   - Pars reticulata
5. Subthalamic nucleus / body of Luy's

Functionally based

- Corpus striatum
  - Caudate nucleus
  - Putamen
- Pallidum
  - Globus pallidus
- Giving a purpose & proportion of the movements
- Planning programming of movements
- Conversion of abstract thought into movement

Anatomical

- Selects the derived movements suppression of other movements



Other side of internal capsule

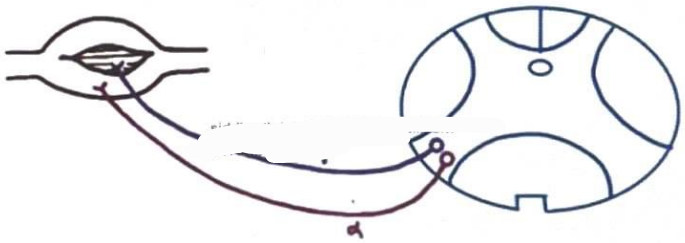
- Caudate nucleus
- Leutiform nucleus
  - Putamen
  - Globus pallidus

In wilson's disease

- Hepato lenticular degeneration due to excess copper deposition

CIRCUITS

- Direct circuit
  - All afferents end in striatum
  - All afferents emerge from internal globus pallidus
  - Fiber coming from cortex is excitatory
  - Fiber reaching back to cortex is excitatory
  - All others are inhibitory (TMG)



  - Pallido thalamic projection ('x') has back ground tonic (at rest) inhibitory activity
  - Basic for tremors at rest in parkinsonism facilitates the movement by disinhibition [inhibition of inhibitory activity]

Indirect circuit

- Inhibition of movement
- Striatum has inhibitory effect on GPE which in turn inhibit STN
- If lifted, it will excite GPI. Which in turn will facilitate the background tonic inhibition?

Substantia Nigra

- Not involved in the circuits directly
- Modulates the activity of striatal neurons – Nigro striatal projections

- Dopaminergic projection (D_1 & D_2)
- D_1 – Facilitates the direct circuit movement facilitated
- D_2 – Inhibition of indirect circuit movement facilitated

Lesions – unpurposefull movement

- Chorea – corpus striatum
- Athetosis – pallidum
- Hemiballism – subthalamic nucleus

Parkinsonism

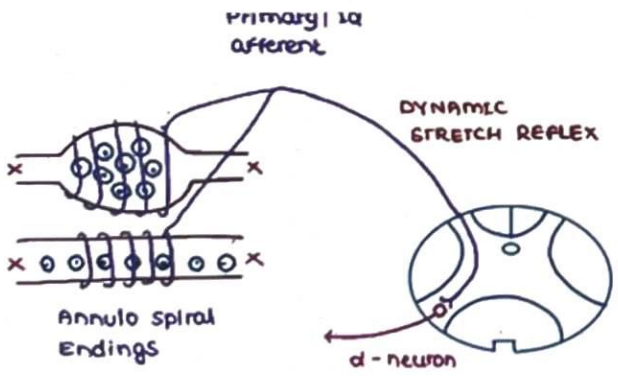
- Degeneration of nigro striatal tracts, extra pyramidal lesion.
- Normally seen 8th decades on beyond of life [70 yrs of beyond]
- Classic triad:
  - Tremor – at rest
  - Rigidity – lead pipe, log wheel
  - Bradykinesia
- Mask like, micrographia
- In treatment dopamine or anticholinergic drugs are given in parkinsonism
- Striato nigral projection, cholinergic projection, reciprocal innervations.

Huntinton's disease

- Trinucleatide repeat disease "CAG"
- N = 42 repeats - ≥ T8 repeats
- Intra striatal degeneration of GABA ergic & cholinergic neurons
- Hyperkinetic movements

Lower motor neuron / anterior motor neuron

- Starts from spinal cord of anterior horn & goes to muscle
- 2 types
  - α motor, γ motor neuron



UMN	LMN
• Hypertonia o Spasticity rigidity • Increase tendon jerks	• Hypotonia • Decrease tendon jerks

- α motor neurons innervates extra fusa fibers
- γ motor neurons innervates intra fusa fibers
- Large extra fusal fibers on outside
- Small intra fual fibers
- Intra fusal fibers connected with surrounding glycocalyx
- Muscle contraction is due to contraction of extra fusal fibers (fibers)
- Intra fusal fiber contributes proprioception

Proprioceptors

1. Muscle spindle
   - In the belly of muscle
   - Formed by intra fusal fibers
   - Detects the length of muscle when muscle is stationary
   - Detects rate of change of length
2. GOLGI TENDON ORGAN (GTO)
   - Present in tendon
   - Made up of tendon fibers
   - Detects tension in the muscle
   - Detects rate of change of tension

Muscle spindle

- 10-12 intra fusal fibers makes 1 muscle spindle
- 2-3 nuclear bag fibers
- 8-9 nuclear chain fibers
- Ratio between nuclear bag & chain fibers 1:3
- Annued spiral Ending
  - Come from central portions of
  - Both joins to form primary / both 1a afferent
  - Enters the spiral cord & ends on motor neuron. Which in turn supplies extra fusal fibers
- This is the circuit for dynamic stretch reflex (Tendon / knee jerk)
- Receptor for knee jerk – muscle spindle

Tap on tendon
↓
Sudden stretch of muscle (intra fusal)
↓
Stimulus sent via 1 degree afferents to SC
↓
Ends on motor neuron
↓
Brief contraction of extrafusal fibers

Flower spray ending / static stretch

- Present at the end of nuclear chain fibers
- Gives secondary / type 2 afferent
- Proximity & its viscoelasticity resemblance to the extra fusal fibers, makes it best suited for static stretch reflex detection.
- Reflex initiated by muscle spindle is mono synaptic reflex
- Excitatory to α - motor neuron

Motor neuron

- Maintains the excitability of muscle spindle by pulling the ends of intra fusal fibers

1. **Jendrassik maneuver**
   - In case of not getting knee jerk properly, hooking of fingers, clenching of the teeth motor neuron discharge to the muscle spidle & maintain the excitability
   - Aids in obtaining proper knee jerk.
2. α-γ LINKAGE
   - During continuous muscle contraction even if contraction occurs, no signal is initiated by muscle spindle

     ↓

     Cerebellum will not receive feedback

     ↓

     Hence, muscle spindle gets unloaded (relaxed)
   - γ motor neurons helps in maintaining excitability
3. Tone
   - Physiologically partial contraction in muscle even when muscle is relaxed that's called muscle tone.
   - It has this because of asynchrony γ-motor neuron discharge on muscle

Clinical examination of tone

- Resistance offered by muscle when joint is moved passively

Golgi Tendon: organ

- Situated in tendons at a ratio of 1:20
- 1 b afferent arises form GTO
- 1 b enters the spinal cord & ends on inhibitory interneuron, which in turns ends on motor neuron
- Reflex initiated by golgi Tendon organ is Di-synpatic reflex
- Always inhibitory to α motor neuron
- This is the basis for CLA SP-KNIFE REFLEX
- Spasticity seen in pyramidal lesions
- Lengthening reaction – muscle lengthen & relaxes completely

A stretch to an already spastic muscle could tear the muscle

↓

GTO initiates reflex to inhibit a motor neuron

↓

LENGTHENING REACTION

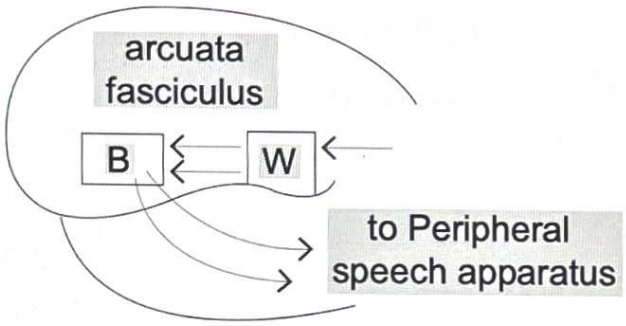
Hypertonias	
Spasticity	**Rigidity**
• Seen in pyramidal tract lesion • Unidirectional • Unidirectional involves one group of muscle (agonists)	• Seen in extra pyramidal tract lesion • Bi directional • Involves both agonists & antagonists • Lead pipe rigidity ↓ Cog wheel rigidity • Velocity depend • motor neuron

39 PHYSIOLOGY OF PAIN

SPEECH

- Central speech apparatus
- Peripheral speech apparatus

Central Speech apparatus



I. Wernicke area: Sensory area of speech present in temporal lobe which receives information from various areas of cortex (eg visual, olfactory, sensory) and based on that input this area will determine what is to be spoken. It sends this information to frontal lobe (inferior frontal gyrus) where we have broca's area.

ii. Broca's area: It is the motor area of speech which executes what was decided to speak by wernicke's area. It sends the signals to muscular involved in speaking.

iii. Arcuate fasciculus: It is the bundle of nerve fibres which connects wernicke's and Broca's area.

Execution of speech

- The Broca's area sends signals to peripheral speech apparatus.

Two steps

i. Phonation: It is the production of sound which occurs when the expired air puts vocal cords into vibration.

ii. Articulation: The second coming from vocal cords in articulated into words by organs of the mouth.

- If there is something wrong in peripheral speech apparatus, it is called dysarthria. i.e. difficulty articulation.

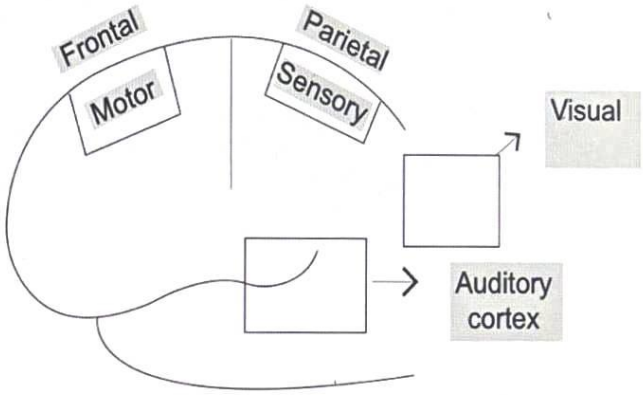
APHASIA

- Loss of speech is called Aphasia
  - Sensory aphasia (lesion of wernicke's)- Not able to comprehend what is to be spoken
  - Motor aphasia (lesion of Broca's) – know what to speak but can't speak

CORTEX

- 90% (Neocortex)
- 10% (Archi cortex)

Neocortex (90%)



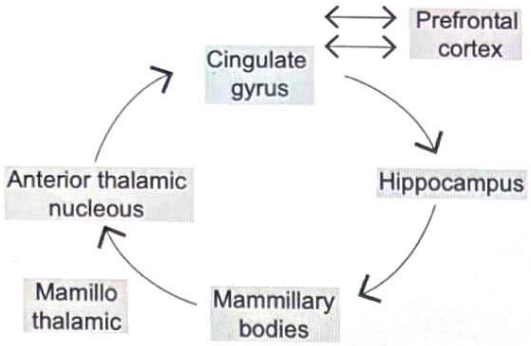
Dominant hemisphere (Categorical)	Non-Dominant hemisphere (Per presentational)
• Speech centre • Language function	• Orientation of body parts with respect to each other and surroundings

- Hemineglect syndrome: (Lesion in parietal lobe) Person neglects opposite half of the body immediate opposite surroundings.

Archi cortex (10%)

i. Limbic system: Mainly associated with our emotions.

ii. Papez circuit: Controls behavioural responses based on our emotions.



Hypothalamus

- A part of diencephalon
- Perform all the vegetative of visceral functions
- It is a part of limbic system hence involved in emotions
- Highest seat of ANS control
- It also controls the secretion of pituitary gland through hypothalamo-hypophyseal axis.

Hypothalamic nucleus	Fibres connections	Function	Lesion
1. Supra optic nucleus	• Osmo-receptors	• ADH synthesis	• Diabetes insipidus
2. Paraventricular nucleus	• Neuro endocrine reflex	• Oxytocin	• Delayed labour
3. Supra chiasmatic nucleus (SCN)	• Visual pathway (CN II)	• Circadian rhythm	• Jetlag
4. Pre-optic nucleus	• Anterior (Androgen sensitive) • Posterior estrogen sensitive	• Sexual function	• Loss of libido
5. • Anterior Hypodense • Posterior hypothalamus	• Warm sensitive neurons • Cold sensitive neurons	• Temperature regulation (Cutaneous vasodilation & sweating) • Shivering	• Hyperthermia • Hypothermic
6. Ventromedial	• (ART anorexigenic)	• Satiety	• Hyperphagia & obesity
7. Lateral	• Orexigenic neurons (Glucostatic)	• Hunger	• Loss of appetite
8. Lateral superior	• Osmo receptors	• Thirst	• ↓ water intake

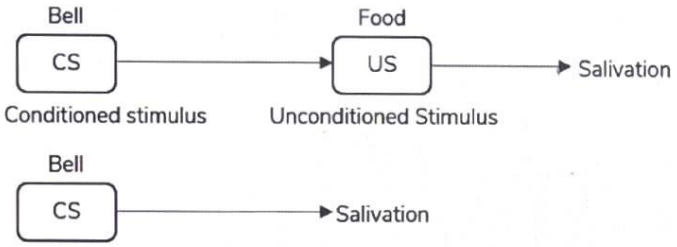
Learning and Memory

- Learning
  - Acquiring new information and skills is learning
  - Storage of that information is called memory

Non-Associative learning	Associative Learning
• Priming • Habituation • Sensitization	• Classical conditioning (Pavlov) • Operant conditioning (Skinner)

i. Habituation: Decreased release of a neurotransmitter at a particular synapse to a particular stimulus.
ii. Sensitization: Increased release of a neurotransmitter at a particular synapse to a particular stimulus.

Classical conditioning (Pavlov's)



- Dog has learnt that every time bell is ring, food is to be given, hence a part of associative learning
- For this learning to develop, the conditioned stimulus should be followed by unconditioned stimulus.
- Their should be no gap of interference b/w the stimuli
- If interference occurs in between then the reflex can get extinct leading to extinction.

Operant condition (Skinner)

- Reinforcement of the reward
- Avoidance of the punishment

Memory

i. Short term memory
ii. Long term
iii. Intermediate term memory

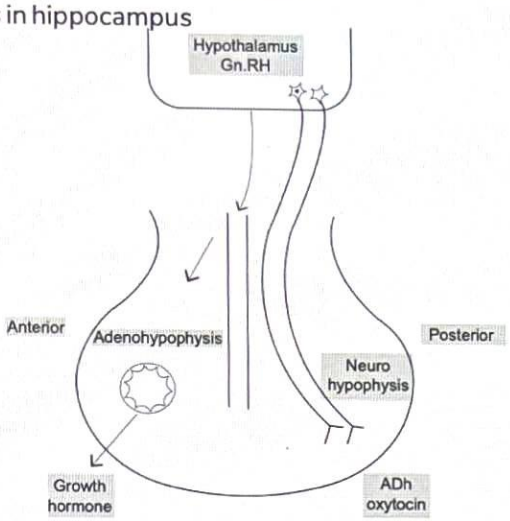
i. Short term memory: Two way

- Post tetanic Potentiation: Extra release of neurotransmitter at a particular synapse
- Pre synaptic facilitation: A neuron makes a parasympathetic

connection for sometime with the main neuron where memory was to be store and facilitates more release of neurotransmitter from the main neuron

ii. Long term memory (Post synaptic event)

- Long term potentiation in the hippocampus neurons. Conversion of short term memory into long term memory occurs in hippocampus



Generation of long term and PSPS

- There are structural changes in long term memory
  - New sympathetic tracts are generated
  - Dendritic tracts are altered
  - Increased no. of receptors of neurotransmitter
  - New protein synthesis is required for long term memory.
  - Working memory is formed in our cortex & cortical neurons are projecting into the hippocampus & inc A, area of hippocampus the working memory will be converted into long term memory & consolidated back in neocortex.

EEG & SLEEP

EEG: (Berger rhythm)

- Electrical activity of cortical neurons recorded from the scalp with help of electrodes
- No action potentials but EPSP & 9 PSPs
- Use of EEG: To diagnose functional diseases of the brain (E.g. Epilepsy's)
- Waves on EEG

i. a-wave: 8 – 12 Hz

  - Waves of quiet wakefulness of eye closed and mind wondering
  - Recorded from occipito-frontal region

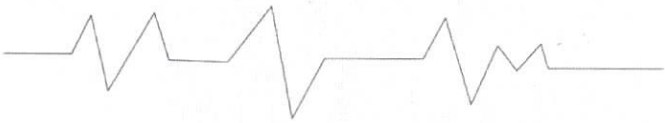
ii. b-wave: 15-30 Hz

  - Small amplitude and high frequency
  - Recorded from parieto-frontal region
  - Alert wakefulness, eyes open & mind focused
  - REM sleep (Paradoxical)

iii. q-wave: 4-7 Hz

  - Recorded in NREM/ Slow wave sleep
  - Recorded mainly in children
  - Recorded in temporo-parietal region
  - Usually in Hippocampus

iv. d-wave: 0 – 4 Hz



  - Slowest frequency wave
  - Recorded in organic brain disease
  - Thalamo-cortical projections are cut, still the d wave will be recorded, not any other wave.
  - Seen in Deep sleep, deep core, deep anaesthesia.

v. Gamma oscillation: 30 – 70 Hz
  - Occurs when very high focus is required

Sleep

- Defined as temporary form of unconsciousness from which a person can be aroused by sensory and other type of stimuli

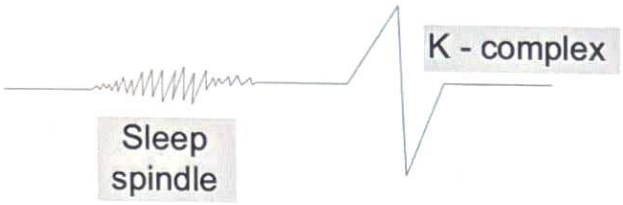
Two Types

i. Rapid eye movement (REM)
ii. Non rapid eye movement (nREM)

90 min → nREM
↓
5 – 15 min → REM
↓
90 min → nREM

NREM sleep (4 stages)

- Stage I: a-wave
- Stage II: Sleep spindles with large K complexes.



- Stage III and IV: Theta waves
  - Night tremors
  - Bruxism
  - Somnambulism: Sleep walking

REM Sleep: (15-20 min)

- Paradoxical sleep
- b- waves
- Rapid eye movements
- Heart and respiration rate become irregular
- 4 – 5 episodes of REM sleep in one right
- Loss of muscles tone: Maximally in the neck extensors.
- Exceptions
  - Extraocular muscles
  - Diaphragm
  - Middle ear muscles.
- Dreaming
- Memory consolidation
- Nightmares
- Penile tumescence & penile erection

Pathology

- Insomnia: Lack of sleep
- Somnolence: Increased sleep
- Narcolepsy's: Loss of tone during wakefulness.

CLINICAL QUESTIONS

Q. Opioids are a commonly used analgesic that can exert their effects at various places in the CNS, including in the spinal cord and dorsal root ganglia. Interneurons that utilize the neurotransmitter enkephalin to inhibit afferent pain signals are most likely to be found in which region of the central nervous system?

A. Dorsal horn of spinal cord
B. Postcentral gyrus
C. Precentral gyrus
D. δ-type A

Answer: A

Solution:

- **Interneurons** in the **dorsal horn** of the spinal cord use **enkephalin** that inhibits pain transmission from tissues of the body.
- The somatosensory cortex is located in the postcentral gyrus, and the primary motor cortex is located in the precentral gyrus; neither of which uses enkephalin to inhibit pain transmission.
- Myelinated δ- type A fibers and unmyelinated type C fibers are not interneurons.
- Interneurons are physically short neurons that form a connection between other neurons that are usually close together.

Reference: Guyton and Hall Textbook of Medical Physiology 13th Edition, Page No. 625

40 AUTONOMIC NERVOUS SYSTEM

NERVOUS SYSTEM

00:00:13

1. CNS } Somatic system
2. PNS }
3. ANS

ANS

00:01:20

- Controls involuntary function
- Includes
  1. Sympathetic Nervous system → prepares the body for challenges
  2. Para sympathetic Nervous System
- Controls day to day (routine) functions of the body
  - Resting HR
  - Secretions & movements GIT
- Their functions are mostly contradictory but sometimes complimentary too

SYMPATHETIC NERVOUS SYSTEM

- Thoraco Lumbar Outflow
- Preganglionic fibres are short
- Post ganglionic fibres are long
- **Sweat glands:** Sympathetic cholinergic nerve (cholinergic fibers)

PARA SYMPATHETIC SYSTEM

- Craniosacral outflow
- CN 3, 7, 9, 10; vagus nerve (most important)
- Pre ganglionic fibres are long
- Post ganglionic fibres are short (anaxonal type)
- Ganglion is located near the organ or at the wall of organ

Preganglionic nerves are cholinergic

- Ganglionic transmission is cholinergic (Ach)

POST GANGLIONIC NERVES

- Parasympathetic: Cholinergic
- Sympathetic: Adrenergic, NA
- TYROSINE→L-DOPA→DOPAMINE → NA → Adrenaline
- Major secretion of adrenaline is in Adrenal medulla gland as
- It consists converting enzyme to convert NA → A

ECEPTORS

00:10:10

PARASYMPATHETIC SYSTEM

Achreceptors

- Nicotinic
  - N_1, N_2
  - Found at ganglia, NMJ, CNS neurons
  - **Nicotinic:** Ligand gated ion channel
- Muscarinic
  - M_1, M_2, M_3, M_4, M_5
  - M_3, M_4, M_5 Mediate excitatory effects (on GIT, Glands vessels) of Ach
  - Metamorphic ion gated channel or cyclin nucleotide gateway or GPCR associated channels
  - M_2 Found in heart
    → Inhibitory on cholinergic actions

SYMPATHETIC SYSTEM

αReceptors

- α_1, α_2
- α_1
  - Mainly immediate excitatory effects of adrenaline
- α_2
- Presynaptic auto receptors
- Modulates the further release of NA

Receptors

- $\beta_1, \beta_2, \beta_3,$
- β_2
  - Mainly inhibitory on Adrenaline & NA
  - Present on skeletal muscle blood vessels 8 bronchi
    → Bronchodilation
    → Vasodilation
- β_1
  - Present in heart
  - Mediate excitatory actions adrenaline

EFFECTS

00:16:57

1. PUPILS

- IRIS
- Circular muscle iris is under the para sympathetic control
  - Causes pupillary constriction (miosis)
- Radial muscle is under the control of sympathetic control
  - Causes pupillary dilatation (mydriasis)

2. HR

- Resting HR is under parasympathetic control

- HR is under Sympathetic control

GIT

- Most parasympathetic
- Secretion motility increased by vagus nerve
- Last part of rectum & colon under the sacral parasympathetic nerve.

Bladder: Detrusor reflex under S_2, S_3, S_4

Sympathetic Alarm reaction

- During extreme stress or challenge
  - Sympathetic nerve secretion by adrenal medulla gland
  - Pupillary dilation
  - Increase HR
  - Increase BP
  - Skeletal vasodilation
  - Glycogenolysis in liver
    → ↑ Blood glucose

Previous Year's Questions

Q. Normal CSF on lye down posture
A. 130 mm of water
B. 130 cm of water
C. 130 mm of Hg
D. 130 drop of CSF

Introduction

- It is the fluid circulating, around the brain and the spinal cord. It is found the ventricles of the brain, in the cisterns around the outside of the brain, and in the subarachnoid space around the brain and spinal cord.

Composition of the CSF

- It is a clear, colorless alkaline fluid; specific gravity: 1005 – 1008
- Volume: about 150 ml
- Daily secretin: About 500 ml
- It is almost cell free and protein free
- It Contains less glucose than plasma; (glucose: About 50 mg% in CSF)

Formation, flow and absorption of CSF

- About 2/3 of CSF is formed as a secretion from the choroid the ventricles, mainly the two lateral ventricles.
- Additional amounts are secreted by the ependymal surfaces. Some amount is also secreted by blood vessels of the and the spinal cord.
- After its formation, it passes from the lateral ventricle into the ventricle. Some fluid gets added here. Then, along the adequate ventricle. Some fluid get added here. Then, along the adequate sylvius it comes into the 4th ventricle from here, it passes out foramina of Luschka and foramen of Magendie, and via cister comes into the subarachnoid space. CSF then circulates in the subarachnoid space around the brain and the spinal cord.
- It is mainly absorbed by the subarachnoid villi into the venous sinuses.

CSF pressure

- About 130 mm of water; in lateral lying position
- 130 mm of water = 13 cm of water
- 13 cm of water = 100 mm of Hg {1 mmHg = 1.3 cm of water}

Function of CSF

- CSF serves as a fluid buffer that provides optimum environment neurons of the CNS.
- Protective function: CSF provides the cushioning effect to the structures of the cranial vault.
- Regulates contents of the cranium: CSF acts as a reservoir and contents of the cranium. For example, if the blood volume of increases the CSF drains away the excess amount of fluid.
- It helps in transfer of metabolic waste products of brain into
- It may serve as a medium of nutrient supply to the CNS.
  - Applied physiology

Lumbar puncture

- It is the procedure by which CSF can be accessed through the lumbar segments of the spinal cord. A needle is inserted between the two lumbar vertebrae ($L_{2,3}$), to reach the subarachnoid space
- For diagnosis
  - CSF is collected by lumbar puncture; it is then analyzed for infections of the CNS, or malignancies
- For therapeutic purpose
  - Drugs can be instilled into the CSF; for the purpose of anesthesia antibiotics against CNS infections

LEARNING OBJECTIVES

UNIT 10 SPECIAL SENSES

SENSORY SYSTEM

- Senses, 3 Neuron path, Laws for encoding
- Receptor
- Ascending tracts
- Cortex
- Physiology of pain

SPECIAL SENSES PART 1

- Structure of eye
- Optic of vision
- Accomodation reaction
- Myopia
- Hyper metropia
- Visual threshold
- Dark adaptation

SPECIAL SENSES PART 2

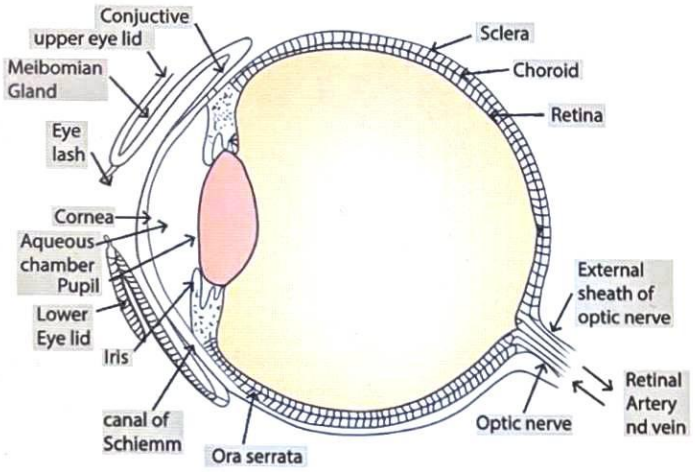
- Light adaptation
- Colour vision
- Vision pathway
- Hearing
- Taste

41 STRUCTURE OF THE EYE

Structure of the eye: It has two components

(I) The optical component: It focuses the visual image, and (II) the neural component: it transforms the visual image into a pattern of electrical responses.

- The wall of the eyeball consists of 3 layers
  a. External layer: supporting layer; it forms sclera all around except the anterior portion. The anterior portion is the transparent cornea; light rays enter the eyeball through the cornea.
  b. Middle layer: It is a vascular coat. Posteriorly it forms the choroid; anteriorly it forms the ciliary body and the iris. The eparture at the center of the iris is called the pupil. By altering the diameter of the pupil, the iris can adjust the amount of light entering the eye.



c. **Inner layer:** Forms the retina; it consists of photoreceptors (rods and cones) and the neural elements.

- The crystalline lens is attached to the ciliary body by the suspensory ligament or zonule of Zinn.
- The space between the cornea and the anterior lens surface is the anterior chamber. The narrow circular space between the iris, the lens, and the ciliary body is the posterior chamber. Both the chambers are filled with a fluid called aqueous humor. The space behind the lens is filled with an amorphous transparent gel called vitreous humor.

  (Vitreous humor has a high viscosity) because it contains high quantities of hyaluronic acid)
- Normal intraocular pressure = 15 mmHg.
- **Macula lutea:** a small (1 mm^2) area at the optical center of the retina. A depressed region at the center of the macula is the fovea centralis. Fovea is specialized for the most detailed and accurate vision.
- **Optic disc:** Slightly to the nasal side of retina; an area where the optic nerve (II N.) leaves the retina. Since there are no photoreceptors here, it results in a "blind spot" in the field of vision. Optic disc (blind spot of the retina) is situated 10 degrees from the fovea centralis situated 10 degrees from the fovea centralis on the nasal side of the retina.
- Receptors for vision: Rods and cones. Rods are mainly concerned with dim light vision ~ the scotopic vision. Cones are mainly concerned with bright light vision ~ the photopic vision. The shifting of maximum sensitivity to wavelength of light when the vision changes from photopic to scotopic (or photopic vision). The shifting of maximum sensitivity to wavelength of light when the vision changes from photopic to scotopic (or vice versa) is called Purkinje shift.

Optics of vision

- Refractive power of a lens is expressed in diopters (D); it is the reciprocal of the focal length (f) in meters. {D = 1/f}
- Whenever light rays enter from one medium to another, there is refraction of the rays. The refraction is proportional to the difference in refractive indices between the two media. As light rays enter the eye, their refraction occurs at 4 surfaces: anterior surface of cornea, posterior surface of cornea, anterior surface of lens, and posterior surface of lens. Greatest refraction occurs at the anterior surface of cornea. Reason: difference in refr... indices is greatest between air and cornea. (Refractive indices: air = 1.00, cornea = 1.38, aqueous

humor = 1.33, lens = 1.40, vitreous humor = 1.34)

- Reduced eye of Listing: (or schematic eye) The eye has a complex mechanism of refraction at various surfaces. Construction of a simplified eye can be considered for understanding. It is called reduced eye. It has
  - A single "principal" plane of refraction, situated 15 mm behind the cornea (in aqueous humor)
  - Optical center or nodal point, situated 7mm behind the cornea or 17 mm in front of the retina (eye is about 24 mm in length). 17 mm would also be the focal length.
  - Total refractive power = 60 D
  - Refraction at cornea = 43 D; Refractive power of lens (at rest) = 17 D.

Accommodation: Changes in the eye for near vision. (i) Increase in anterior curvature of the lens; it increases diopteric strength of the lens. Maximum amplitude of accommodation= 12 D. Thus, refractive power of eye can increase upto

Accommodation reaction

- Occurs in order to see near: objects clearly
  - Increase Power of Lens
  - Medial rotation of eyes
  - Constriction of pupil
- Involves cortex & CN 3 & its Edinger Westphal nucleus

Near point of vision: The nearest point that can be seen with maximum contraction of ciliary body, that is, with maximum accommodation. It recedes throughout life. It is at 9 cm from the eye, at the age of 10; 83 cm at the age of 60.

Emmetropic eye: When ciliary muscle is relaxed, parallel light rays focus on the retina. It is the optically normal eye.
Ametropia: An eye with refractive error. It may be of following types:

- Axial ametropia: Abnormal length of the eyeball
- Curvature ametropia: Abnormal curvature of refractive media (cornea/lens)
- Index ametropia: Abnormal refractive index of refractive media

Ametropia may be myopia (short-sightedness), hypermetropia (far-sightedness), or astigmatism (irregular curvature)

1. Myopia: (short-sightedness): Horizontally oblong shape of the eyeball leads to formation of image of distant objects in front of the retina. Correction is done by placing concave lens in front of the eyes.
2. Hypermetropia: (far-sightedness): Vertically oblong shape of the eyeball may cause image of the near objects behind the retina; near point of vision moves farther from the eye. Correction: convex lens
3. Astigmatism: Irregular or egg-shaped curvature of the lens or cornea. Such a curvature has two refractive planes with different refractive indices. Correction: Cylindrical lens

At birth, the eyes suffer from axial Hypermetropia. The eyeball lengthens as the child grows.

- The degree of hypermetropia that is detected without paralyzing the accommodation is called manifest hypermetropia; and that is detected after paralyzing accommodation is termed total hypermetropia. The difference between the two is known as latent hypermetropia
- **Anisometropia**: State of refraction of the two eyes is different.
- **Aniseikonia**: Size of retinal image is different in two eyes. A 5% difference in the size of the retinal images can be tolerated.

Visual acuity: (ability to view the fine details)

- It is measured in terms of minimum separable; that is, any two points can be seen separately only if they are separated by a minimum distance or more. This "minimum separable" is expressed in terms of visual angle. Two points can be seen separately
- Nodal Point of Eye: Present at the junction of anti 2/3rd & posterior 1/3rd of Lens
- 1 Minute Angle at nodal point of eye corresponds to 4.5 M distance at retina
  - Width of a Single cone (Photoceptor): 2.5-2.8
  - It ensures atleast 1 Photo receptor left unstimulated b/w the 2 images
- Visual Acuity is maximum at fovea centralis
  - Only cones are present, no rods
  - Slender & densely packed cones
- Cone ganglion cell ratio is 1:1

- Rowards peripheral part of retina
  - Population of rods increases
  - Many rods converge on 1 optic nerve fiber (60 on 1 fibers)
  - The visual threshold is low
  - The visual threshold is (ow

    → By tower amount of light, theg can be excited

Visual acuity in the central fovea is about 40 times that at the retinal border

- The **visible spectrum**: The range of wavelengths (of light) that can stimulate the receptors for vision ~ between 400 and 750 nm.

Field of vision

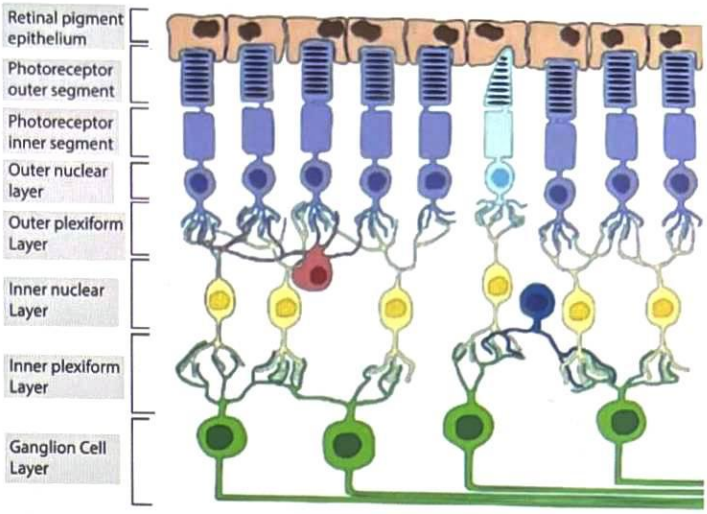
- Least on the nasal side (about 60), followed by upper and lower. It is largest on temporal side (more than 90).
- It is most extensive for white object and becomes successively smaller for blue, red and green objects.

Visual threshold: The minimum amount of light which can just be detected is called visual threshold.

- Threshold for rod excitation [illegible] quantum of light. However, threshold for retinal excitation, to give light sensation, is about 5-7 quanta of light. Reason: There is spontaneous random discharge from retina even in complete dark ("dark noise"). For true light/visual sensation, at least 5-7 rods should discharge simultaneously. Thus, 5-7 quanta of light would be required to evoke

- Threshold for visual sensation for the human eye is 54-147 quanta. Reason: For 5-7 quanta of light to reach the retina and produce light sensation, 54 -147 quanta should fall on the cornea because light is absorbed and reflected by different ocular media.

- Stiles-Crawford effect: For cones to produce light sensation, light rays entering through the center of the pupil are more effective than the rays that enter through peripheral part of a dilated pupil.
- Visual threshold is lowest at the periphery of the retina. Reasons: (i) Rods have a low visual threshold compared to cones. As one moves toward periphery of the retina, rod population goes on increasing. (ii) The ratio of rod-to-ganglion cell increases toward periphery. As many as 200 rods converge on single optic nerve fiber, so that the signals from the rods summate.

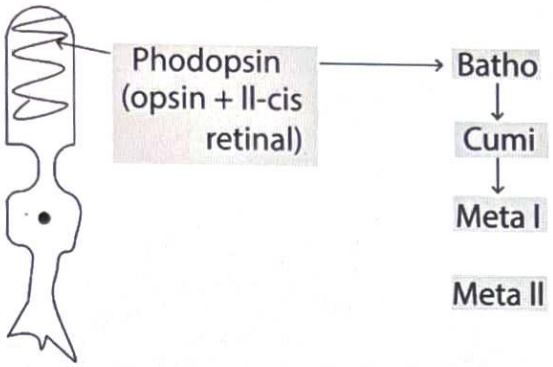


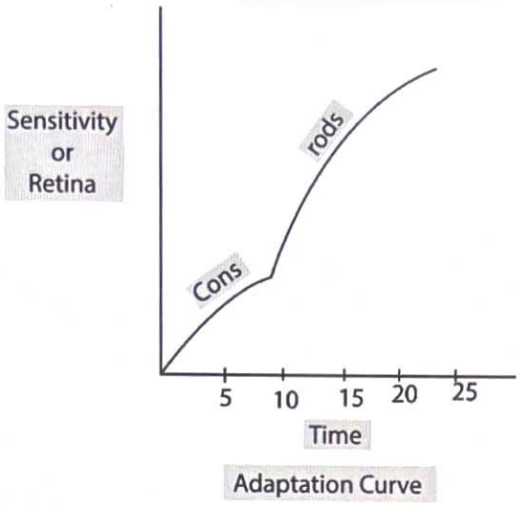
- Muller cells: The glial cells that maintain geometry of the retina.
- Receptors: Rods and cones. They synapse with bipolar cells which in turn synapse with ganglion cells. Thus, most direct pathway consists of cones/ rods → bipolar cell → ganglion cell.
- There are two interneurons that modulate the signals transmitted in the direct pathway and are involved in lateral integration: (i) horizontal cell-modifies the signal from rods/cones, it acts by lateral inhibition; (ii) amacrine cell - signal from bipolar to ganglion cell is processed by amacrine cell. Amacrine cell is the only cell that secretes Ach as transmitter in the retina.

- **Unique feature in retinal circuitry:** The neural elements transmit signals by electrotonic potentials and not action potentials. Only from ganglion cells, signals are transmitted onward in the form of APS.
- A characteristic of the bipolar and ganglion cells (and neurons in visual pathway) is that
- Rod receptor potential is hyperpolarizing and Not depolarizing

Element in retinal circuit	Response on stimulation
Rods/ Cones, horizontal cells	Hyperpolarization
Bipolar cells	Hyperpolarization or depolarization
Amacrine cells	Depolarization
Ganglion cells	Propagated spikes

The photochemical changes involve bleaching of rhodopsin present in the photoreceptors. Metarhodopsin II, the activated rhodopsin, excites electrical changes via activation of G- protein - transducin.





Adaptation Curve

DARK ADAPTATION

- Retinal Sensitivity to light increases to less light rays (Dark)
- CHANGES
- Pupillary dilation, to accommodate
  - Increase sensitivity of Retina occurs within 25-30 min by 25,000 fold
- Red colour provides a faster adaptation
  - It will remain for a longer duration
- Red coloured gogglex are used as night goggles

Light Adaptation

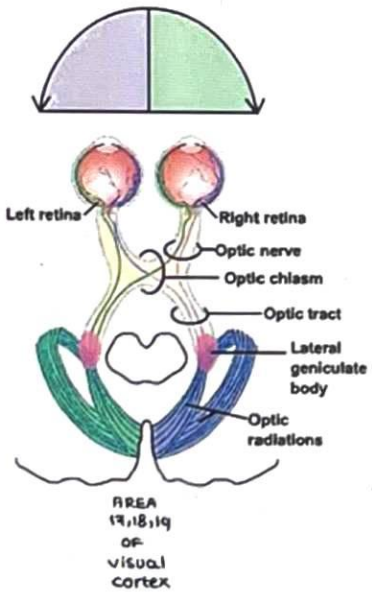
- Completes in 5-7 min & opposite changes occurs
- Constriction of pupil
- ↓ sensitivity of Retina
- Best adaptation is for yellow colour in light

42 SENSES PART 2

- Light adaptation
  - Decreased sensitivity of the eye in the light.
  - About 90% decrease in sensitivity occurs within 50 msec. This is called alpha-adaptation is released to nervous inhibition. It is seen in all parts of the retina.
- Then the sensitivity decrease slowly; and light adaptation is completed in about 5 minutes. This slow decline in sensitivity is called beta-adaptation. It is related to photochemical changes in the cones. It is confined to the stimulated area only.

~Colour vision:

- Granit's dominator and modulator theory:
  - According to this theory, there are some ganglion cells which are stimulated by the entire visual spectrum; these ganglion cells are called dominators. They signal light intensity. Some ganglion cells are stimulated by a narrow wavelength of light. These cells signal different sensations
  - According to young-Helmholtz' trichomatic theory of colour vision: There are 3 types of cones. Each one contains a photo pigment which absorbs light best at a particular wavelength
    - → Blue cones: maximal absorption at a wavelength of 445 nm
    - → Green cones: maximal absorption at a wavelength of 535 nm
    - → Red cones: maximal absorption at a wavelength of 570 nm



  - Normal individuals are trichromats, i.e. all cones present. Dichromats have one cone lacking. It can be (i) protanopia – red cone absent; (ii) deuteranopia – green cone absent; (iii) tritanopia – blue cone absent; Rarely, even two cones may be absent monochromats.

[Figure: the visual pathway. Two sets of fibers carry the visual impulses from the retina – nasal and temporal. Note that the temporal field of vision is carried by the nasal fibers from the retina, and nasal field of vision is carried by the temporal fibers from the retina. Effects of visions at various levels in the visual pathway are also shown in the figure. (A) optic nerve lesion produces blindness of the corresponding eye. (B) Optic chiasm – crossing of the nasal half of the fibers from both eyes. These fibers carry temporal fields of vision. Lesion here will cause bitemporal hemianopia. Left eye blind on the left side and right eye blind on the right side heteronymous hemianopia". (C) Optic tract – Ipsilateral temporal fibers and contralateral nasal fibers. Lesion at this site will cause loss of nasal field of the same eye and loss of temporal filed of the opposite eye. Thus (refer to the rare) both eyes will have hemianopia in the same direction (say, to the right) – homonymous hemianopia. (D) Geniculocalcarine fibers – from the lateral geniculate nucleus of thalamus to the calcarine fissure; the fibers end in the visual cortex in the occipital lobe. Lesion at this level produces the infect similar to the optic tract lesion.]

  - Optic nerves carry the visual impulses from retina.
  - Optic chiasma: Nasal fibers from both retinae cross to opposite side; temporal fibers remain on the same side.
  - Optic tract: contralateral nasal fibers and ipsilateral temporal fibers.
  - Lateral geniculate nucleus (LGN): fibers are organized in 6 layers. Layers 1 & 2 – magnocellular / large cells (receive signals from M ganglion cells of retina); layers 3 to 6
  - Parvocellular / small cells (receive signals from P ganglion cells of retina)
- LGN receives only about 10-20% fibers from the retina. Other fibers are corticofugal, that is, inputs from visual cortex and other regions of brain. These are involved in visual processing related to the perception of orientation and motion.

- Also note:-m on each side, layers 1,4, and 6 of LGN receive input from the contralateral eye; and, layers 2,3, and 5 receive input from the ipsilateral eye.
- Fibers from LGN – geniculocalcarine fibers – are projected to the calcarine fissure. These are called optic radiations. The fibers end in the visual cortex.
  - Visual cortex: occipital lobe. Primary visual cortex (V1) Broadmann's area 17. Association areas – 18,19
  - The magnocellular and parvocellular neurons of the LGN end in the layer 4 of the visual cortex. Magnocellular pathway is concerned with detection of location of an object in the visual field and its movement across the visual field. Parvocellular pathway is concerned with detection of shape of an object.
  - There is also an interlaminar region in the LGN. Cells in this region receive input from P ganglion cells. Axons arising from this region end in the layers 2 and 3 of the visual cortex. These layers contain clusters of cells, called blobs. They are concerned with color vision.
  - The output of the retina consists primarily of ganglion cells axons from (1) sustained. Linear P cells with small receptive fields that convey information about colour, form and fine details, and (2) phasic, non-linera M cells with larger receptive fields that convey

1. PRE TECTAL NUCLEUS

- Visual pathway given out of fibers that ends in pretectal nucleus, which is connected with EWN of 3rd nerve
- Constriction of pupil occurs in response to light rays passed.
- In consensual light reflex, other pupil constriction is because the pre tectal nucleus is connected with EWN of same side as well as the opposite side

2. Suprachiasmatic nucleus

- Concerned with CIRCADIAN RHYTHM
- In night time

Signals
↓
Suprachiasmatic nucleus
↓
Superior cervical ganglion
↓
Pineal gland
↓
Melanin secretion

Lesions of visual pathway

Lesions in retina

- Leads to scotoma (defect in the field of vision)
- Physiolohical scotoma – positive / negative
  - AKA blind spot
  - Area in the field of vision, where nothing is visible
  - Physiological defect

Lesions of optic nerve – complete blindness of contraceptive eye Optic tract transection

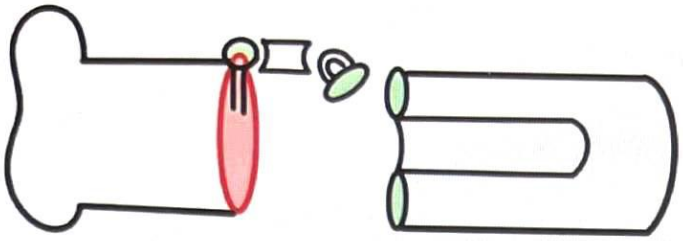
- Nasal fibers from opposite eye, temporal fibers from rame eye has been sectioned
- Nasal field of opposite eye carry temporal half of vision – temporal vision lost
- Temporal field of same eye carry nasal half of vision – nasal half of vision lost on same side
- Homonymous hemianopia

Optic chiasma lesion

- Both nasal fibers cut, they carries temporal field of vision of respective eyes
- Heternonemous hemianopia or bitemporal hemianopia

- **Hearing**
  - Frequency of sound is measured in Hertz (Hz).
  - The range of human hearing is between 20 and 20,000 Hz.
  - Human speech frequency: 1000-3000 Hz.
  - Amplitude or intensity of sound is measured using a logarithmic scale. The unit of intensity of decibel (db).
    → $db = 20. Log (P_{sound}/P_{SPL})$
- P_{sound} = pressure of the sound stimulus; and
- P_{SPL} = the sound pressure level (SPL) at the threshold for human hearing.
- The actual SPL intensity is 0.0002 dynes /cm^2. It is the minimum pressure for hearing.
  - According to the formula given above, a sound stimulus that has a pressure 10 times greater than the other will be 20 db greater in intensity than the other sound. (log of 10=1)
  - The sound pressure during normal conversation is about 1000 times that of threshold, or 60 db. (log of 1000=3)
  - An airplane produces a sound pressure of about 1, 00,000 times that of threshold, or 100 db.
  - Sound pressures above 140 db, that is 10^7 times threshold, are painful and damaging to the cochlear hair cells.
  - Noise is sound composed of many unrelated frequencies
  - Noise is sound composed of many unrelated frequencies.
  - White noise: a mixture of all audible frequencies

- Ear is composed of 3 parts: external, middle and inner ear.
  - **External ear**: conducts sound to the middle ear.



  - Middle ear: composed of tympanic membrane (ear drum) and a chain of 3 ossicles – malleus, incus, and stapes.

[Figure: Structural components of the hearing chambers, basilar membrane, and the organ of corti.]

Role of the middle ear in transmission of sound to the inner ear:

- Impedance matching – (creates greater pressure while entering cochlear)
- Surface area of tympanic membrane is 17 times the surface are of footplate of stapes.
- Stapes moves with 1.3 times greater
- Sound wave vibrations from external ear, passes through TM & via ossicles reach inner ear
- Foot plate of stapes is connected with oval window of inner ear force / pressure increased by

1. When handle of malleus moves, stapes moves with 1:3 times more
2. Tympanic membrane SA is 17 times that of foot plate of stapes

- Vibration of sounds concentrated 17 times more at foot plate of stapes $1.3 \times 17 = 22$

Attenuation reflex

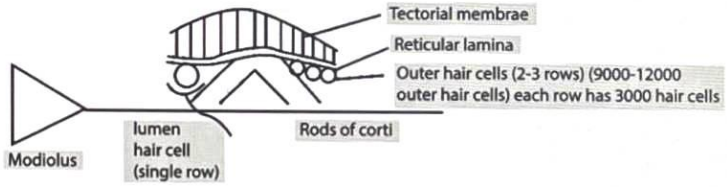
- Deleterious sound pressure are dampened to prevent damage to cochlea
- Develops in 40 ms
- Contributed by

1. Tensor tympani } Handle of malleus stapes moves
2. Stapeidus } inwards outwards

- Oscicular chain rigidity – dampers the pressure

Inner ear
Cochlear
Parts

- Base – LIMBUS
- Bony center – MODIOLUS
- Apex – HELICOPTREMA
- SCALA VESTIBULI } Separated by REISSNER's membrane
- SCALA MEDIA
- SCALA TYMPANI } Separated by BASILAR membrane
- Vestibule & tympani become one chamber at the apex of cochlea
  - HELOCOTREMIA
- Perilymph
  - Fills scala vestibuli & tympani
  - Similar to CSF
- Endolymph
  - Fills scala media
  - ECF but resembled ICF (due to increase K+)
- Basilar fibers
  - Present on basilar membrane
  - Sound wave crosses basilar membrane & vibrate basilar fibers
  - Transduction of sound caused by organ of corti
  - Present on basilar fibers
- Basilar fibers are short & thick near the base of cochlear
- Basilar fibers are long & thin – towards apex
- Organ of corti
  - Inner hair cell concerns with hearing
  - Outer hair cell create receptor potential (cochlear microphonics)



  - Sides & base of inner hair cell synapse with VIII CN
- Transduction

Basilar fibre vibration
↓
Shearing force created in reticular lamina & tectorial membrane
↓
Bending of stereocilia
↓
Opens K+ channels influx of K+
↓

Hair cell depolarization

↓

Cochlear N transmits impulse to auditory cortex

- Structures in the auditory pathway: from the dorsal and ventral cochlear nuclei →lateral lemniscus → to inferior colliculi → medial geniculate body → auditory cortex.
- Cochlear fibers from both ears also converge

TASTE:

- 5 basic taste sensations: sweet, sour, bitter, salty, and umami. Umami taste is pleasant and sweet; it is triggered by monosodium glutamate (MSG).

Taste sensation	Triggered by	Recptor
Salty	NaCl	ENaCs (epithelial sodium channels)
Sour	Protons	ENaCs, HCN (hyperpolarizati on- activated cyclic nucleotide channels)
Umami	Purine 5 ribonucleotides (IMP & GMP) in food, glutamate	Metabotropic glutamate receptor – mGluR4
Bitter	Poisons, alkaloids, quinine, strychnine, etc	Receptor linked to G-protein gustducin, and other receptors of T2R family
Sweet	Sugars, saccharine, etc	Receptor linked to G-protein gustducin.

- Taste intensity discrimination is possible only when there is 30% change in the concentration of the substance being tasted.
- Miraculin: a taste modifier protein; it makes acids taste sweet.
- Ageusia: absence of taste sensation drugs such as captopril, penicillamine may cause temporary ageusia.

OLFACTION:

- Olfactory receptor cells – in the olfactory mucous membrane, in the roof of the nasal cavity near the septum. Each olfactory receptor is a bipolar neuron. A unique feature: for this sensory transduction, transducer and spike generator is located on the same cell.
- Olfactory mucous membrane can be receptor is a bipolar neuron. A unique feature: for this sensory transduction, transducer and spike generator is located on the same cell.
- Olfactory mucous membrane can be distinguished from surrounding respiratory mucous membrane by the presence of Bowman's glands with yellow-brown pigment secretion.
- Olfactory receptors /neurons are replaced regularly. A bone morphogenic protein (BMP) is known to exert inhibitory influence on this renewal process.
- In the olfactory bulbs: the axons of the olfactory receptors contact the primary dendrites of the mitral cells and tufted cells to form complex synapses called olfactory glomeruli. Both mitral & tufted cells send axons into the olfactory cortex. In addition, olfactory cells contain inhibitory. Interneurons – periglomerular cells and granule cells. They form dendrodendtritic reciprocal synapses with the dendrites of the mitral cells.
- Axons of mitral and tufted cells pass through medial & lateral olfactory stria to the olfactory cortex. Lateral olfactory stria → primary olfactory area (which includes prepiriform cortex). Medial olfactory area → amygdaloid nucleus.
- There are at least 6 odor qualities: floral (roses), ethereal (pears), musky (musk), camphor (eucalyptus), and putrid (rotten eggs), and pungent (vinegar). {natural stimuli for the odors in brackets}

CLINICAL QUESTIONS

Q. An Aesthesiometer is a device for measuring the tactile sensitivity of the skin (or mouth, or eye, etc.). The distance by which 2 touch stimuli must be separated to be perceived as 2 separate stimuli is greatest on?

A. The lips
B. The palm of the hand
C. The back of scapula
D. The dorsum of the hand

Answer: C

Solution:

Two-point discrimination:

- It is the **ability to distinguish between two adjacent mechanical stimuli** applied to the skin.
- It depends on the **receptor density** and **receptive field sizes** of the sensory neurons.
- The area of the skin, when stimulated, causes an activity in the sensory neuron is called the **receptive field** of the neuron.
- **Receptive field sizes are small over finger tips, lips and face area.** Hence, two-point discrimination ability is greater in these parts.
- On the **back, the large receptive field sizes cause this distance to be 50-60 mm.**
- **Aesthesiometer:**
  - **Weber's compass aesthesiometer** is used for testing two-point discrimination.
  - **Von frey's hair aesthesiometer** is used to measure touch threshold.

Reference: Guyton and Hall Textbook of Medical Physiology 13th Edition, Page No. 614

PREP NUGGETS

Prep Nuggets

Glucose transporters and functions

Transporter	Location	Role
GLUT-1		
GLUT-2	Beta cells of islets, liver, epithelial cells of the small intestine, kidneys	
GLUT-3		
GLUT-4		
GLUT-5		Fructose Transport

Prep Nuggets

Heart sounds and associated events

	Sound		Associated events
1.	S_1	a.	
2.	S_2	b.	
3.	OS	c.	Opening of a stenotic mitral value
4.	S_3	d.	
5.	S_4		

Prep Nuggets

Erlanger - Gasser's classification of sensory and motor neurons

	Fiber type		Function		Conduction velocity (m/sec)
1.	A α	a.		i.	70-120
2.	Aβ	b.		ii.	
3.	Aγ	c.		iii.	15-30
4.	A	d.	Pain, temperature	iv.	
5.	B	e.		v.	
6.	C (dorsal root)	f.		vi.	
7.	C (Sympathetic)	g.	Postganglionic sympathetic	vii.	

Prep Nuggets

Postural Reflexes and their centres

	Reflexes		Integrated in
1.	Stretch reflex	a.	Spinal cord
2.	Tonic labyrinthine and tonic neck reflexes	b.	
3.	Labyrinthine righting reflexes	c.	
4.	Optical righting reflexes	d.	
5.	Negative supporting reaction	e.	

Prep Nuggets

	Hormones	Site of secretion	Action
1.	Gastrin	a.	i.
2.	Cholecystokinin	b.	ii.
3.	Secretin	c.	iii.
4.	Gastric inhibitory peptide	d.	iv.