BASIC CONCEPTS

Concept 1. Body Composition: Values and Measurement

Values

a) Body Composition (as % of Body ***weight***)

Water	60%*
Proteins	18%
Minerals	7%
Fats	15%

*Body Water as % Body weight

TBW = 60%
ECF = 20%
Plasma = 5%
Interstitial fluid → 15%
ICF = 40%

(Total blood volume = 8% of body weight; since plasma volume is 5% of body weight, blood ***cell*** volume = 3% of body weight)

Measurement of the various body fluid compartments

This is done by the principle of ***volume of distribution***. (or dye-dilution method)

$$v = \frac{Q-e}{C}$$

where

v = volume
Q = quantity of indicator given
C = concentration of the indicator
e = The amount of indicator which has either been lost or metabolized

Indicators

Compartment	Indicator used
Plasma volume	Evans' blue (T1824)
RBC volume	Tagging RBC with ^{51}Cr, ^{59}Fe, 32P; also antigenic tagging
ECF volume	Inulin, sucrose, Mannitol, Sodium thio sulphate, sodium thiocyanate
Interstitial fluid	Cannot be measured directly; can be calculated as ECF volume – Plasma volume
ICF	Cannot be measured directly; can be calculated as Total body water – ECF
Total body water	D_2O is most frequent used; also, tritium oxide, aminopyrine

Other points

Water content of lean body mass = 71-72 mL/ 100 gm of tissue
(Lean body mass = body mass devoid of fat)
Note that fat does not hold water

Total body water
- Somewhat lower in women
- Tends to decrease with age

Concept 2: Expressing Solute Concentrations

Mole (or mol)

Definition: It is ***molecular weight*** of a substance ***in grams*** i.e. it is gram molecular weight

Example:

a) Calcium → Molecular weight = 40;; therefore, 40 gm = 1 mol of calcium

b) NaCl → Atomic weight of
- Na = 23
- CL = 35.5

Therefore, 23+35.5 = 58.5 gm of NaCl = 1 mol of NaCl

Note

1. In S.I. system, mole is the standard used to express amount of any substance
   Dalton: It is a unit of mass; 1 Dalton = $1/12^{th}$ of the mass of carbon atom – 12
2. Molecular weight is a dimensionless ratio.

Equivalent (Eq.)

$$1\ \text{Equivalent} = \frac{1\ \text{mol of an ionized substance}}{\text{Valence}}$$

1) 1 equivalent of calcium = 40/2 = 20gm
2) 1 equivalent of Sodium = 23/1 = 23gm

Osmole

1 OSMOLE = Mol ÷ Number of freely moving particular each molecule liberates in solution

It expresses concentration of osmotically active particles

Examples

1) 1 mol of NaCl = 2 osmoles because each NaCl molecule given one Na^+ and one Cl^- particle is solution
2) 1 mol of Na_2SO_4 = 3 osmoles because each Na_2SO_4 molecule gives 2 Na^+ and 1 SO_4 is solution
3) 1 mol of $CaCl_2$ = 3 osmoles, because each molecule of $CaCl_2$ give 3 particles (1 calcium and 2 Cl^-) in solution

1 mol of Na_2SO_4 has 4 equivalents and 3 osmoles

Note :

One osmole (or one can say 1 mol of an undissociated substance in an ideal solution) of any substance has the following properties :

i) it depresses freezing point by 1.86^0C*
ii) it exerts an osmotic pressure of 22.4 atmospheres
iii) it has 6×10^{23}, molecules (Avagadro's number)

*This fact can be used to measure the osmolal concentration of a substance.

Difference between osmolarity and osmolality

Osmolarity is the number of osmoles ***per litre*** of solution;

osmolality is the number of osmoles ***per kg of solvent***. Osmolality is not affected by changes in volume of solution or by temperature.

Tonicity

Definition: This is the osmolality of a solution with respect to plasma osmolality

Example : 0.9% NaCl is isotonic ; 5% glucose is isotonic initially; later is become hyptomic

Plasma osmolality

Out of the 290 mosm,

1) Na^+ and its associated ions (Cl^- / HCO_3^-) = 270 mosm
2) Urea = 5 mosm
3) Glucose = 5 mosm

Approximate formula for finding the plasma osmolality:

Plasma osmolality = Na^+ concentration (in mEq/l) x 2 + glucose(mg/dL)/18 + BUN (mg/dL)/2.8

Osmolal Gap:

The most accurate way of finding out the osmolality is by freezing point depression (see above)

The approximate formula is as given above

If there is a difference between the two calculations, it is called osmolal gap. Osmolol gap indicates the presence of a foreign substance.

Concept 3: Transport Across Cell Membranes

1. Active : Primary and secondary
2. Passive
3. Exocytosis / Endocytosis (This is an active process)

1. Active Transport

Definition: Energy is used

Types:

i) Primary active transport: Energy is derived directly by hydrolysis of ATP by the transporter itself.
(Note: All transporters ending with "ATPase" are primary active)
Eg. Na+ K+ ATPase pump;

ii) Secondary active transport : Energy is derived indirectly

Eg. Sodium – linked glucose transport (i.e. SGLT) in kidney & GIT

(Note: All transport mechanisms which are linked to Na^+ entry or K^+ exit are secondary active)

The secondary active transport can be a

a) Counter transport or antiport (exchanger) where two substance are transported in the opposite direction
Or
b) Co- transport (symport) where two substances are transported in the same direction

2. Passive transport – (No energy required)

i) Diffusion

This can be

a. Simple diffusion
b. Facilitated diffusion
c. Nonionic diffusion

a. Simple diffusion

Characteristics

- No carrier molecule involved
- No Tm (No transport maximum i..e not saturable)
- Follows ***Fick's law*** of diffusion

Fick's Law of diffusion

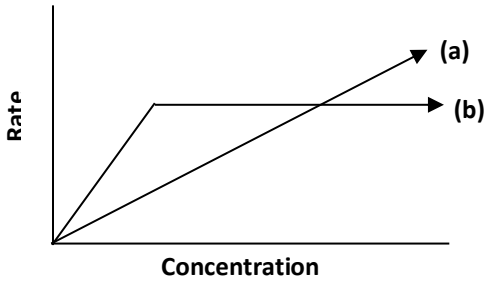
$$J = - DA \, \Delta C/\Delta x$$

Where
J = Net rate of diffusion
D = Diffusion coefficient
A = Area
(Delta C = Concentration difference on the 2 sides of the membrane)
(Delta x = thickness of the membrane)
(The negative sign indicates the direction of diffusion)
(For diffusion from higher to lower concentration, the sign is negative)
The time required for diffusion is directly proportional to the ***square*** of the diffusion distance
Example of simple diffusion : O_2/CO_2 exchange in alveoli

b. Facilitated diffusion

Characteristics
- no energy is required
- A carrier molecule is involved to which the substance binds, therefore, it is also called passive carrier – mediated transport
- Has a Tm (it is saturable)
- It can be competitively and noncompetitively inhibited
- It follows the enzyme – substrate kinetics of Michaelis - Menten

Eg. Glucose transport by glucose transporters (***GLUT***)



(a): Simple diffusion

c) Non – ionic diffusion

In case of weak acids or bases, where the acid / base can cross the membrane in the non – ionized form but cannot cross the membrane in the ionized form
Eg. ***Ammonia*** transport in GIT / Kidney. The mucosal toxicity of non – steroidal anti inflammatory drugs can be explained on this basis.

ii) Osmosis

Definition: Diffusion of a solvent into a higher concentration of solute to which the membrane is impermeable
Osmotic pressure for an ideal solution is given by

$$P = \frac{nRT}{\nu}$$

Where P = osmotic pressure
N = number of particles
R = Gas constant
ν = volume
T = Absolute temperature

Osmotic pressure depends on the number rather than the type of particles in solution. Such properties which depend on the number the rather than the type of particles in called ***fundamental colligative property***
Other examples of fundamental colligative property are:
Vapour pressure lowering
Freezing point depression
Boiling point elevation

iii) Filtration: This is the movement of fluid across capillaries, this is governed by ***Starling's forces***. The starling's forces are
a) Hydrostatic pressure (a 'push' force) and
b) Oncotic pressure (a 'pull' force)
c)

iv) Bulk flow or solvent drag

This refers to the movement of particles / solutes along with movement of water

Concept: Some Equations
1. Donnan effect / Gibbs – Donnan equilibrium
2. Nernst equation
3. Goldman – Hodgkin – Katz (G-H-K) equation or, Goldman constant field equation or chord conductance equation

1. Donnan effect

Presence of an impermeant ion (e.g A- in side 2) on one side of the membrane repels similarly charged permeant ions to the other side and holds opposite charged permeant ions to the same side.

Side 1 Side 2

2. Gibbs – Donnan equilibrium

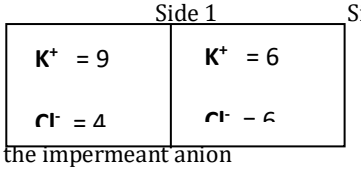
This can be considered as the 'mathematics' of the Donnan effect.

The effects the presence of the impermeant ion on the distribution of permeant ions are

a) It causes an asymmetric distribution of the permeant ions
b) More osmotically active particle on the side containing the impermeant ion
c) The product of the concentration of the permeant ions on one side equal, the product of the concentration of the permeant ions on the other side
d) However, the total number of positive charges on one side equals the total number of negative charges.

Illustrate example

Side 1 Side 2



A is the impermeant anion

3. Nernst equation

Gives the value of ***equilibrium potential or isoelectric potential***. (E) Equilibrium potential is the membrane potential at which equilibrium is reached (i.e. there is no net flux of that ion).

Examples

E_{Na+} = +60mv
E_{K+} = - 90mv
E_{CL-} = - 70mv

Note: The E_{Cl} is the closest to the RMP.

4. Goldman constant Field equation

Gives the magnitude of the membrane potential. It depends on

(i) The distribution of Na^+, Cl^-, K^+
(ii) Permeability of the membrane to each of these ions

Concept: Resting Membrane potential (R.M.P)

Definition: Every cell shows a potential difference, with the inside being negative. Its value varies from cell to cell

Genesis of R.M.P.

i) Diffusion of K+ : This is the most important cause
ii) Na+ - K+ ATPase
- By itself, it contributes a small percentage; its contribution towards RMP is more in those cells with low RMP

[Note: Pacemaker tissues have a low 'R'MP]

- More importantly, it maintains the diffusion gradient for K^+

iii) Donnan effect: This also maintains the diffusion gradient for K^+

Value (mV) : Neuron – 70, skeletal muscle – 90, SA node –30 to –40, ventricle –90, smooth muscle –30

Effect of change in Na^+/K^+ on RMP

1) Changes in Na^+ : No change in RMP

Reason: Low permeability of membrane to sodium

(Note: However, a decrease in external Na^+ concentration decrease the height of the action potential)

2) Change in K^+

Increase in K^+ concentration in ECF decreases RMP

Eg. From – 70 mV, it may become – 65 mV

(Note: While commenting on the change in the membrane potential (eg. From – 70 mV to – 65 mV) the sign (positive or negative) has to be ignored. Thus, -70mV to – 65mV should be considered as a decrease in potential or depolarization. (-70mV to – 90mV is hyperpolarisation)

Some Important Data

	ECF (in mEq/litre)		
Cations			Anions
Na	145	Cl	100
K	5	HCO3	27
Ca	2	PO4---	2
Mg	2	SO4--	1

		Organic acids	5
		Proteins	**19**
Total	154	Total	154

	ICF (in mEq/litre)		
Cations			Anions
Na	10	Cl	10
K	150	HCO3	10
Ca	3	PO4---	90
Mg	15	SO4--	15
		Organic acids	-
		Proteins	52
Total	177	Total	177

	Total	**Exchangeable**
Na	3900 mEq (90 gm)	80%
K	3400 mEq (90 gm)	95%
*(only one-third of Na in bone is exchangeable		
Na	3900 mEq in 70 kg or ***56 meq/Kg***	
K	3400 mEq in 70 kg or ***50 meq/Kg***	

ELECTROLYTES

Losses

(in mEq/day in a 70 kg man in temperature climate)

	Na	**K**	**Cl**
Urine	40-90	20-60	40-120
Sweat	50-100	5	50-100
Faeces	1.5	4	0.5
Total	140 (3.2 gm)	60 (2.4 gm)	200 (7 gm)

Sodium

ECF = 90% (ECF sodium is maximum in bone)

ICF = 10%

Potassium

ECF = 10% (ECF potassium is maximum in bone)

ICF = 90% (ICF potassium is maximum in skeletal muscle)

Atomic weights of some common elements

Ca = 40

Na = 23

K = 39

Cl = 35.5

O = 16

H = 1

C = 12

S = 32

N = 14

Molecular weights of :

Glucose = 180

BUN = 28

Urea = 60

NERVE

I. Anatomy

Axon hillock : The thickened area of cell body from which axon arises

Initial segment : The first 50 to 100 μm of the axon; it has the lowest threshold for excitation; it is the site of generation of action potential in a spinal motor neuron

Axon telodendria : Also called synaptic knobs or terminal buttons

Peculiarities of a neuron:

1. Nissl substance (also called Nissl bodies or granules) This is composed of large aggregations of rough endoplasmic reticulum. The Nissl substance extends into the dendrites but is absent in axon hillock and axon.
2. Neurofibrils:
   These represent the microfilaments and microtubules of other cells of the body.
3. No centrioles

Myelin formation

i) In peripheral nerves : By schwann cells.
Schwann cell forms myelin on one axon

ii) In CNS : By oligo dendrogliocytes
Oligodendrogliocyte from myelin on many axon

Myelin is absent at
- Nodes of Ranvier
- Axonal endings
- Soma
- Initial segment

Position of cell body
- It is often at the dendritic zone end of axon
- Sometimes, it is within the axon eg. auditory nerve
- Sometime, it is attached to the side of the axon eg. cutaneous nerve

II. Functional Areas of Neuron

Receptor	Dendrites
Generation of action potentials	i) The initial segment in spinal motor neuron ii) The initial node of Ranvier in cutaneous sensory neurons
Transmission of action potential	Axonal process
Release of synaptic transmitter	Nerve endings

III A. Axoplasmic Transport

I. Fast (20-400mm/day)	**II. Slow (0.2-0.4mm/day)**
1. Anterograde - By kinesin - Transport of mitochondria, reticulum, small vesicles etc.	This is always anterograde - Transport of soluble enzymes, tubulins of microtubules etc
2. Retrograde - By Dyenin - Transport of proteins, small molecules, also tetanus toxin	

III B. Nerve degeneration / regeneration

Nerve degeneration	**Nerve regeneration**
1. Anterograde (Wallerian) i) Axoplasm breaks down ii) Myelin breaks down	1. Anterograde i) Macrophage eating away the debris, leaving an empty endoneureal tube. ii) Schwann cell regeneration iii) Axonal sprouting
2. Cell Body i) Chromotolysis (Nissl bodies break down) ii) Cell swelling iii) Nucleus move to periphery	2. Cell Body i) Nissl bodies and Golgi apparatus gradually reappear ii) Cell regains its normal size iii) Nucleus returns to central position

Regeneration occurs at the rate of 1mm/day or 2.5 cm/month

IV. Potentials/ Recording

1) **CRO (Cathode ray oscilloscope)**

This is used to measure electrical events in living tissue; the advantage being that it is an inertia less, instantaneously responding lever

2) Concept of polarity

All cells have a resting membrane potential (refer : general physiology)

If a cell with a R.M.P. of say, -70mv changes to say –60mv, the cell is said to be depolarized (note that one has to ignore the negative sign while commenting on the change of polarity)

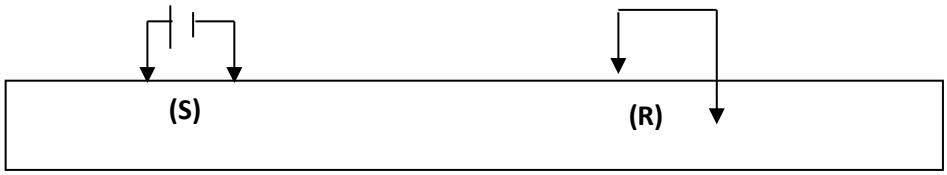
Other illustrative examples

From	To	State

-70mv	-90mv	Hyperpolarized
-70mv	+40mv	Depolarized
-70	-40mv	Depolarized

3) Changes seen during stimulation of a nerve

One would require a set of stimulating electrodes (S) and a set of (R) recording electrodes



The recording electrodes can be such that one electrode is on the surface and the other, inside the cell; or else, both recording electrodes can be on the surface. When both the electrodes are on the surface, a **biphasic action potential** is recorded.

Note:

- Nerve is a poor conductor of electricity
- Nerve can conduct impulses in both directions
- However, once it starts going in one direction, it cannot come back because it finds the previous part of the nerve refractory
- Stimulation almost always occurs at cathode

While stimulating the nerve, the following changes/ events occur

i) Electro tonic potentials

These are potential changes that occur in the nerve due to passive addition of charge; for example, at the cathodal end of the stimulating electrode, negative charge are added on the surface and at the anodal end of the stimulating electrode, positive charges are added

Illustrative examples

RMP ⟶ -70mv

Addition of '1' negative charge at cathodal surface ⟶ -69mv (Depolarized) [-70 –(-1) = -69]

Addition of '1' positive charge ⟶ -71mv (Hyperpolarized) At anodal end [-70-1 =-71]

Therefore, electrotonic potential, can be either cat-electrotonic or an-electro tonic

ii) Local response

Upto say –70mv to –63mv, electrotonic potentials can be seen i.e., the addition of '7' negative charge at the cathode causes exactly 7mv change. However, beyond this, a further addition of '1' negative charge may cause the potential to change by more than 1 eg. from –63mv, it may become –61mv. This is called the local response i.e. the change in the potential is more than what you would expect on the basis of passive addition of charge. This shows that the membrane is now participating is the process

The local response in due to opening up to some of the voltage gated sodium channels

iii) Action potential

When the local response brings out a change of say 15mv (i.e. from –70mv to –55mv), the firing level is reached wherein a large number of voltage – gated sodium channels open up and cause the action potential

To summarise,

Electrotonic potential *(is due to)*	Passive addition of charge
Local response *(is due to)*	Opening up of some of the Na^+ channels
Action potential *(is due to*)	Opening up of many Na^+ channels

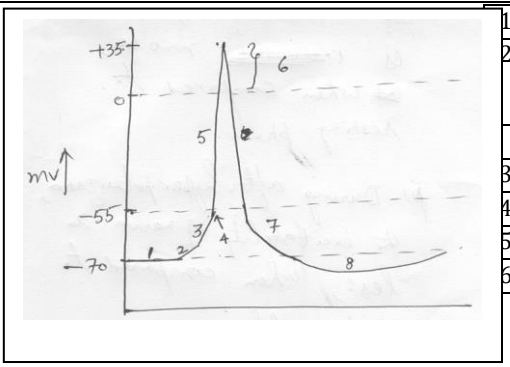
[Difference between Local potentials and Action potential]

(Example of Local potential: EPSP/IPSP, dendritic potentials, Motor End-plate potential, receptor potential, synaptic potential, generator potential, electrotonic potential)

Local Potential	**Action potential**
1. Does not follow all or none law	Follows all or none law
2. Not self – propagating	Self – propagating
3. Travels with decrement	Travels without decrement
4. Can be depolarizing/hyperpolarizing	Always depolarizing
5. May or may not be followed by action	Always followed by action

4. Phases of an action potential

Depolarization in Various Tissue	



1) Nerve	Na^+
2) Skeletal muscle	Non specific cation channel
	Na^+ channel
3) Smooth muscle	Ca^{++}
4) S4 Node	Ca^{++}
5) Ventricular muscle	Na^+
6) Endolymphatics potentials	K^+ influx

1 = R.M.P.
2. Cat – electrotonic potential
3. Local response
4. Firing level / threshold
5. Depolarization
6. Overshoot
7. After – Depolarization
8. After – hyperpolarization

Note:
(I) During after-depolarization, the excitability of nerve is more when compared to resting phase.
(II) During after-hyperpolarization, the excitability of nerve is less, when compared to resting phae.

5. Strength – duration curve

i) Rheobase	The minimum strength of current to stimulate a nerve, regardless of the time it takes
ii) Utilization time	Time taken for the rheobase current to stimulate a nerve
iii) Chronaxie	Time taken fro twice the rheobase current to stimulates a nerve

6. Other terms

i)	Biphasic action potential	This type of record is obtained when both the recording electrodes are on the surface of the nerve
ii)	Compound action potential (multi peaked action potential)	Seen in a mixed nerve, wherein there may be several fibre types
iii)	Accommodation	Slowly rising currents fail to fire (stimulate) the nerve Cause : The opening of K^+ channels balances the gradual opening of Na^+ channels

V. Nerve Fibre Classification

1. Erlanger and Gasser classification

Fibre types		Functions	Fibre diameter (μm)	Conduction velocity (m/s)
A	*Alpha*	Proprioception; somatic motor	12-20	70-120
	Beta	Touch, pressure	5-12	30-70
	Gamma	Motor to muscle spindles	3-6	15-30
	Delta	Pain , cold, touch	2-5	12-30
B		Preganglionic autonomic	<3	3-15
C	Dorsal root	Pain, temperature, some mechanoreceptor, reflex responses	0.4-1.2	0.5-2
	Sympathetic	Postganglionic sympathetic	0.3-1.3	0.7-2.3

A and B are myelinated; C are unmyelinated

2. Numerical classification (for sensory neurons only)

Number	Origin	Fibre type
Ia Ib	Muscle spindle, annulo spiral ending Golgitendon organ	Aα Aα
II	Muscle spindle, flower-spray ending; touch, pressure	Aβ
III	Pain and cold receptors; some touch receptors	Aδ
IV	Pain, temperature and other receptors	Dorsal root C

VI. Conduction of action potential or nerve impulse

Mechanism

Action potential
↓ Causes

Local currents ("current sink")
↓ Which in turn causes
Action potential and so on

Main factor affecting conduction velocity

1. Axon diameter
   More the diameter, more the speed of conduction
2. Myelination
   Increases conduction velocity by saltatory conduction

VII. C.N.S. glial cells

Oligodendrogliocytes	Formation of myelin
Microglia	Scavengers
Astrocytes	Induce capillaries to develop tight functions to form blood brain barrier

MUSCLE – SKELETAL MUSCLE

I. Hierarchy of muscle structure

Muscle
↓ Made up of
Muscle fibre (or muscle cell)
↓ Made up of
Muscle fibril
↓ Made up of
Muscle filaments
↓
(Made up of contractile proteins)

II. Cytoskeletal proteins

1. Contractile
   i) Myosin (The type of myosin present in skeletal muscle is myosin II)
   ii) Actin
2. Regulatory ('or relaxing')
   i) Tropomyosin ii) Troponin
3. Anchoring
   i) α-actinin ii) Titin iii) Nebulin iv) Dystrophin

III. Bands / Lines

Bands – A, I, H ; Lines – Z, M
A band – Dark, made up of myosin
I band – Light, made up of actin, mainly
H – The lighter portion of A band, where there is no overlap of actin and myosin
Z line – The actin filaments get anchored here; the length of the muscle between 2 Z-lines is called s sarcomere
M line – The central bulge in the myosin filament

When a muscle contracts, the two Z- lines come closer; the length of the A band remains constant whereas the length of I and H band decreases. The M – line becomes more prominent.

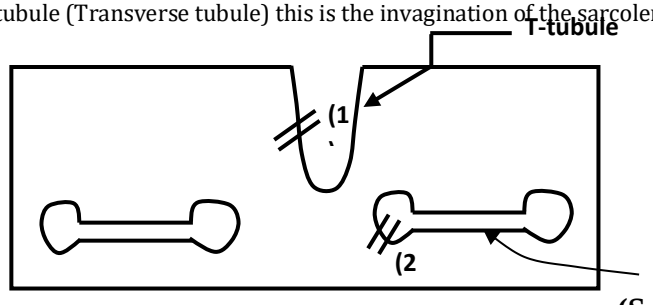
IV. Structure of Thick/thin filaments

1. Thick filament is made up of myosin (myosin II)
   Myosin II has 2 globular heads; (Myosin I has one globular head)
   The globular head has (i) actin – binding site
   (ii) Catalytic site for hydrolysis of ATP
2. Thin filament
   Is made up of actin (mainly), tropomyosin and troponin (troponin I,T,C)

V. Sarcotubular system

Made up of

1. L-tubule (Longitudinal tubule)
   This is the sarcoplasmic reticulum.
2. T – tubule (Transverse tubule) this is the invagination of the sarcolemma into the muscle cell



(Sarco-plasmic

The L-tubule (Sarcoplasmic reticulum) has got 'distended ends' called cistern
The 2 cisterns associated on either side of the T-tubule – is called a triad

Receptors

1) T-tubule has dihydrophyridine receptor [(1) in the diagram above] This is nothing but a voltage-gated Ca++ channel
2) The L tubule cistern has ryanodine receptors [(2) in the diagram above]; ryanodine receptor is a ligand gated calcium channel

Functions of the T – tubule and L –tubule

(i) The transverse tubule is continuous with the membrane of muscle fibre. It forms a grid perforating the individual muscle fibrils. The space between the 2 layers of the T- system is an extension of the extra cellular space
The T system allows rapid transmission of action potential from cell membrane to all fibres in muscle

(ii) The L – tubule
The L-tubule (sacroplasmic reticulum) is concerned with Ca^{++} movement and muscle metabolism

VI. Excitation – contraction coupling

The process by which depolarization of the muscle fibre initiates contraction is called excitation – contraction coupling

Events

1. Action potential generated in a nerve has to cause action potential in the muscle cell membrane
2. In the muscle cell membrane, depolarization normally starts at the motor end plate, the specialized stricture of the muscle cell membrane under the motor nerve ending
   The depolarization at the motor-end plate is called end plate potential (EPP)
3. The depolarization at motor-end plate, if large enough, causes action potential in the adjacent parts of the muscle cell membrane
4. The action potential thus generated is able to reach all the muscle fibrils in the muscle cell interior via the T-tubules
5. This triggers release of Ca^{++} from the terminal cisterns of the L-tubule
6. The released, Ca^{++} binds to troponin – C (There are 3 'parts' of troponin – troponin I, T and C)
   (Troponin T : binds the other troponin components to tropomyosin)
   (Troponin I : inhibits interaction of myosin & actin)

(Troponin C : has Ca^{++} binding sites that initiates contraction)

7. This allows he troponin to get 'lifted off' the tropomyosin
8. The tropomyosin 'moves away', uncovering the sites where myosin heads bind to actin
9. This triggers the cross-bridge cycling, including the power-stroke
10. Relaxation is brought about by the active pumping of Ca^{++} back into the sarcoplasmic reticulum

(Note that the troponin – tropomyosin complex is the relaxing protein that inhibits the actin myosin interaction)

VII. Motor Unit

Definition: Each single spinal motor neuron along with the muscle fibres if innervates is called a motor unit
A motor unit follows the all or none law
Size principle : Slow motor units innervate slow muscle fibres, fast motor units innervate fast muscle fibres,
Henneman principle : In large muscles, the small, slow units are recruited first; then if required, the large units are recruited
Summation : 2 types
1. Temporal = A single motor unit, stimulated many times by the same strength of stimulus
2. Spatial = Many motor unit, stimulated at the sametime by increasing the strength of the stimulus

VIII. Muscle fibre types

	Type I	**Type II**
Other names	Slow, red, Oxidative	Fast, White, glycolytic
Function	For long, slow contractions	For fine, skilled movement
Fatiguability	Fatigue late	Fatigue early
Myosin ATPase activity	Slow	Fast
Ca++ pumping capacity of sarcoplasmic reticulum	Moderate	High
Diameter	Moderate	Large
Glycolytic capacity	Moderate	High
Oxidative capacity	High	Low
Examples	Back muscles	Extra ocular muscles

VIII. Isometric and Isotonic contraction

Isometric	Isotonic
Constant length	Constant load
Length remains same	Length decreases
No external work is done	External work is done
Head released is less; more energy efficient	Heat released is more; less energy efficient

IX. Length – Tension Relationship

There is definite length – tension relationship in skeletal muscle. There is a particular initial length at which the active tension developed is maximum. This is called the resting length (also called optimum length) The tension developed depends upon the number of cross-bridges that can be formed between actin and myosin

X. Energy for muscle contraction

1. ATP stores
2. ATP from creatinine phosphate
3. ATP from glycolysis
4. ATP from aerobic metabolism

XI. Fibrillation / Fasciculation

Fibrillation : Potentials arising spontaneously in single denervated muscle fibres; Not visible grossly.

Fasciculation: Involuntary contraction of a single motor unit; Visible grossly.

MUSCLE – Cardiac Muscle

I. Functional histology

- Muscle fibres branch and interdigitate
- Intercalated disks are present at Z-lines Intercalated disc is the place of mechanical electrical coupling of muscle fibres

(Electrical coupling is by means of gap junctions)

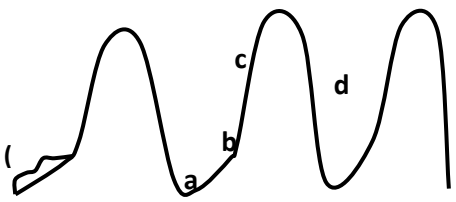
- The T-tubule system is at Z lines (In skeletal muscle it is at A-I band function)

II. Electrical activity

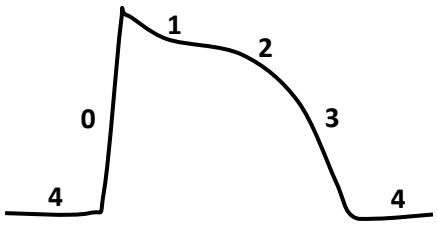
This is different in the

1. Pacemaker cells
   And
2. Contractile cells

1) Pacemaker Cells Viz SA node, AV node



2) Contractile Cell



(A) Prepotential **Cause**

a) Early part: ↓ in K^+ efflux

b) Late part: ↑ in Ca^{++} influx (through Ca^{++} T channels)

(B) Action potential

c) Depolarization: ↑ in Ca^{++} influx (through Ca^{++} T channels)

d) Repolarisation: ↑ in K^+ efflux

Phase	Name	Cause
0	Initial rapid depolarization and overshoot	Opening of Na^+ channels
1	Initial rapid repolarisation	Closure of Na^+ channels; Efflux of K^+ through i To channels
2	Plateau	Ca^{++} influx and K^+ efflux
3	Final repolarisation	Closure of Ca^{++} channels; K^+ efflux through various types of K^+ channels
4	RMP	

After depolarization or After potentials

Introduction: It's occurrence is abnormal. As the name suggests, these are basically potentials or depolarisations that develop after a conducted action potential.

Classification: Depending on which phase of the ventricular action potential the after depolarisations occur, it can be classified as

1) Early after depolarisations (EAD)
2) Late after depolarisations (DAD)

Significance: Both EAD and DAD can set up tachycardia. They can do this either on their own or because they can trigger an activity in an already formed automatic tissue (secondary to ischaemia is an infarcted tissue etc.)

EAD: Appears at the end of phase 2 or in phase 3 of the ventricular action potential. They are associated with prolonged Q-T interval i.e. it tends to occur at slower heart rates. Thus, quinidine, which decreases the heart rate, can actually set up tachycardia (by causing EADs); this is called *torsades de pointes*. The exact cause of EAD is not known.

DAD: Appears near the very end of phase 3 or beginning of phase 4 of ventricular action potential. They are exaggerated by tachycardia. The cause is due to increased intracellular calcium; this induces a transient diastolic inward current, possibly by promoting Na-Ca exchanger. The current causing the repetitive after depolarization is switched on by an increased intracellular calcium level. Therefore, the Ca++ antagonist verapamil and a low external Ca++ level both inhibit DAD. DADs are thought to be underlying the development of ventricular automaticity during digitalis poisoning.

III. Mechanism of contraction

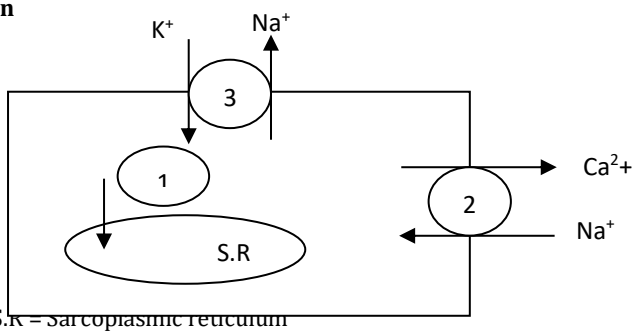
This is similar to skeletal muscle.

The T tubules are wide and filled with mucopoly-saccharide

There is also the phenomenon of calcium triggered calcium release (or calcium-induced calcium release). This means that

Ca^{++} entry from ECF into the cardiac muscle cell triggers the release of more Ca^{++} from the sarcoplasmic reticulum

IV. Relaxation



S.R = Sarcoplasmic reticulum

Relaxation is by decreasing the cytosolic Ca^{++} level by

(1) Ca^{++} pump in sarcoplasmic reticulum
(2) Ca^{++} Na^{+} antiport
(3) Na^{+}- K^{+} ATPase

(Phospholamban inhibits the Ca++ pump in S.R. This activity of phospholamban is inhibited by its phosphorylation)

V. Relationship between electrical and mechanical events

The action potential in ventricular muscle fibres is prolonged one and therefore the refractory period is also relatively prolonged. This is the reason as to why cardiac muscle cannot be tetanised

VI. Length – tension relationship

Within physiologic limits, force of contraction (as reflected by stroke volume) is directly proportional to the initial length of the muscle fibre (as determined by the end-diastolic volume). This is known as theFrank- starling's law

MUSCLE – Smooth Muscle

I. Nerve supply

The nerve shows varicosities; the nerve establishes functional contact at several points on the muscle as it courses alongside it; this is called synapse en passant. There can be excitatory or inhibitory functional potentials.

II. Functional anatomy

- No troponin or tropomyosin
- No Z – lines (The anchorage for the actin filaments is provided by structures called dense bodies)
- No T-tubule
- No (or rudimentary) sarcoplasmic reticulum

III. Types

1. Visceral (single – unit)
   This is the type of smooth muscle present in hollow viscera. There are gap junctions between muscle fibres
2. Multi – unit
   Eg. Intraocular muscle of the eye (ciliaris, iris)
   It behaves like skeletal muscle in the sense that its response can be graded

IV. Electrical activity

- There is no steady resting membrane potential in smooth muscle
- There is presence of slow-waves (pacemaker potentials). These are generated in multiple foci that shift from place to place

- Action potentials (spike potentials) are formed → superimposed on the slow-waves

V. Excitation / inhibition in smooth muscle

1. Multi – unit
   Can be excited only by nerves
2. Single unit

The response can be

i) Spontaneous
ii) From adjacent cells (through gap junctions)
iii) Nerves (i.e. by neurotransmitters)
iv) Hormones
v) Stretch
vi) Cold

VI. Mechanism of contraction

(Excitation contraction coupling in visceral smooth muscle is a very slow process)

1. First Ca++ entry into the cell
2. Ca^{++} binds to calmodulin
3. The Ca^{++} calmodulin complex activates myosin light chain kinase (MLCK)
4. Activation of MLCK causes phosphorylation of myosin which causes increased myosin ATPase activity and binding of myosin to actin
5. This initiates the cross-bridge cycling & contraction
6. Relaxation is by dephosphorylation of myosin by myosin phosphatase

VII. Some unique features of smooth muscle contraction

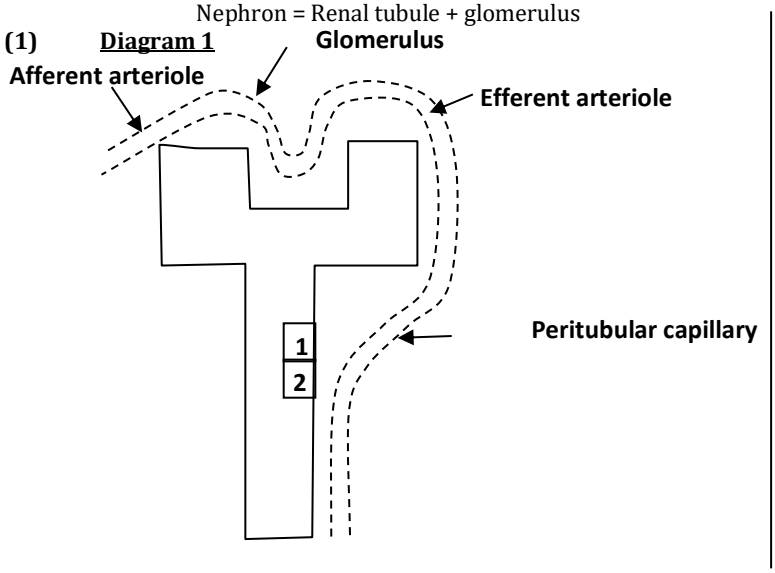
1. The process is slow
2. It is a low-energy mechanism
3. It shows the presence of latching or latch state. This is the state in smooth muscle where, even after dephosphorylation of myosin, the cross-bridges continue to 'cling on' for sometime. The advantage is that it allows sustained contraction with minimum energy expenditure
4. There is a higher percentage of shortening
5. There is no fixed length-tension relationship in smooth muscle. It shows the property of plasticity
6. Smooth muscle can generate as much or even more tension than skeletal muscle/cardiac muscle.

KIDNEY

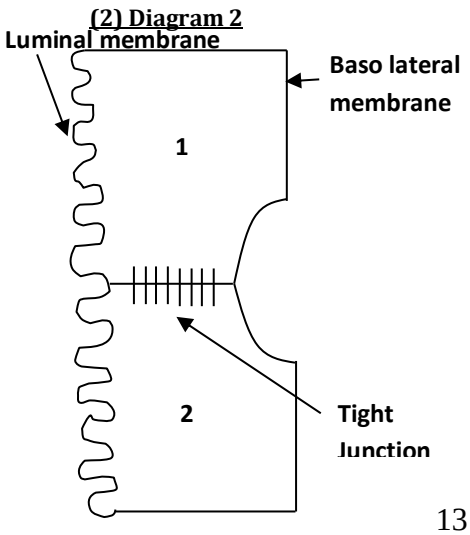
I. Functional Anatomy

Nephron = Renal tubule + glomerulus

(1) Diagram 1



(2) Diagram 2



Note that there are 2 'routes' through which a substance can enter the renal tubule Viz '(A)' and '(B)'
[(A) – By Glomerular filtration,
(B) – By peritubular capillary exchange]

Nephron = renal tubule + glomerulus

Length in mm of the different parts of the nephron :

Total = 45 – 65
PCT = 15
DTS and ATS = 2 – 14
TAL = 12
DCT = 5
CD = 20

Glomerulus

Diameter = 200 micrometer
Area = 0.8 square meter

Total surface area of

Renal capillaries = 12 square meters
Tubules = 12 square meters

Salient histological features:

PCT : Brush border (microvilli) (1 x 0.7 micrometer); leaky tight junctions
TAL : Cuboid cells, numerous mitochondria, basilar portion is invaginated
DCT : epithelium is lower than PCT; has microvilli but no brush border; tight tight junctions
CD : has P cells and I cells

(3) Glomerular membrane

The barriers through which filtration has to take place

a. **Glomerular endothelial cell layer** : The glomerular capillaries are fenestrated, the pore size of the fenestrae is 70 – 90 nm.
b. **Basement membrane**: Permeability of basement membrane depends on:
   i. Size of particle
      Neutral substances which are < 4nm are freely filtered; > 8nm are not filtered
      Between 4 nm and 8nm, the permeability is inversely proportional to the diameter
   ii. Charge of the particle
      Since the sialoprotein in the glomerular capillary wall are negatively charged, filtration of positively charged particles is facilitated whereas negatively charged particles are repelled

c. Visceral epithelial layer of Bowman's capsule. The visceral epithelial cell is called a podocyte; each podocyte has many foot processes, which inter digitate to form filtration slits: The size of filtration slits = 25 nm.

(5) Difference between proximal tubular cell and distal tubular cell

PCT	CD
i) Brush border present	No brush border
ii) Carbonic anhydrase present in luminal membrane	No carbonic anhydrase in luminal membrane
iii) Has 'leaky' tight junctions	Has 'tight' tight junction

(6) Difference between cortical and juxtamedullary nephron

Cortical nephron	Juxtamedullary nephron
i) Form 85% of the nephrons	Form 15% of the nephrons
ii) Short loop of Henle	Long loop of Henle
iii) Peritubular capillary network is short	Form vasa recta
iv) Blood flow is large	Blood flow is less
v) O_2 extraction is very less	O_2 extraction is large
vi) PO_2 is 50mmHg	PO_2 is 15mmHg

(7) Special cells in collecting tubule

(I) P (Principal) cell: For Na^+ reabsorption

(II) (Intercalated) cell: For acid secretion

(8) Mesangial cells

2 sites

i) Glomerular mesangial cells
(Lying between glomerular capillary loops)
These are contractile cells and play a role in regulation of glomerular filtration
(Note: When these contract, the GFR decreases because the effective area of filtration is reduced)

ii) Extra glomerular mesangial cells (Lacis cells)
These form part of the juxta – glomerular apparatus

(9) Juxtaglomerular apparatus

Components are

(i) Juxtaglomerular cells
These are modified smooth muscle cells in the tunica media of the afferent arteriole. The cells have renin – containing granules.

(ii) Macula densa
This is the modified region of the tubular epithelium; it marks the beginning of DCT

(iii) Lacis cells

(10) Renal vessels / Renal nerves

Renal vasodilation: Dopamine, prostaglandins, acetyl choline, high protein diet

Renal vasoconstriction:

(i) Angiotensin II
Constricts efferent arteriole more than afferent arteriole

(ii) Norepinephrine
Constricts afferent arteriole more than efferent arteriole

Effect of stimulation of sympathetic nerves to kidney

(i) Vasoconstriction (Which decrease renal blood flow and GFR)

(ii) Increases renin output

(iii) Increases Na^+ reabsorption

KIDNEY: BLOOD FLOW/O_2 CONSUMPTION

(WEIGHT = 300 GM)

1. Renal Blood Flow

Total	1260 mL/min
Cortical	5 mL/Gm/min
Outer Medulla	2.5 mL/Gm/min
Inner Medulla	0.6 mL/Gm/min

Effective Renal plasma flow (ERPF) = 625 mL/min

Renal plasma flow (RPF) = 700 mL/min

2. O_2 Consumption

Total	18 mL/min
Cortex	9 mL/100 gm/min
Inner Med.	0.4 mL/100 gm/min

(A-V) O_2 Diff. = 14 ml/L

OTHER POINTS

1. Total Blood Flow (mL/min)	Liver>Kidney>Sk MSL > Brain 1500) (1260) (840) (750)
mL/100g/min	Kidney>Heart>Liver>Brain (420) (84) (58) (54)
2. A-V O_2 Diff (mL/L)	Heart>Brain>Sk MSL> Liver > Kidney (114) (62) (60) (34) (14)
3. O_2 Consumption (mL/min)	Liver >Sk MSL > Brain > Heart > Kidney (51) (50) (46) (29) (18)
4. O_2 Consumption	Heart > Kidney > Brain > Liver

(mL/100g/min)	(9.7)	(6)	(3.3)	(2.0)

The following table shows the blood flow in different tissues under basal conditions (reference : Guyton, 11th edition, page 196)

Tissue	**%**	**Ml/min**	**Ml/100gm/min**
Brain	14	700	50
Heart	4	200	70
Bronchi	2	100	25
Kidneys	22	1100	360
Liver	27	1350	95
Portal	21	1050	
Arterial	6	300	
Muscle (inactive state)	15	750	4
Bone	5	250	3
Skin (cool weather)	6	300	3
Thyroid	1	50	160
Adrenal	0.5	25	300
Other tissues	3.5	175	1.3
Total	100	5000	

Spleen = 150 ml/min ; Weight of spleen = 150 gm (reference : Harrison)

II. Glomerular filtration

This is governed by the same forces (Starling's forces) as that across capillary.

$GFR = K_f [P_{GC} - P_T) + (\pi_t - \pi_{GC})]$

Where Kf = filtration coefficient
GC = Glomerular capillary
T = Tubule
P = Hydrostatic pressure
π = Oncotic pressure

(Hydrostatic pressure is a 'push' force and Oncotic pressure is a 'retaining' or pull force)

III. Clearance : Clearance for a substance 'A' is

(i) Definition: defined as that volume of plasma that is required to contain that much amount of the substance A which is present in one minute's urine. *Its unit is mL/min*

(ii) Formula

It is given by the formula:

$$C = \frac{U V}{P}$$

Where

C = clearance
U = concentration of the substance in the urine
V = urine flow
P = concentration of the substance in the plasma

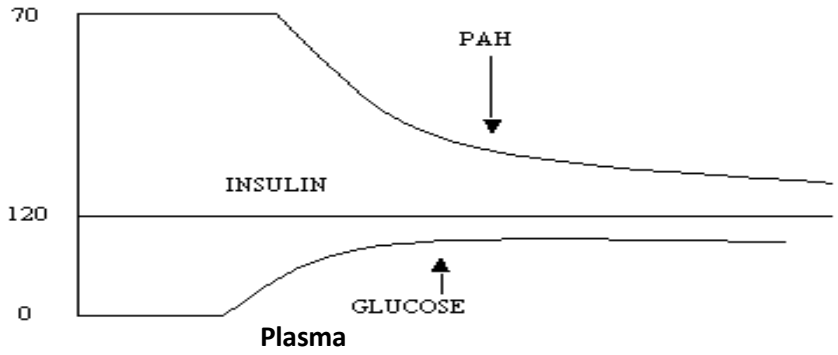
(iii) Uses

- Clearance of Inulin gives GFR (125ml/min)
- Clearance of paramino hippuric acid (PAH) gives renal plasma flow (625 ml/min)
  Since the extraction ratio of PAH is 0.9 (90%), the value obtained is effective renal plasma flow (ERPF)

$$\text{The actual RPF} = \frac{\text{ERPF}}{0.9}$$

(iv) Other Points

Clearance is just a mathematical (theoretical) concept eg. Clearance of glucose is normally zero because there is no glucose in the urine. It does not mean that there is no glucose in blood !



Graph showing the effect of increasing plasma concentration on clearance.

IV. Tubular reabsorption

1. Sodium reabsorption

It occurs in all parts of the tubule except the thin descending part. It is active reabsorption except in thin ascending portion (where it is passive).

The various mechanisms in different parts of the tubule are

PCT	1) SGLT 2) Na – Amino acids 3) Na – Citrate / PO4 / SO4 / Lactate
PST	Cl- driven Na+ transport
DTS	No reabsorption
ATS	Passive (no transportation)
TAL	Na^+- K^+ - $2Cl^-$; Na-H
DCT	Na^+ - Cl^-
CD	P cell (ENaC)

(P cell = principal cell; ENaC = Epithelial sodium channel)

(Aldosterone acts on collecting duct to increase Na+ reabsorption. It does this by increasing the number of open EnaCs and also by increasing the number of Na^+ - K^+ ATPase)

Other points

Out of the total filtered load of Na^+, 99.4% is reabsorbed → 65% in PCT; 25% in Henle; 10% in DCT/CT.

Na^+ reabsorption is increased by aldosterone (which acts on collecting duct) and by angiotensin II (which acts on PCT)

Most of the sodium is reabsorbed along with Cl

Natriuresis is caused by PGE_2, IL-1, ANP, ouabain, Endothelin

2. Glucose

Glucose is reabsorbed by secondary active transport. All the glucose is reabsorbed in PCT.

The **TmG** (tubular maximum for glucose i.e. the maximum rate of absorption of glucose by the tubule) is 375 mg/min in males and 300mg/min in females. Given that the TmG is 375mg/min in males, by calculation, the renal threshold for glucose in blood would be 300mg/dL.

However, The actual value of renal Threshold is much less than this; it is 200mg/dL in arterial and 180mg/dL in venous blood.

This deviation in the renal threshold (from the calculated predicted value) in called splay. The reason for splay is heterogeneity of nephrons (i.e. not all nephrons have TmG of 375 mg/min); further, not all nephrons are maximally active simultaneously

3. Water

Water reabsorption is passive, following the osmotic gradient. The total glomerular filtered load is approximately 180L/day. Out of this, the amount of urine output can vary from 500mL (osmolality of 1400 mosm/L) to 23.3 Litres (osmolality of 30 mosm/L). Water reabsorption is facilitated by water channels (aquaporins) There are various types of aquaporins:

Type	Site
Aquaporin 1	Luminal membrane of PCT
Aquaporin 2	Luminal membrane of CD
Aquaporin 3	Basolateral membrane of CD
Aquaporin 4	Brain
Aquaporin 5	Salivary, lacrimal, respiratory system

The % of water reabsorption in the various segments is as follows

a) PCT 60-70%
b) Loop of Henle 15%
c) Distal Tubule 20%
   (i) DCT 5%
   (ii) CT 15%

- Cortical CT 10%
- Medullary CT 4.7%

The tonicity of tubular fluid at various segments

a) At the end of PCT : Isotonic
b) As it goes down the descending limb : Hypertonic
c) As it goes up the ascending limb : It first, isotomic, then hypotonic. At the top of ascending limb,

it is hypotonic
(The ascending limb is called the diluting segment)
The permeability characteristics of the tubular

segments to water is as follows:

		Water	**NaCL**
a)	Thin Descending Limb	Highly permeable	±
b)	Thin ascending limb	Not permeable	Highly permeable
c)	Thick ascending limb (TAL)	Not permeable	±
	[However, TAL has Na^+ - K^+ - Cl^- cotransporter]		

d) The DCT is relatively impermeable to water (Therefore, there is continued dilution of the tubular fluid as it goes along the DCT)
e) Collecting Duct
It becomes permeable to water in the presence of ADH; ADH inserts aquaporin 2 channels in the luminal membrane of collecting duct cells

Counter current mechanism

There are 2 counter current mechanisms in kidney

i) Counter current multiplier, in loop of Henle
ii) Counter current exchanger, in vasa recta

The counter current mechanism depends on the gradient of osmolality in the medullary interstitium. The medullary interstitial gradient depends on

i) Active transport of Na^+ at thick ascending limb (by Na^+ - K^+ - $2Cl^-$ Co- transporter)
ii) Passive movement of Na+/Cl- out of thin ascending limb without water
(Refer to the permeability characteristics of the tubule)
iii) Permeability of thin descending limb to water
iv) Urea, also contributes
The inner medullary collect duct is significantly permeable to urea; ADH increase this permeability)

The longer the loop of Henle, the greater can be the medullary interstitial osmotic gradient created; thus, the concentration ability is determined by the length of the loop of Henle.
Once the interstitial osmotic gradient is established by the counter current multiplier, it is maintained by the counter current exchange mechanism of the vasa recta; without the counter current exchange mechanism, all the good work of the counter current multiplier will soon be lost. The counter current multiplier mechanism is active whereas the counter current exchange mechanism is passive
Once the medullary interstitial osmotic gradient is established, water can move from the collecting in the presence of ADH
Note that in the cortical collecting duct segment, the urine can at best be concentrated up to isotonicity only; as it moves down the medulla collecting duct, the urine can be concentrated up to the maximum limit determine a by the maximum gradient existing in the medullary interstitium.

Difference between Water and Osmotic diuresis

Water diuresis	**Osmotic diuresis**
i) This is by inhibition of ADH	This is by osmosis
ii) Absorption in PCT is normal	Absorption in PCT is decreased
iii) Maximum limit of diuresis is 16ml/min	No such limit

Free Water clearance (C_{H2O})

This is the difference between actual urine output and the urine output calculated based on clearance of osmoles

That is,

$$C_{H20} = V - \frac{Uosm \times V}{Posm}$$ where V = actual urine output

(If the value is positive, the urine is hypotonic; if the value is negative, the urine is hypertomic)

4. Potassium

Active reabsorption in PCT; secreted in DCT. K^+ secretion is decreased when the amount of Na+ reaching the DCT is small.
K^+ secretion is also decreased when the H^+ secretion is increased

(In DCT, Na^+ is reabsorbed and K^+ and H^+ compete for their secretion for the amount of Na+ reabsorbed)
K^+ is the only electrolyte that is reabsorbed as well as secreted.
65% of the K^+ is reabsorbed in PCT, 25% in loop and < 10% reaches the distal rephron
For K+ and H+, remember the terms 'hypokalem i.e. alkalosis and hyperkalemic acidosis'.

5. Hydrogen secretion

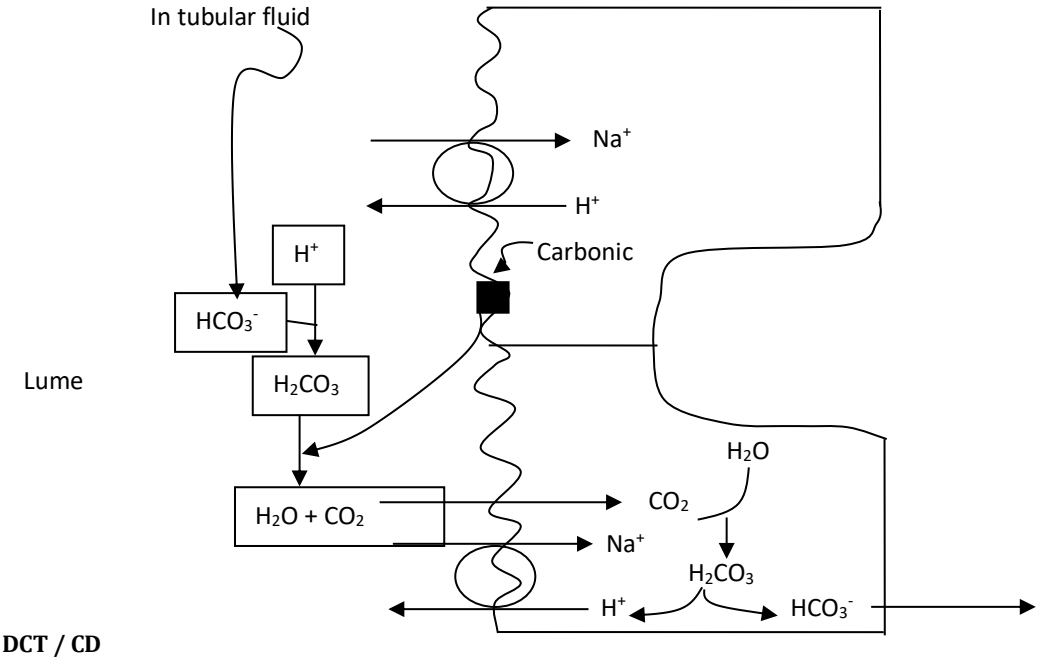
Occurs in PCT, DCT and CD
Mechanisms

a) **In PCT**

Na^+ - H^+ exchanger
For each H^+ that is secreted, effectively 1 Na^+ and 1 HCO_3^- is reabsorbed.
(The handling of the secreted H^+ in PCT is by carbonic anhydrase)

The secreted H^+ in PCT does not acidity the urine; it only helps in the reabsorption of Na^+ and HCO_3^-.

Since the secreted H^+ in the PCT is quick by handled, the secretion of H+ in, PCT can be called a high-capacity, low-gradient system. i.e. the capacity is high but the acidification is not there.



b) **In DCT / CD**

i) ATP – driven proton (H^+) pump
ii) H^+ - K^+ ATPase

The secreted H^+ here helps to acidify the urine. Since the secreted H^+ is not as quickly handled (recall that there is no carbonic anhydrase in the luminal membrane of DCT), the limit of H^+ secretion is reached quickly. Therefore, the H^+ secretion here can be called a low-capacity, high-gradient system. i.e. the capacity is low but the acidification is significant.

Urinary Buffers

Type of buffer	PK	Sites
Bicarbonate	6.1	In PCT, it is mostly bicarbonate buffer
Phosphate	6.8	In DCT/CD
Ammonia	9.0	Both PCT & DCT

Limiting pH of urine = 4.5
Factors affecting acid secretion
i) Intracellular PCO2
When PCO2 in high, acid secretion is increased
ii) K^+ depletion
This increases acid secretion

Note:

Hypokalemia tends to cause alkalosis and vice versa.

Hyperkalemia tends to cause acidosis and vice versa.

iii) If carbonic anhydrase is inhibited, acid secretion is decreased
iv) Aldosterone
This increases Na^+ reabsorption and increases K^+ and H^+ secretion

Titratable Acid :- This is measured by the amount of alkali to be added to urine to make the pH 7.4. Titratable acid mainly reflects the buffering by phosphate buffer.

Net acid excretion: Titratable acid + NH_4 excreted – HCO_3^- excreted.
Net HCO_3^- gain: Same formula as for net acid excretion.
Plasma anion gap

Formula = Na+ - (Cl- + HCO3-)
Value = 8 to 16 meq/litre
Mostly due to the unmeasured plasma proteins
It is used to classify different types of metabolic acidosis

Causes of high anion gap acidosis

Mnemonic : CUTE DIMPLES

C = cyanide poisoning
U = uremia
T = toluene poisoning
E = ethanol poisoning

D = diabetic ketoacidosis
I = INH poisoning
M = methanol poisoning
P = propylene glycol poisoning
L = lactic acidosis
E = ethylene glycol poisoning
S = salicylate poisoning

CARDIOVASCULAR SYSTEM

Electrical events

1. **The conducting system is made up of modified cardiac muscle**. Though there are 'latent pacemakers' in other portions of the conducting system, the **SA node** is the normal pacemaker of the heart because its prepotential (refer- cardiac muscle) is the steepest. The atrial and ventricular muscle normally do not show prepotential. The SA node is situated at the junction of superior vena cava and right atrium.

(The AV node is situated in the right posterior portion of the inter atrial septum)

Innervation of SA node & AV node

	SA node	AV node
Parasympathetic	Right vagus	Left vagus

Sympathetic	Right stellate ganglion	Left stellate ganglion

Stimulation of

Right vagus	Inhibits SA node	↓es heart rate
Left vagus	Inhibits AV node	Slows A-V conduction
Right stellate ganglion	Stimulates Sa node	↑es heart rate
Left stellate ganglion	Stimulate AV node	Shortens AV conduction time and refractoriness

2. Conductions speeds

Tissue	Rate (m/s)
SA node	0.05
Atrial pathways	1
AV node	0.05
Bundle of His	1
Purkinje system	4
Venticular muscle	1

Reference for the above table : Ganong

Note : In some other books, the conduction speed of AV node is given as 0.03 m/s. Therefore, in mcqs, it can be noted that the conduction speed of the AV node is the slowest. This normal AV nodal delay allows sufficient time for ventricular filling.

AV nodal delay = 0.1 second

AV node can conduct up to 230 impulses/minute.

3. Spread of cardiac excitation – (Depolarization begins in SA node)

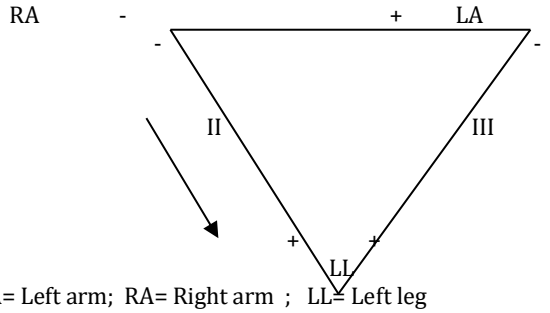
a) Ventricular depolarization- the first part of the ventricle to get depolarized is the *left endocardial surface* of the *interventricular system;* then the *right endocardial surface* of the *interventricular system*. It then passes down and through the *Purkinje system* depolarizes the ventricles from *endocardium to epicardium*. The top of the interventricular septum and the base of the heart are the last to be depolarized.

b) Ventricular repolarisation- *The apical epicardial surface is the first to repolarise; the base endocardial surface is the last to repolarise.*

II. ECG – The 12 lead ECG consists of

- 3 bipolar limb leads viz lead I, II, III (also called standard limb leads)
- 3 unipolar (augmented) limb leads viz avR, avL, avF
- 6 unipolar chest leads viz V1 to V6

1. Unipolar limb leads – the connection of the bipolar limb leads is :



LA= Left arm; RA= Right arm ; LL= Left leg

For example, Lead I is between LA and RA, with the LA 'positive' and RA 'negative'. The direction of the lead axis is taken from negative to positive e.g the arrow indicates the direction of lead II.

The basic electrical recording principle are

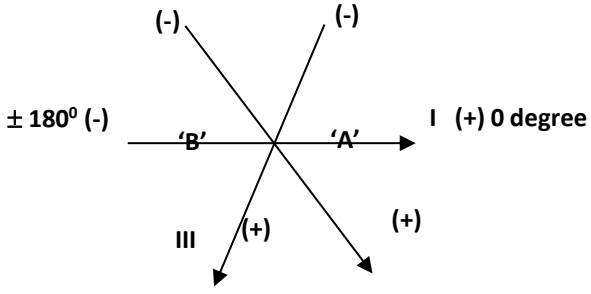
i) If the direction of the cardiac impulse is towards the recording electrode, a positive (upward) deflection is recorded; if it is moving away from the recording electrode, a negative (downward) deflection is recorded.

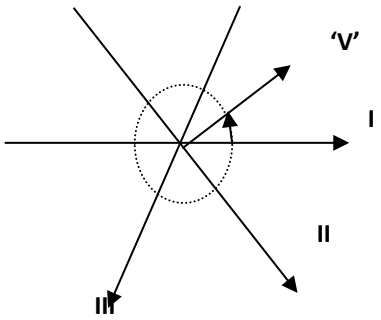
ii) The height of deflection depends on

a. The strength of the cardiac impulse vector.

b. How the vector is oriented to the lead axis. If it is parallel, it records maximum deflection; if it is perpendicular, it records minimum deflection.

Calculation of axis- The connections of the bipolar limb leads can be represented in another way;

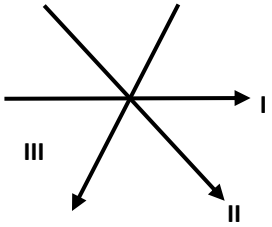


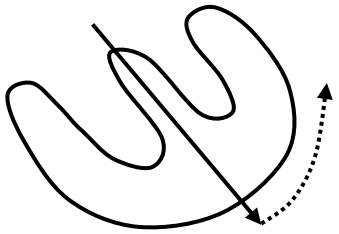


If one goes 'clockwise' from point ' A' to point 'B' it is from 0^0 to $+180^0$; if one goes 'anticlockwise' from point 'A' to point 'B' it is from 0^0 to -180^0. Illustrative example:	The vector 'V' can be taken as -30^0 or as $+330^0$. Similarly, direction of lead II is $+60^0$ or - 300^0

The normal direction of the mean QRS vector is generally between- 30^0 to $+110^0$.

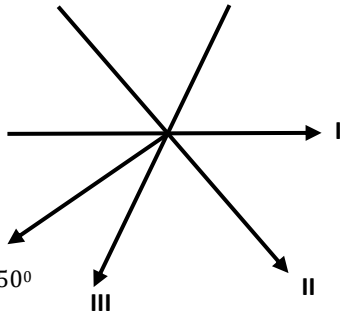
Normally, the maximum deflection is recorded in lead II because the direction of the mean QRS vector is most parallel to lead II.



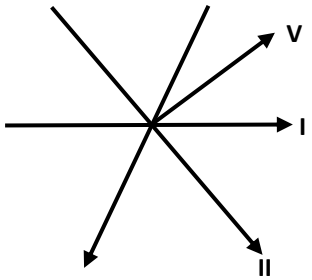


<u>If there is a left ventricular hypertrophy, the vector will 'shift' in the direction shown by dotted arrow; in which case, the vector would become most parallel to lead I. So, if one wants to know the value of vector, the vector can be 'superimposed' on the triaxial system.</u>

e.g.



Value of V = 150^0



Value of II = 60^0 or + 300^0

<u>Einthoren's law : Mean deflection is lead II = Mean deflection in lead I + Mean deflection in lead III i.e II = I + III</u>

1. Augmented unipolar limb leads – the unipolar limb leads are VR (right arm), VL (left arm) and VF (left foot); the *augmented limb leads are aVR, aVL and aVF*. The 'augmentation' is in terms of amplitude of deflection i.e aVR amplitude is 1½ times the amplitude in VR (the configuration remains the same). In the unipolar leads, one electrode that is kept at the point where the potential is to be measured is called the exploring electrode. The other electrode (called indifferent electrode) is kept at near zero potential by connecting 3 wires from the right arm, left arm and left leg, through a resistance (of say 5 kilo ohm). This is also called the

2. ***<u>Wilson's terminal.</u>***

<u>Note that the bipolar leads measure the potential difference whereas the unipolar leads measure the actual potential at that point.</u>

3. **<u>Some generalizations in normal ECG</u>**

Lead	Feature(s)
aVR	All the deflections are negative
aVL / aVF	Predominantly positive or biphasic
V_1, V_2	No Q wave; deep S wave
V_3, V_4	Biphasic
V_5, V_6	Small Q wave, Tall R wave
Lead I, II, III	All positive deflection; largest in lead II

4. **<u>ECG in some abnormal condition</u>**

i) Accelerated A-V conduction

a) Wolff- Parkinson White Syndrome : (Here, the abnormal connection is between atria & ventricle, it is called the bundle of Kent)

- Short P- R interval
- Prolonged QRS deflection, which is slurred on the upstroke
- P- J interval is normal

b) Lown- Ganong- Levine syndrome : (Here, the abnormal connection is between atria and bundle of his; if is called James bundle)

- Short P - R interval
- Normal QRS
- P – J interval is decreases

ii) M.I

a) **Changes due to current of injury** – ST segment elevation. This is most noticeable in chest leads just over the infarcted area (current of injury: the infarcted area is negative (extra cellularly) relative to the surrounding area; this results in flow of current into the infarcted area from the surrounding areas.)

The ST segment elevation is because of 3 basic abnormalities of cardiac muscle in M.I

- Rapid repolarization (seconds after the infarct)
- ↓ in RMP (minutes after the infarct)
- Delayed depolarization (half an hour after infarct)

b) **Changes due to electrical silence** –(after days/ weeks, the infarct becomes electrically silent)

- Q wave changes
- R wave changes (failure of progression)

c) Changes due to conduction abnormalities

- Heart block
- Arrhythmias (due to reentry and increased automaticity)

iii) *Electrolytes*

a) Decrease of Na^+: Causes low voltage ECG

b) Hyper kalemia: Tall peaked T waves. At higher levels, ; Paralysis of atria, prolongation of QRS ventricular arrhythmia. Since the RMP ↓es as ECF K^+ ↑es, eventually heart stops in diastole

c) Hypokalemia:

- ST ↓
- Prominent U waves

d) Increase in Ca^{++} in ECF : increases myocardial contractility; if too much calcium, there is calcium rigor and the heart stops in systole.

e) Decrease in Ca^{++}

- ST segment prolongation
- QT interval prolongation

5. His Bundle Electrogram (HBE)

i) This is used to study events in the
   a) AV node
   b) Bundle of His
   c) Purkinje system

ii) There are 3 waves in HBE:

Wave	Denotes
A deflection	AV nodal activation
H spike	Transmission through bundle of His
V deflection	Ventricular depolarization

iii) There are 3 intervals described (marked with the help of HBE and standard (ECG):

Interval	From – to	Represents
PA (27 ms)	First appearance of atrial depolarization to 'A' wave in HBE	Conduction time from SA node to AV node
AH (92 ms)	'A' wave to start of 'H'	AV node conduction time
HV (43 ms)	Start of 'H' to start of QRS	Conduction in bundle of His and branches

[Note that PA ++ AH+ HV internal = PR interval]

From the HBE, a distinction can be made between supra ventricular tachycardia (H spike present) and ventricular tachycardia (No H spike)

III. Mechanical events

Note that mechanical events *follow* electrical events; atrial systole starts after 'P' wave and ventricular systole starts near the end of 'R' wave and ends just after 'T' wave.

Duration of 1 cardiac cycle = 0.8 second
Ventricular systole = 0.3 second
Ventricular diastole = 0.5 second
Atrial systole = 0.1 second
Atrial diastole = 0.7 second

1. Phases in the cardiac cycle

i) Ventricular systole
- Isovolumic contraction
- Rapid ejection
- Slow ejection

ii) Ventricular diastole
- Isovolumic relaxation
- Rapid filling
- Slow filling (diastasis)

(70% of the ventricular filling is passive; 30% is because of atrial contraction) (Note that during isovolumic phase, all the 4 valves are closed)

2. Pressures (mmHg)

i)	Pulmonary artery	25/10
	Mean	10-15
ii)	Aorta	120/80
	mean	100
iii)	Left atrium	5
iv)	Pulmonary capillaries :	8
v)	Left ventricle:	120/ 0
vi)	Right ventricle:	25/0

3. Parameters

i) Stroke volume (SV): This is the amount of blood ejected by each ventricle per stroke; it is between 70-90 ml

ii) End- diastolic volume (EDV): This is the amount of blood in the ventricle at the end of diastole; it is around 130ml

iii) End- systolic volume = EDV- SV (it is around 50ml)

iv) Ejection fraction = $\frac{SV}{EDV} \times 100$

= 65%

v) Cardiac output = S.V. x Heart rate

vi) Blood pressure = C.O x peripheral resistance

Heart Sounds

S1: Closure of A-V valves
S2: Closure of semilunar valves
S3: Rapid ventricular fillings
S4: Forceful atrial contraction

4. **Arterial pulse**- this is because of the pressure wave set up in the walls of the vessels. The rate of the pressure wave is

i) Aorta 4m/s
ii) Large arteries 8m/s
iii) Small arteries 16m/s

(Note that the rate of blood flow at the root of the aorta is 40cm/s)

With age, the arteries get thickened and the pressure wave, moves faster. The strength of the pulse is determined by the pulse pressure (the difference between systolic and diastolic pressure); it bears no relation to the mean arterial pressure. The dicrotic notch corresponds with the closure of aortic valve.

5. Waves in JVP

Waves	Due to
a	Atrial systole
c	Bulging of tricuspid valve into right atrium during isovolumic ventricular contraction
v	Filing of right atrium before the tricuspid valve opens in diastole

X descent:
Due to pulling down of tricuspid valve during rapid ejection phase of ventricular systole
Y descent:
Due to rapid ventricular filling

Some abnormalities in JVP

Giant 'C' wave: Seen in tricuspid regurgitation
Giant 'a" wave (common wave) : Seen in complete heart block

6. Cardiac output:
Definition: Amount of blood ejected by each ventricle per minute
Value = 5L/ min
Formula= C-O =S.V X H.R

$$\text{Cardiac Index} = \frac{\text{C. O.}}{\text{Body surface area}}$$

Its value is 3.2 L/Sq.m/min

Measurement :

i). Fick method
ii). Dye dilution / thermo dilution
iii). Doppler plus echocardiograph

Regulation of cardiac out put

Since C-O = HR X SV, it can be regulated by HR and SV
i). HR: This is influenced by sympathetic and parasympathetic innervation
ii). S.V: This can be changed by

a. Heterometric regulation: - This is based on Frank Starling Law; more is the initial length of the cardiac muscle preload, as indicated by EDV) , more will be the SV (with in physiologic limits).

b. Homocentric regulation:- This S.V can also be changed for the same initial length . This is called homometric regulation. For example, *positively inotropic agents like catecholamines , xanthines , glucagon and digitalis - increase the S.V; negatively inotropic states like hypercapnia , hypoxias , acidosis , certain drugs ,(eg barbiturates ,quinidine) heart failure , M.I - decrease the S.V .*
To summarise, *C.O can be either regulated by heterometric regulation (Frank starling law) with regulation based on a change in initial length or EDV) or by homometric regulation*.

	Related to
Inotropic	= Force
Chronotropic	= HR
Dromotropic	= Conduction velocity
Bathmotropic	= Excitability
Lusiotropic	= Relaxation time.

7. Work done / O_2 consumption
i). Work done :- Ventricular work per beat correlates well with O_2 consumption
Left ventricular work/ beat = S.V. X M.A.P in aorta
Right ventricular work/ beat = S.V. X M.A.P in pulmonary artery
(MAP= Means Arterial pressure)
Since aortic pressure is nearly 7 times pulmonary arterial pressure , the left ventricular stroke work is 7 times right ventricular stroke work.
Out of the pressure work and volume work (since work= volume X pressure, the pressure work produces a greater increase in O_2 consumption than volume work)

ii). O_2 consumption by the heart:- The beating heart at rest consumes 9 ml / 100g /min of O2.
The arterio – venous O_2 difference is maximum in the heart.
The O_2 consumption is determined by
a). Intra myocardial tension
b). Contractile state of myocardium
c). Heart rate

Note:- Myocardial O_2 usage is most closely related to the tension time index (TTI).
The tension time index is a product of the mean systolic pressure , the duration of systole and the heart rate
(The higher the heart rate the greater is the myocardial O_2 usage, for any given cardiac output.)

IV. Vessels

1. Type of blood vessels	
Type	**Features**
1. Wind Kessel vessels	Eg. aorta, major arteries: have a lot of elastic tissue; show elastic recoil
	effect (wind kessel effect), when stretched
2. Resistance vessels	Eg. arterioles, have some elastic tissue. Have a lot of smooth muscle
	(have the maximum wall thickness to lumen ratio)
(Vena cava –minimum thickness /lumen ratio). They are very richly innervated	

3. Precapillary sphincters	No innervation , respond to local metabolites
4. Exchange vessels	Capillaries . No innervation, Controlled by precapillary sphincters
5. Capacitance vessels	Veins . Have some innervation
6. Shunt vessels	A – V anastomoses . They have thick muscular wall; very richly innervated
	Eg. fingertips , earlobes etc.

Note:- I). Cross sectional area: is minimum for aorta and maximum for capillaries
ii). % of blood volume : is maximum in capacitance vessels and minimum in arterioles.

2. Capillaries:-

i). 3 types a.) Continuous eg. brain, skin
b). Fenestrated eg. GIT, glomeruli of kidney, endocrine glands, circum ventricular organs
c). Discontinuous (Sinusoids) eg. liver, bone marrow

The least permeability of capillaries is that is the brain

ii). Pericytes:

These are associated with capillaries and post capillary venules. They are similar to the mesangial cells in the renal glomeruli.

i). They are contractile
ii). They release vasoactive agents
iii). They synthesize and release constituents of bone marrow and extra cellular matrix.

One of their functions is to regulate the flow through the junction between the endothelia cells, especially during inflammation

3. Biophysical principles:-

i**). F=P/R** (Where F= flow , P= effective perfusion pressure , R= resistance)
or
R=P/F

If P is expressed in mm Hg and flow is expressed in ml/second, then resistance will be expressed in 'R' units [Or peripheral resistance units (PRU)]

Blood flow measurement

Direct method	**Indirect method**
a). Electro magnetic flow meters	a). Fick method
b). Doppler flow meter	b). Indicator method eg. Kety method for cerebral blood flow using N_2O
	c). Plethysmography

While applying the biophysical principles, one must bear in mind that vessels are not rigid tubes and that blood is not a perfect fluid. Thus there can be differences between in vivo and in vitro conditions.

Flow can be laminar (streamline) or turbulent:

Laminar	**Turbulent**
a. Silent	a. Noisy
b. Paraboloid velocity profile – flow is maximum in the center of the flow and goes on decreasing towards the wall	b. No such gradient in flow rate from center of the flow towards the vessel wall exists
c. More efficient (less energy consumption)	c. less efficient

ii). The probability of turbulence in a given flow can be determined by Reynold's number:

Re= PDV/ η

(Where Re = Reynold 's number, P = Density of the fluid, D= Diameter of the vessel, V= Velocity of flow and η = Viscosity)

More the Reynold's number, more the chances of turbulence

If D is measured in cms , V in cm/s, η in poises ,
Then if Re is < 2000 there is usually no turbulence; if Re is > 3000, turbulence almost always there.

iii). Average velocity of flow

V= Q/A (Where V= velocity, Q= Quantity / amount of fluid and A= Area)

So , if area is more, velocity is less, Therefore the flow is least in the capillaries (maximum cross-sectional area) and maximum in the aorta (least cross-sectional area)

iv). Calculation of resistance:

R= $8\eta L/\pi r^4$ (Where R= resistance, η= viscosity, L= length of the vessel and r= radius)

Since Flow = Pressure/Resistance

$$\text{Flow} = \frac{(P_1-P_2)}{8\eta L^2} \times \pi r^4$$

The above formula is called the **Poiseuille – Hagen formula**

Viscosity

As seen in the calculation of resistance, one of the factors on which resistance depends is the viscosity of the blood. Viscosity in turn depends mostly on haematocrit. However the change in viscosity with change in haematocrit is much less in vivo than in vitro.

Newtonian and Non- Newtonian fluid: - A Newtonian fluid is a fluid whose viscosity is independent of the rate of shear eg. Plasma, Saline.

A non-Newtonian fluid is a fluid in which the viscosity changes with the changes in the shear rate.

At very low shear rates, the viscosity is greatly increased; at high rates of flow the fluid behaves almost as a newtonian fluid. *Blood is a non-Newtonian fluid.*

V. Critical closing pressure:- It is the pressure below which flow completely stops; the value of this pressure is not zero but above zero.

VI. Law of Laplace:- This gives the relationship between the distending pressure (P) , the wall tension (T) , the wall thickness (W) and the radius in a hollow viscous organ

$$T = \frac{P\,r}{W}$$

Law of Laplace helps to explain as to why

1) Capillaries do not rupture inspite of being thin walled.
2) Dilated hearts have to work more.
3) Alveoli do not collapse during expiration

In thin walled structure, 'W' can be ignored.

In a spherical structure, P= 2T/r

In a cylindrical structure, P= T/r

B.P.:-

i). Pulse Pressure = Systolic B.P. – Diastolic B.P

ii). Mean Pressure = Diastolic B.P. + 1/3 pulse pressure

The maximum pressure drop in the vascular circuit is at the level of the arterioles.(as the maximum resistance is at the arterioles)

Effect of gravity on B.P.: Above the heart level , the B.P. falls and below the heart level , the B.P increases The value is 0.77 mm Hg per cm. This is true for arterial as well as for venous pressure.

V. Cardio vascular regulation:-

1. **Auto regulation: -** The ability of an organ to regulate its blood flow (on its own independent of nervous/ systemic influences) with changes in perfusion pressure (with in a range)

Many organs show auto regulation e.g.. Brain, Kidney, Skeletal muscle, liver, heart , etc.

Skin does not show autoregulation.

Theories of auto regulation

i). Myogenic:- This depends upon the inherent property of the smooth muscle to contract ,when stretched. More the perfusion pressure, the more it contracts to decrease the calibre of the vessel and hence to decrease the blood flow

ii). Metabolic:- Less the perfusion pressure, more is the accumulation of local metabolites which can dilate the vessel and thus increase blood flow.

iii) Tissue pressure theory – This is applicable in encapsulated organs e.g. kidney

Some of the vasodilator metabolites are ↓ O2, ↑CO2, ↓pH, ↑ Osmolality, ↑ temperature, K+ , Adenosine, Lactate etc.

(Note:- The local effect of hypoxia & hypercapnia is vasodilatation in all the blood vessels except pulmonary vessels where they cause vasoconstriction)

2. Circulating hormones:

These can be vasoconstrictors / vasodilators.

Examples of vasoconstrictors:

i). Epinephrine /Norepinephrine

Norepinephirine causes generalized vasoconstriction where as epinephrine dilates the vessels in skeletal muscle and liver.

Parameter	Norepinephrine	Epinephrine
Systolic B.P	↑	↑
Diastolic B.P.	↑	↓
Mean arterial Pressure	↑	Only slight ↑
Pulse pressure	only slight ↑	↑↑
Heart rate	Reflex bradycardia	↑
Cardiac output	↓	↑

ii). Dopamine: Causes vasoconstriction everywhere except in renal vessels where it causes renal vasodilatation

iii). Angiotensin II: It causes generalized vasoconstriction , increases water intake and stimulates aldosterone secretion.

3. Sympathetic vasodilator system

Site: Vessels of skeletal muscles

Pathway: From the cortex to the vessels .It does not influence the vasomotor center in the medulla.
Neurotransmitter: The neuro transmitter at their postganglionic neurons is acetylcholine.
Functional role: It plays **no role** in the vasodilation in skeletal muscles during exercise;
it may play a role in the vasodilation by the thought of exercise.

4.Axon reflex:- Peculiarities /features:

i). It is *a local reflex* ; the impulse does not reach the spinal cord
ii). Antidromic conduction
iii). The neurotransmitter is substance P
iv). Produces vasodilatation and increased capillary permeability
v). It is responsible for the 'flare' of triple reaction (Flare is because of arteriolar dilatation)
vi) Asynaptic

5. Neural regulation: - The main cardiocascular 'centre' is in the medulla.
There are 2 'centers' viz

i). Vasomotor centre (VMC)
ii). Cardio inhibitory centre (CIC)
i). The VMC is in the rostral ventrolateral medulla (RULM); it has connection with the (inter mediolateral grey horn) of the spinal cord from which sympathetic innervation arises for the heart and blood vessels.
ii). The CIC is in fact the nucleus of the vagus . It innervates the heart. The nucleus ambiguus by the vagus is the CIC

Inputs to the VMC:

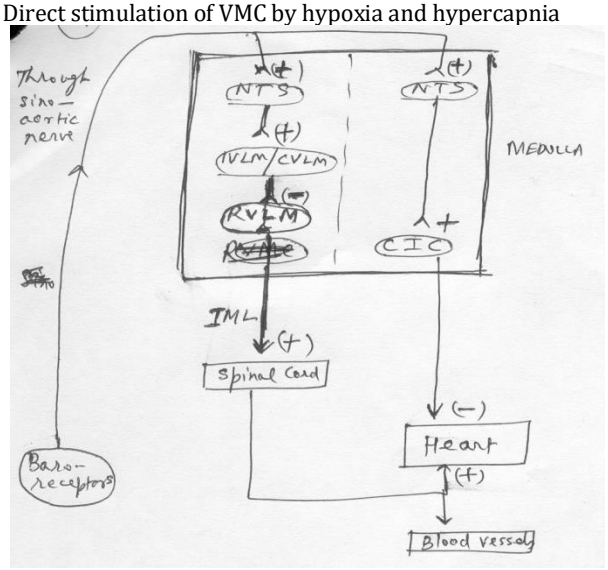
i). Inhibitory inputs

a. From cortex via hypothalamus
b. Lungs
c. Baroreceptors

ii). Excitatory inputs

a. From cortex via hypothalamus
b. Pain pathways
c. Chemo receptors

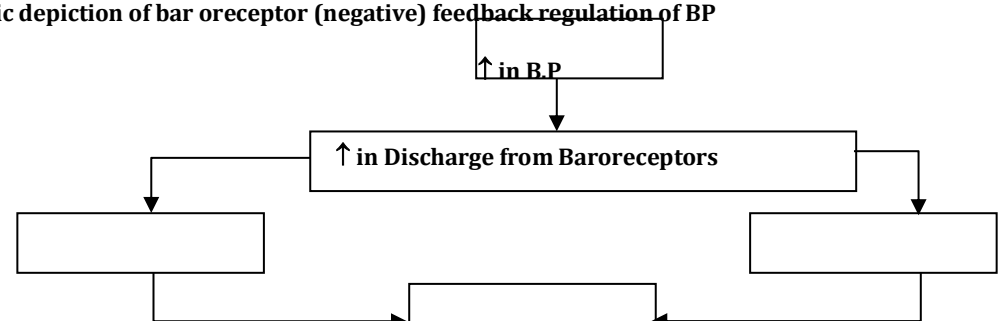
iii). Direct stimulation of VMC by hypoxia and hypercapnia



NTS= Nucleus of tractus solitarius
CVLM = Caudal ventrolateral medulla
IVLM = Intermediate ventrolateral medulla
RVLM = Rostral ventrolateral medulla which is the VMC
CIC = Cardio inhibitory centre
IML = Inter mediolateral horn
The above structures are bilaterally present. For clarity, structures on only one side are shown.

Baroreceptors: One of the important inputs to the VMC is the inhibitory input from the baroreceptors. The baroreceptors are stretch (mechano) receptors. The high pressure baroreceptors are present in the carotid sinus and aortic arch (in the adventitia of the vessels) [The low – pressure baroreceptors are present in the walls of the right and left atrium and in the pulmonary circulation (the cardio pulmonary receptors)

Schematic depiction of bar oreceptor (negative) feedback regulation of BP



+ CIC **- VMC**

↓ BP

Cutting the nerves from the carotid sinus and aortic arch receptors (and also bilateral lesions of the NTS) produces neurogenic hypertension.

Note: ***Stimulation of baroreceptors -> decreases BP***
Stimulation of chemoreceptors -> increases BP

Atrial Stretch receptors

Type A : Discharge primarily in atrial systole
Type B : Discharge primarily (late in) atrial diastole.
The response is vasodilatation and ↓ BP but and increase in heart rate (not a decrease in heart rate)

When ECF volume decreases

↑sympathetic discharge → ↑ Renin → ↑ Aldosterone

↓ central venous pressure → ↓ firing of atrial stretch receptors → ↑ ADH

Reflexes:-

i. Bainbridge reflex
ii. Bezold – Jarisch reflex
iii. Cushing's reflex Or the C.N.S. ischaemic response or Last Ditch effort

i. Bainbridge reflex: -
Infusion of blood or saline causes increase in heart rate (if the initial heart rate is low)
Receptors involved: Atrial stretch receptors

ii. Bezold – Jarisch reflex:- (Coronary chemoreflex)
Injections of veratridine ,serotonin , capsaicin etc into the coronary arteries supplying the left ventricle causes apnoea followed by rapid breathing , ↓ in BP and ↓ in heart rate.
Receptors involved: Left ventricular (C fibre endings)

iii. Cushing's reflex:- (C.N.S. Ischaemic response)
Increase in intracranial pressure causes hypoxia and hypercapnia in medulla, which directly stimulates the V.M.C.This results in an increase in B.P.
The ↑ in B.P. through the baroreceptor mechanisms causes *reflex Bradycardia*.

Effects of chemoreceptor stimulation of VMC: -

Stimulation of chemoreceptor → Stimulates VMC → Vasoconstriction, ↓ in H.R

Hypoxia →

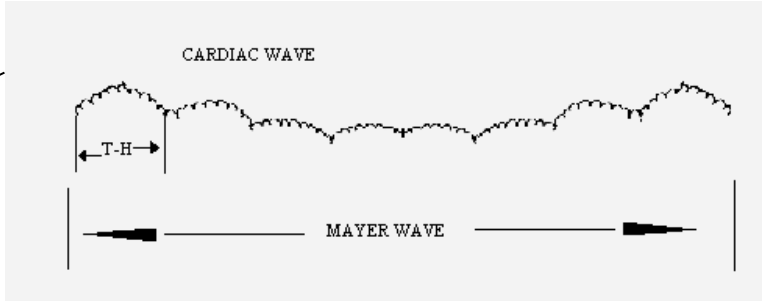
Also Causes **↑ in H.R ↑ in C.O**

- **Hyperpnoea**
- **Increase in catecholamine Secretion from adrenal medulla**

(H.R=Heart rate)

[Note that the effect of hypoxia on heart rate is an increase (because of hyperapnoea) and a reflex decrease because of stimulation of VMC. Therefore, its effect on heart rate is variable.

Blood Pressure Waves: -
In direct record (intra arterial) of B.P., many types of waves can be seen;
i. Cardiac waves - These are the waves because of the systolic rise and diastolic fall
ii. Traube – Hering (T-H) Waves – These are the fluctuation in the B.P., synchronous with respiration.
iii. Mayer Waves – These are seen in conditions like hypotension. The wave pattern is 1 per 20-40 second
The wave patter is 1 per 20 – 40 seconds



Valsalva manoeuvre:-
This is forced expiration against a closed glottis. It is one of the tests used for assessing the baroreceptor responses. Characteristic changes in heart rate and BP are seen during the various phases of the Valsalva manoeuvre:
i. At the beginning of the manoeuvre: ↑ in BP
ii. During the maneuver: ↓ in B.P
↑ in H.R.
iii. Immediately after the end of the manoeuvre ↑ in B.P.
↓ in H.R.

RESPIRATION

I. Functional anatomy

1. **Weibel's classification of airway generations:** From trachea to alveolar sacs, the airways divide 23 times. (Trachea is generation '0'). The first 16 generations form the conducting zone (consisting of bronchi, bronchioles and terminal bronchioles); the remaining 7 generations are the transitional and respiratory zones (consisting of the respiratory bronchioles, alveolar ducts and alveoli)

2. Presence of cilia, smooth muscle, glands, cartilage in the air passages

a. Cilia : Present upto respiratory bronchioles
b. Cartilage : Only in trachea and bronchi
c. Glands : Only in trachea & bronchi
d. Smooth muscle : Maximum in terminal bronchiole

3. Types of cells

a) Alveolar epithelial cells :
i) Type I (There form the main living)
ii) Type II (also called granular pneumocytes), These secrete surfactant
b) Other cells in lungs:-
Pulmonary alveolar macrophages, lymphocyte, plasma cells, APUD cells, mast cells

4. Bronchoconstriction and dilation

Bronchoconstriction : Reflexly (by irritants; this is cholinergically mediated), cool air, exercise, expiration, leukotrienes, substance P , cholinergic stimulation, early morning (around 6 A.M.)

Bronchodilation : Adrenergic stimulation, by non adrenergic – non cholinergic nerve stimulation (NANC) where the neurotransmitter is VIP, inspiration, in the evening (around 6 P.M.)

Gas Laws

1. **Dalton's law of partial pressure**: The partial pressure of a gas in a mixture of gases is equal to the total pressure times its percentage
2. **Boyle's Law**: P X 1 / V, if T is constant
3. **Charle's law**: P X T (if V is constant) and V X TC if P is constant
4. **Henry's law**: The dissolved gas is already proptional to its partial pressure
5. **Graham's law**: The rate of effusion is reversely proportional to the square

II. Mechanics

1. Different types of pressures

a. Intrapleural pressure :
This is pressure within the pleural space (also called intrathoracic pressure) Oesophageal pressure measures intrapleural pressure
b. Intrapulmonary pressure

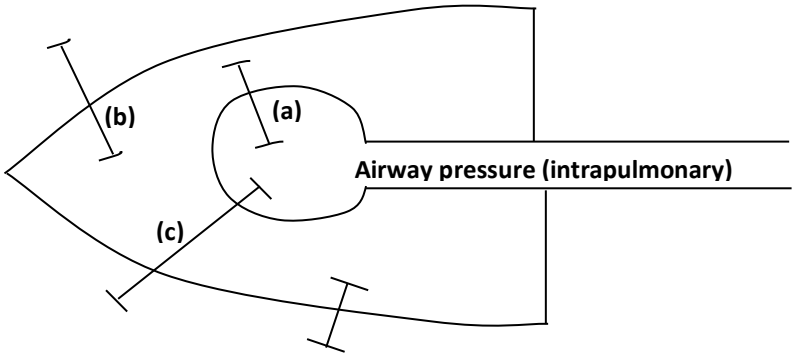
This is the pressure in the airways

The transmural pressure are

i) Transpulmonary : The pressure difference between intrapleural and intrapulmonary pressure

ii) Transthoracic : The pressure difference between the intrapleural pressure and atmospheric pressure

iii) Also, one can talk of the pressure difference between the intrapulmonary pressure and atmospheric pressure



(a) Transpulmonary
(b) Transthoracic
(c) Pressure difference between intra pulmonary and atmospheric pressure
(Trans respiratory)
(Trans respiratory pressure)

2. Inspiration and expiration

Muscles involved in quiet respiration

Inspiration : Diaphragm is the main muscle; also external intercostal muscle

Expiration : No expiratory muscle (passive)

Muscles involved in forceful respiration

Inspiration : Scalene, sternocleidomastoid

Expiration : Internal intercostal muscles,
Anterior abdominal muscle

Pressure changes during respiration

i) Intrapleural pressure: At the beginning of quiet inspiration, it is – 2.5 mmHg subatmospheric i.e. 2.5 mmHg less than atmospheric pressure of 760 mmHg; at the end of inspiration, it becomes – 6.0 mmHg.

ii) Intra alveolar pressure : At the peak of inspiration, it is – 1 mmHg; at the peak of expiration, it is +1 mmHg.

At the beginning and at the end of both inspiration and expiration, the interalveolar pressure is zero i.e. same as atmosphere pressure

Respiratory obstruction

This can be: i) Intrathoracic or extrathoracic
ii) Variable or fixed

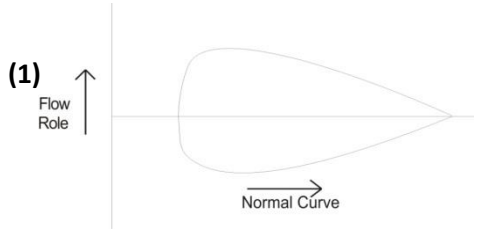
Flow-volume curve

This is a graph between flow rate on the Y-axis and volume on the X-axis.

It can be used to identify whether a variable obstruction is intrathoracic or extrathoracic.

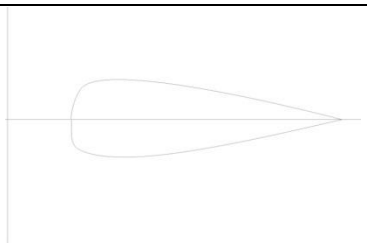
(It cannot identify fixed intrathoracic or extrathoracic).

In variable intrathoracic obstruction, the inspiratory flow-volume curve is less affected than the expiratory flow-volume curve. In variable extrathoracic, obstruction. The expiratory flow-volume curve is less affected than the inspiratory flow-volume curve.



Showing the Normal Flow-volume curve

1. Expiratory flow-volume curve
2. Inspiratory flow-volume curve



Showing fixed obstruction

Showing variable extrathoracic obstruction

Showing variable intrathoracic obstruction

3. Compliance

This is defined as the change in volume for a unit change in pressure

$$\text{Compliance} = \frac{\Delta V}{\Delta P}$$

A plot of the change in volume with a change in pressure is the volume-pressure curve or the relaxation-pressure curve. When the relaxation – pressure curve is plotted for the total respiratory system (i.e. taking into account the interaction between the recoil of the lungs and recoil of the chest) the volume of the gas in lungs when the pressure is zero is called the relaxation volume. The relaxation volume equals the functional residual capacity.

Types of compliance measurements

i) Static compliance : This is the measurement made without taking into account the effect of the different phases of respiration
ii) Dynamic compliance : Compliance measurement during the difference phases of respiratory
iii) Specific compliance = $\frac{\text{Compliance}}{\text{FRC}}$

Factors affecting compliance

i) Lung volume : Smaller the lungs, smaller is the compliance. Therefore, specific compliance measurement normalizes the effect of lung size on compliance.
ii) For a given lung size, the compliance becomes less at extremes of lung volume.
iii) Compliance is more during deflation than during inflation
iv) If surface tension is more, compliance is less
v) Compliance measured with saline is more than compliance measured with air.

Condition in which compliance is affected

i) Compliance decreased : Pulmonary congestion, pulmonary fibrosis etc.
ii) Compliance increased : Emphysema, old age

4. Alveolar surface tension

This is exerted by the film of fluid that lives the alveoli; this surface tension is less at lower lung volumes (this is due to the effect of surfactant)

5. Surfactant

The alveolar fluid also has a surface-tension lowering agent called surfactant. This is secreted by type II (granular pneumocytes) alveolar epithelial cells. It is a mixture of dipalmitoyl phosphatidylcholine (phosphatidyl choline is also called lecithin) other lipids, protein and carbohydrates. The maximum percentage in the surfactant is that of dipalmitoyl phosphatidyl choline.

Functions of surfactant

i) Prevents alveolar collapse
ii) Prevents pulmonary oedema

The surface – tension lowering ability of surfactant depends upon its concentration per unit area. When the lung volume is less, the alveoli are smaller and therefore the concentration Eg. surfactant per unit area is more. Consequently, the surface tension is less at lower lung volumes.

6. Work of breathing

This is required to do

i) Elastic work (65%)

a) Tissue elasticity (1/3rd)

b) Surface tension elasticity (2/3rd)

ii) Non-elastic work (35%)

a) Viscous resistance (7%)

b) Airway resistance (28%)

The work of breathing can be calculated from the relaxation – pressure curve.

The work of breathing for the lung alone is more than that for the total respiratory system. Since the airway resistance becomes more during turbulent flow, the work of breathing is more during turbulent flow than during laminar flow.

The work of breathing is increased in conditions such as emphysema, asthma, congestive heart failure

7. Hysteresis loop

If there were no frictional resistance due to airway and viscous resistance, the relaxation – pressure curve would be a straight line. However, because of the frictional resistance, any change in volume which is expected because of change in pressure does not happen immediately but happens after a time delay. This causes the relaxation – pressure curve to take a curved shape (instead of a straight line). This is called hysteresis.

8. Ventilation – perfusion gradients from base to apex of the lung (in the upright position)

i) Ventilation per unit lung volume decreases from base to the apex

ii) Perfusion decreases from base to the apex

iii) The ventilation – perfusion ratio <u>increases</u> from base to apex

iv) The intrapleural pressure <u>decreases</u> from base to the apex

9. Dead space

i) Anatomical dead space = The respiratory system volume up to alveoli (or total)

ii) Physiologic dead space = Anatomic dead space + wasted ventilation due to overventilated alveoli
In other words, physiologic dead space is the volume of gas not equilibrating with blood
Normally, physiologic dead space = anatomic dead space = 150 mL.

10. Diffusion capacity of lung

Definition: The diffusion capacity of the lung (D_L)is defined as the volume of gas diffusing across the respiratory membrane in 1 minute when the pressure gradient is 1 mmHg.

Factors

$$D_L = \frac{K \times A \times S}{\sqrt{d \times w}}$$

Where k is proportionality constant

A = Area of the membrane

S = Solubility of the gas

W = molecular weight of the gas

D = thickness of the membrane

$\frac{S}{\sqrt{w}}$ is called the diffusion coefficient; the diffusion coefficient is entirely based on the characteristic of the gas.

Measurement

Diffusion capacity of carbon monoxide (D_{LCO}) is taken as an index of diffusion capacity. D_{LO2} is never measured directly, it is expressed with D_{LCO} as the index.

Value

D_{LO2} = 25 mL/ min / mm Hg

D_{LCO2} is 20 times D_{LO2}

<u>Conditions in which D_L is affected</u>

i) D_LO_2 increases in exercise

ii) D_LO_2 decreases in sarcoidosis, beryllium poisoning, pulmonary fibrosis etc.

11. Methods for measuring lung volumes, capacities and dead space

i) Spirometry : Measures all volumes and capacities except those involving measurement of residual volume;

Therefore, it cannot measure residual volume, functional residual capacity and total lung capacity

ii) Single breath nitrogen technique

b) Measures anatomical dead space. It can also measure

c) Closing volume (the lung volume above the residual volume of which the airways in the lower, dependent parts of the lung begin to close off because of lesser transmural pressure in these areas)

d) Residual volume

iii) Helium dilution method / nitrogen washout method : Measures FRC

iv) Bohr equation

a) Measures physiologic dead space

b) Can also be used to measure anatomic dead space

III. Gas transport

1) **Symbols**

	P	=	partial pressure
	I	=	Inspired air
	E	=	Expired air
	A	=	Alveolar
	a	=	arterial
	v	=	venous
—	v	=	mixed venous
	B	=	Barometric
	F	=	Fractional percentage

PI_{O2} means partial pressure of O_2 in inspired air

2) Partial pressure of O_2 / CO_2 at different sites (in mmHg)

	P_β	I	Alveolus	Arterial	Capillaries	Veins	E
O_2	160	150	100	95*	40	40	116
CO_2	0.3	0.3	40	40	46	46	32

* The partial pressure of blood leaving the pulmonary capillaries is 97 mmHg but it falls to 95 mmHg in the systemic arterial blood because of physiologic shunt. The physiologic shunt is due to a part of the bronchial blood flow and a part of the coronary blood flow which bypasses the pulmonary capillaries

3) O_2 transport

Most of the O_2 in the blood is carried along with Hb (99%) Each Hb carries 4 molecules of O_2. Hb exhibits the 'relaxed' and the 'tense' state. When Hb takes up O_2 the beta chains move closer and the haem enters the relaxed state. The relaxed state favours binding of O_2 while the tense state decrease binding.

Oxygen – Hb dissociation curve (O-HDC)

This is a plot of the partial pressure of O_2 and the % saturation of Hb with O_2 It is normally sigmoid-shaped.

If the OHDC is shifted to the right, it means that the affinity of Hb for O_2 has become less (which favours O_2 delivery).

Shift to the right is caused by

i) ↓ pH
ii) ↑ in temperature
iii) ↑ in 2,3 – DPG

P_{50} = The partial pressure of oxygen as which Hb is 50% separated. It value = 26 mmHg. (or 3.45 Kpa). When the OHDC shifts to the right, P_{50} increases. (1Kpa = 7.5 mmHg)

Factors affecting 2,3 DPG

i) ↓ in pH inhibits 2,3 – DPG
ii) Bank blood → 2,3 – DPG is decreased
iii) Thyroid hormones, Growth hormone, androgens, high attitude, exercise, anemia, disease causing hypoxia → all increase 2,3 – DPG
iv) HbF binds 2,3 – DPG poorly; hence it has a greater affinity for O_2

Effect of pH on O-HDC

i) ↓ pH
- Direct effect : shift to right
- By decreasing 2,3 – DPG, shift to left

ii) ↑ pH
- Direct effect : shift to left
- By increasing 2,3 – DPG, shift to right

Bohr effect

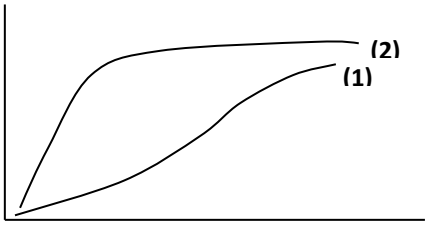
There is a decrease in O_2 affinity for Hb with a decrease in pH

Calculation of O2 carrying capacity of blood

i) 1 gm of Hb, when fully saturated, contains 1.34 ml of O_2. At a pO_2 of 40 mmHg (as exists in Venous blood), Hb is only 75% saturated. Therefore, 1 gm of Hb would carry 1.34 X 75 / 100 mL of O2 at pO_2 of 40 mmHg
ii) The amount of dissolved O_2 in plasma is 0.003/ dL / mmHg of pO_2. At a pO_2 of 40mmHg, the amount of dissolved O_2 is 0.003 X 40 = 0.12 mL of O2 / dL.

Myoglobin

This is present in skeletal muscles. 1 mole (OMDC) cule of myoglobin binds / 1 molecule of O_2. The shape of O_2 myoglobin dissociation curve is a rectangular hyperbola. It lies to the left of the O_2 – Hb dissociation curve.



(1) : O – H DC
(2) : O – M DC

4) CO_2 transport

i) Different ways in which CO_2 is transported in :

a) Plasma

i. In dissolved form of

ii. As carbamino compound with plasma proteins

iii. Getting hydrated $CO_2 + H_2O$ H_2CO_3 $H^+ + HCO_3^-$ The H+ gets buffered with plasma proteins. Since there is no carbonic anhydrase in plasma, the process of hydration is slow.

b) RBC

i. In dissolved form

ii. As carbamino compound with Hb

iii. Getting hydrated

$CO_2 + H_2O$ H_2CO_3 $H^+ + HCO_3^-$ The H+ gets buffered by Hb; 70% the HCO_3^- enters plasma and Cl^- enters RBC (chloride shift)

(Since there is carbonic anhydrase in RBC, the process of hydration is rapid.)

It is clear from the above that for each CO_2 molecule that goes into RBC, there is either one HCO_3^- or one Cl- inside the RBC; the chloride content of the venous blood RBC is more than that of arterial blood RBC. Therefore, there is an increase in the volume of RBC in venous blood and hence the haematocrit of venous blood is more.

Out of the 49ml of CO2 / dL in arterial blood, 2.6 mL is dissolved 2.6 mL of CO_2 exists as carbamino compound and 43.8 mL is transported as HCO_3^-

IV Regulation of respiration

1. Voluntary control
   This is from the cortex directly to the spinal cord
2. Automatic control

The structure involved are the pons and the medulla. The automatic pattern generator lies in the medulla (in the pre-Bottzinger nucleus)

The pneumotaxic centre and the apneustic centre lie in the pons.

The pneumotaxic centre and the vagi put the brakes on inspiration.

One could say that automatic respiration originates in the medulla and the pons does the fine tuning.

Factors affecting the respiratory centre

1. Chemical
   CO_2 / O_2 / H^+
2. Non – chemical

i) Vagal afferents from airways / lungs

ii) Pons / hypothalamus / limbic system

iii) Proprioceptors

iv) Baroreceptors

A Chemical control

The chemoreceptors for chemical control are the

2. Peripheral chemoreceptors Viz the carotid and the aortic bodies
3. Central chemoreceptors situated in the ventral surface of the medulla

Peripheral chemoreceptors

There respond to an ↑ increase in CO_2 and H+ and a decrease in O_2

Each carotid and aortic body (glomus) contains 2 types of cells, type I and type II cells. The type I (glomus cells) respond to hypoxia; they have O_2 – sensitive K^+ channels

The carotid body has a very high blood flow. Because of this, if does not respond to anaemic hypoxia (since the dissolved oxygen meets the needs)

Central chemoreceptors

There respond to H^+ only.

They are sensitive to the H^+ in the CSF and the brain interstitial fluid. CO_2 can influence these central chemoreceptors only indirectly by getting converted into H^+. By virtue of this, CO_2 is able to act on both central (60-70% of the effect of CO_2) as well as on peripheral (30-40% of the effect of CO_2) chemoreceptors.

Ventilatory response to CO_2

The link between metabolism and ventilation is CO_2 and not O_2

There is a linear relationship between respiratory minute volume and alveolar pCO_2

Ventilatory response to O_2 lack

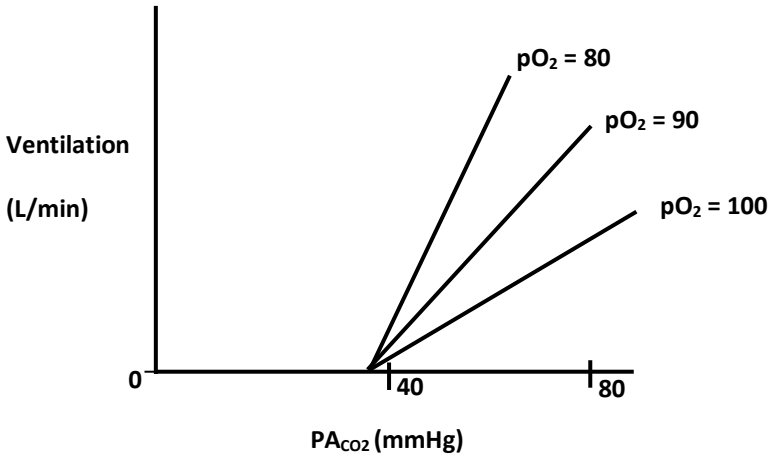
There is no increase in ventilation till the PAO_2 (alveolar PO_2) becomes less than 60 mmHg. The reasons for this lack of response are :

(i) Hb is a weaker acid than HbO_2; therefore with less O_2, there is more Hb which by being weaker acid tends to inhibit the ventilation

(ii) Also, as ventilation increases, the CO_2 that is washed out counters the increase in ventilation

Ventilatory response to CO2 and O_2

This exhibits a complex relationship, the effect of CO_2 excess and O_2 lack is more than additive. If one were to plot a curve between CO_2 and ventilation at different fixed O_2 levels, one would get a fan of curves. The slope of the curve (between CO_2 and ventilation) would increase significantly with decreased O_2 levels.



The intersection of these fan of curves is at one single point.

Since this point of intersection is below the normal value of PA_{CO2} of 40 mmHg, it shows that there is normally a slight but definite CO_2 drive of the respiratory centre.

Ventilatory response to H^+ and CO_2

Here, the effect is simply additive

Breath Holding

The breaking point is the point at which breathing can no longer be voluntarily inhibited (because of increase in CO_2 and decrease in O_2)

Breath holding can be prolonged by

1) Removal of carotid bodies
2) Breathing 100% O_2 before breath holding
3) Hyperventilating room air (because of the initial ↓ in CO_2 of arterial blood)
4) By breathing gas mixture low in O_2 and high in CO_2, breath holding can be prolonged for an additional 20 seconds
5) Encouragement

B. Non – chemical influences

1. Responses mediated by receptors in the airways and lungs (all are vagally mediated)

Vagal innervation	Type of receptors	Location in interstitium	Stimulus	Response
Myelinated	Slowly adapting	Among airway smooth muscle	Lung inflation	i) Inspiration time ↓ed ii) Hering - Breuer reflexes iii) Bronchodilation iv) Tachycardia
	Rapidly adapting	Among airway epithelial cells	i) Lung hyper inflation ii) Irritants	i) Hyperpnoea ii) Cough iii) Bronchoconstriction iv) Mucus secretion

Unmyelinated C fibres	Pulmonary C fibres (J receptors) Bronchial C fibres	Close to blood vessels	i) Lung hyper – inflation ii) Irritants	iii) Apnoea followed by rapid breathing iv) Bronchoconstriction v) ↓ HR vi) ↓ BP vii) Mucus secretion

2. Bar receptors stimulation

Inhibits respiration ; the effect is almost of no physiologic importance

3. Effect of sleep

There is a decrease in sensitivity to CO_2 during slow wave sleep; during REM sleep ,there is even further decrease in sensitivity to CO_2

V. Hypoxia

	Hypoxic	**Anaemic**	**Stagnant**	**Histotoxic**
Underlying cause	PaO_2 is ↓ed	Amount of available Hb decreases	O_2 carrying capacity is normal but O_2 delivery is decreased	No utilization at tissue level
Examples	High altitude, lung disease	Anaemic, CO poisoning	Heart failure shock hemorrhage	Cyanide poisoning
PaO_2	↓ed	Normal	Normal	Normal
O_2 Content dissolved	↓ed	Normal	Normal	Normal
Combined (with Hb)	↓ed	↓ed	Normal	Normal
Chemoreceptors stimulation	Stimulated (+)	Not stimulated	Strongly stimulated (+++)	Strongly stimulated (+++)
Amount of reduced Hb	↑ed	Total Hb ↓ed, HHb ↑ed	↑↑↑ed	↓ed
Cyanosis	Can be present	Unlikely	Can be present	-

2. C.O. poisoning

Produces anaemic type of hypoxia. The affinity of Hb for CO is 210 times that for O2. C.O. poisoning is especially dangerous because

i) Less Hb is available for carrying O_2
ii) It does not stimulate the chemoreceptors
iii) There is a shift of the O_2 – Hb dissociation curve to the left

3. Acclimatization to high altitude

i) Ventilatory response: It is small initially; later it increase because of active transport of H+ into CSF
ii) ↑ in erythropoietin
iii) At tissue level, there is increase in mitochondria, cytochrome oxidase myoglobin.
iv) O-HDC (Oxygen – Hb dissociation curve)

The alkalosis tends to shift the O-HDC to the left; recall that alkalosis also favours formation of red cell. 2,3 – DPG which tends to shift the O-HDC to the right. The net effect is a slight shift of the O-HDC to the right (i.e the P50 increase slightly)

Other points

1) PB (the atmospheric pressure) decrease
2) Composition of the air remains the same
3) PH_2O remain the same
4) P_AO_2 decreases
5) P_ACO_2 decreases (because of hyperventilation)
6) The sensitivity of the carotid body to hypoxia does not increase; in fact, prolonged hypoxia decrease the sensitivity

4. P(A – a) O2 gradient

This is affected in hypoxic hypoxia, in other types of hypoxia, it is normal

In hypoxic hypoxia due to high altitude and hypoventilation, it is decreased, in hypoxic hypoxia due to diffusional defect and night to left shunt, it is increased.

CENTRAL NERVOUS SYSTEM

RECEPTORS

Cutaneous receptors can be classified as

I Tactile receptors
II Thermo receptors
III Nociceptors

Thermoreceptors and nociceptors are naked nerve endings.

Tactile receptors

These can be further classified as

A. Rapidly Adapting
B. Slowly Adapting

A. Rapidly Adapting (or phasic)
   These include
   1. Pacinian corpuscles
   2. Meissner's corpuscles
   3. Krause's end bulb

B. Slowly Adapting (or tonic)
   These include
   1. Merkel's disc
   2. Ruffini endings
   3. C-mechanoreceptors

Rapidly adapting receptors sense vibration;
Slowly adapting receptors sense pressure.
Rapidly adapting receptors are encapsulated nerve endings.
Slowly adapting receptors are expanded nerve endings.
Itch is carried by C-mechanoreceptors.

Sensory Pathways

1. Anterolateral system:
2. Dorsal (or posterior) column system.
3. Anterolateral system:
   This includes
   1. Anterior (or ventral)
      Spinothalamic tract: This carries crude touch
   2. Lateral Spinothalamic tract: This carries pain and temperature
   3. Dorsal column
      This carries the rest of the sensations e.g. proprioception, vibration, fine touch, etc.

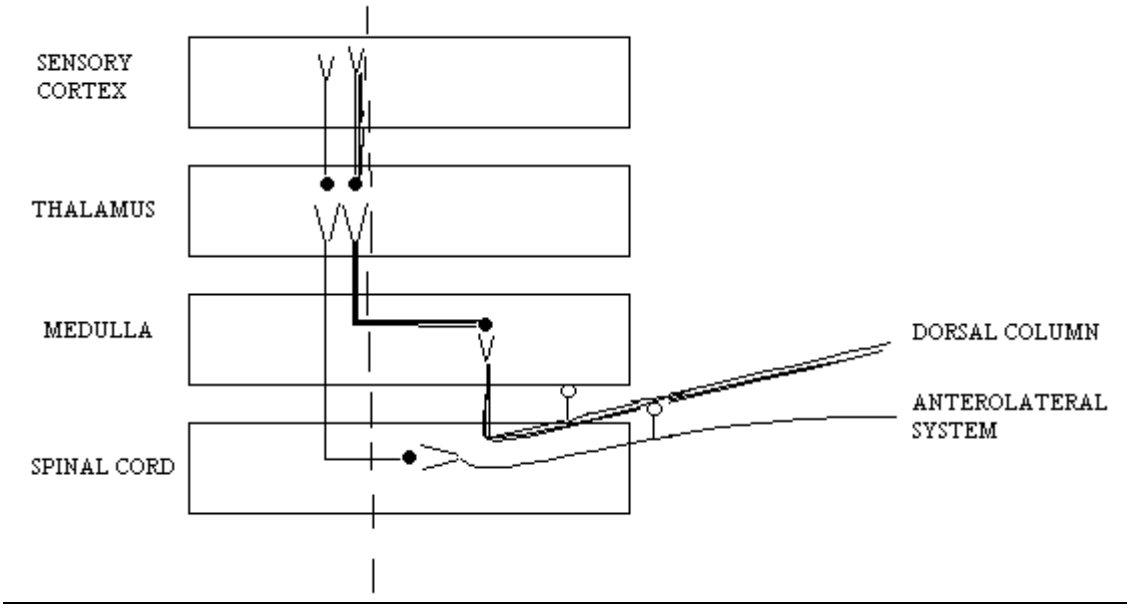


Diagram Showing the sensory pathway

Brown Séquard Syndrome

This is hemi-section of the spinal cord

Opposite side:

- Loss of pain and temperature sensation

Same side:

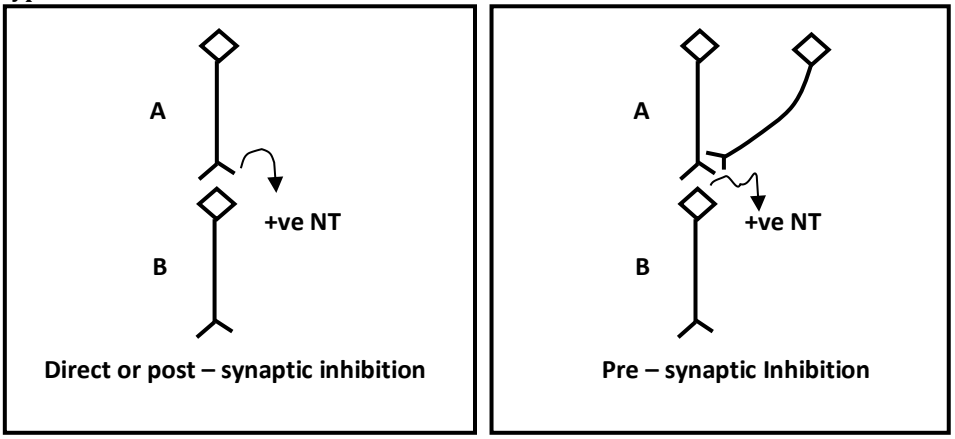
- Other sensations lost (except touch)
- LMN type of paralysis or the level of lesion
- UMN type of paralysis below the level of lesion

Laws related to sensory physiology

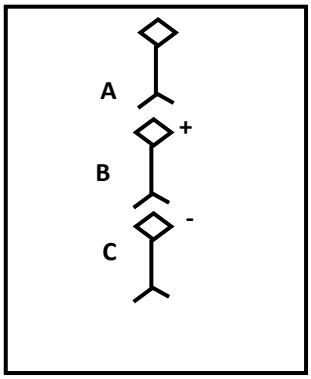
1. **Muller's Doctrine of specific nerve energies:**
   No matter where along the nerve pathway one stimulates, the type of sensation will depend on which part of the brain is finally going to be stimulated.
2. **Law of Projection:**
   No matter where along the nerve pathway one stimulates, the sensation will be felt at the site of the receptor.
3. **Weber Fechner Law & Stevens' power law**
   These two laws relate the sensation felt (S) to the intensity of the stimulus (I).
   $S = K \log I$ – Weber-Fechner Law
   $S = KI^a$ – Steven's Power Law
4. **Bell-Magendie Law**
   This law states that the dorsal root is sensory and ventral root is motor
5. **Labelled – line theory**
   All the sensations from the different parts of the body travel along specified paths.
   e.g.

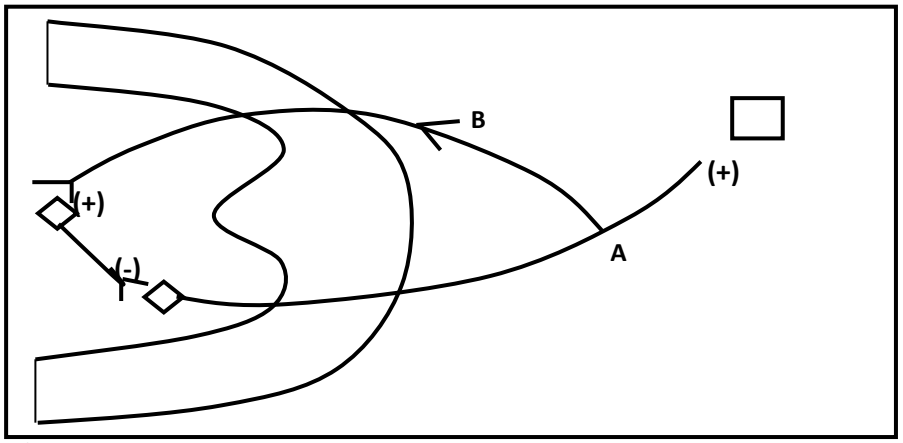
(i) In the lateral spinothalamic tract, fibers from the lower parts of the body are placed laterally.
(ii) In the posterior column, fibers from the lower parts of the body are placed medially.

Types of Inhibition



This is because of the release of an inhibitory neurotrasmitter (NT) from neuron A; this produces an IPSP in neuron B.	Pre-synaptic Inhibition 'A' releases an excitatory NT, to excite B. But 'C' ends presynaptically as 'A' to decrease the release of the excitatory NT. Salient Features of Presynaptic Inhibition o It is example of axo-axonic synapse o It is stimulated by general anaesthetics o It is inhibited by picrotoxin o It is mostly due to GABA o





B... the

Feed-forward inhibition
'A' stimulates 'B'; but 'B' inhibits 'C'

Feedback or Renshaw cell inhibition
'A' stimulate the muscle. However, a collateral from A ('B') ends on an inhibitory interneuron (C) in the anterior horn of the spinal cord. This inhibitory interneuron is called a Renshaw cell.

Lateral or afferent or surround inhibition
This is one of the cornerstones of sensory physiology. Stimulation of required neuron inhibits the adjacent neurons (by a collateral). This enhances contrast and sharpens the image.

Reflexes

1. Asynaptic reflex e.g. Axon reflex
2. Monosynaptic reflex e.g. Stretch reflexes (deep tendon reflexes)
3. Di or Bi-synaptic reflex e.g.
    i. Inverse stretch reflex.
    ii. Reciprocal innervation.
4. Polysynaptic reflex e.g.
    i. Superficial reflexes.
    ii. Withdrawal response
        1. Flexor
        2. Crossed – extensor

RETICULAR FORMATION

It is a network of nerve cells and fibers in the central core of the brainstem (It is present in the mid ventral portion of the medulla, pons and midbrain). It is a complex poly-synaptic pathway and has many of the important centers in the medulla viz deglutition center , vomiting center , respiratory center , center for cardiovascular regulation

Connections

Afferents
- Collaterals from the specific sensory pathways (ascending sensory tracts)
- Cerebral cortex (corticofugal fibres)
- Cerebellum
- Basal ganglia

Efferents from reticular formation
- Ascending pathway – the ascending reticular activating system (ARAS) to the cerebral cortex (via the thalamus – cf thalamus)
- Descending pathway- the reticulo spinal tract

Functions of the reticular system

maintenance of sleep / wakefulness cycle : stimulation of ARAS causes arousal, awakefulness and alertness
modulation of muscle tone :
reticular formation is one of the supraspinal influences for the stretch reflex
(e.f. regulation of posture)
it is the location of all the vital centers as mentioned above
EEG
- it is concerned with synchronization / desynchronisation of E.E.G waves
- stimulation of reticular formation : desynchronisation of EEG
- inhibition of reticular formation : synchronization of EEG

Sensation
- it modulates / controls sensory input to CNS eg supraspinal control of pain (gate control theory of pain)
- it modulates sensory impulses of muscle spindle
- it has role in focusing of attention (selective attention) probably by cutting off all other signals

It is necessary for learning and conditioned reflex

THALAMUS

Classification of thalamic nuclei

Non-specific nuclei - These are the midline and intralaminar nuclei . these project diffusely and non-specifically to the whole of the neocortex. These nuclei receive input from the reticular formation (the ARAS). Impulses from the nuclei are responsible for the diffuse secondary response (EEG) . The alerting effects of reticular activation, are relayed through them.

Specific nuclei

Sensory relay nuclei
medial geniculate body (concerned with hearing)
lateral geniculate body (concerned with vision)
ventro posterior lateral and ventro-posterior medial :

These nuclei are the sites of termination of the ascending somatic afferent tracts the medial lemniscus (carrying sensation from all parts except the face) ends in the ventroposterior lateral ; the trigeminal leminscus (carrying sensations from face and taste sensation) ends in the ventroposterior medial nucleus

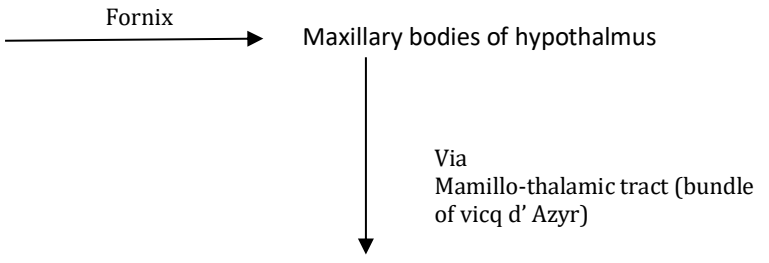
Nuclei concerned with control of posture and movement

Ventrolateral nucleus -This is the chief motor nucleus of the thalamus. It receives fibres from the cerebellum (the dentato – thalamic fibres cf cerebellum). Fibres from the ventrolateral nucleus project to the primary motor cortex (area 4) and pre- motor cortex (area 6)

Ventro anterior nucleus -It receives fibres from the cerebellum and basal ganglia. It projects to the premotor cortex.

Nuclei concerned with visceral efferent control mechanism

a)



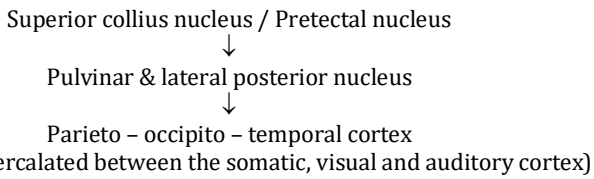
The above circuit is called the papez circuit

b). Lateral dorsal nucleus -Its connections are similar to anterior thalamic nuclei.

c) Dorsal – medial nucleus

iv. Thalamic nuclei serving integrative and perceptual function:

a) Pulvinar and lateral posterior nucleus:



(which is intercalated between the somatic, visual and auditory cortex)

b. Reticular nucleus

Functions of thalamus

These can be predicted from the connections mentioned above

1. It is a great sensory relay station

it is an important relay station for all sensory systems except smell

2. Motor function
it is also a relay station for the motor fibres from the basal ganglia and cerebellum on their way to the cerebral cortex
3. It also relays a part of the ARAS

EEG

Hans Berger made the first systematic analysis of EEG

Waves in the EEG

Delta , theta , alpha , beta (from delta to beta , the frequency increases and the amplitude decreases)

Salient features of the different waves

Alpha rhythm -this is the wave seen at rest , with the eyes closed and the mind wandering .Its frequency is 8-12 /second and the amplitude is 50-100 μv . it is most marked in the parieto – occipital lobe. The frequency of the alpha rhythm is decreased by

- low blood glucose
- low body temperature
- low level of adrenal glucocorticoid hormones
- high $Paco_2$

Alpha block

(also called arousal response / alerting response / desynchronisation)
the alpha rhythm can be made to disappear by focused attention, by mental concentration and sensory stimulation .
(the ascending reticular formation activity is responsible for the EEG alerting response ; stimulation of ARAS causes the EEG rhythm to change from slow to high frequency small waves)

Beta rhythm -it has a frequency of 18-30 / second. It is seen over the frontal region. It is the wave seen when the eyes are opened; It is the wave seen in the alerting response

Theta rhythm-frequency is 4-7/second. It has large amplitude. It occurs in children

Delta rhythm -frequency is < 4/second

Sources of EEG

It is due to the constantly shifting / fluctuating dipole between the dendrites of the cortical cells and the cell bodies

Evoked cortical potential

This is an EEG change produced by some form of stimulation
Evoked cortical potential consist of

1. **Primary evoked potential**

This consist of positive and a small negative wave. It has a latency of 5-12 ms. It is highly specific in its location (over the primary receiving area of the cortex for the particular sensory pathway that has been stimulated to evoke). It is produced by conduction of sensory signal through specific sensory pathway.

2. **Diffuse secondary response**

This consists of a larger, more prolonged positive deflection . It has a latency of 20-80 ms and may last 30 seconds. Its activity can be recorded form most of the cerebral cortex. It is produced due to spread of impulses through the ARAS to cerebral cortex.

Sleep

NREM sleep (slow-wave sleep)-4 stages
REM sleep

	Characteristics
Stage 1 of NREM	Low amplitude, high frequency EEG activity
Stage 2 of NREM	Sleep spindles (alpha – like 10-14 /seconds , 50 μv amplitude), K complexes
Stage 3 of NREM	Low frequency , increased amplitude
Stage 4 of NREM	Maximum slowing , (least frequency), large waves (rhythmic slow waves, synchronized)
REM	Rapid , low voltage EEG

All the stages of sleep are reversible except the stage from REM to awake state
Duration / percentage of various stages
Percentage of REM out of total sleeping time
- Premature infants =80%
- Full term neonates =50%
- 20-65 years = 25%
- After 65 years, it decrease (in elderly = 15%)

REM sleep

i. Also called paradoxical sleep
ii. Body muscle tone is decreased; face muscle tone is increased.
iii. Subject is still but the B.P , heart rate , respiratory rate are all raised
iv. Partial or full penile erections occur
v. P-G-O (ponto- geniculo-occipital) spikes

NREM sleep (slow – wave sleep)

i. It is generally a restful state with a

ii. Regular low BP, heart rate and respiratory rate
iii. Any restless movements are made during these stages
iv. Somnabulism and nocturnal enuresis are associated with slow – wave sleep (or more specifically , during arousal from slow- wave sleep)
v. Bruxism

Genesis of sleep

1. REM

The mechanism that triggers REM sleep is located in the pontine reticular formation. PGO spikes originate in the lateral pontine tegmentum. The spikes are due to discharge of cholinergic neurons

2. NREM

Stimulation of certain sleep zones can produce sleep

i. Diencephalic sleep zone
(In the posterior hypothalamus and the near by intralaminar and anterior thalamic nuclei)
for producing sleep it requires low frequency stimulation
ii. Medullary synchronizing zone
(In the reticular formation of the medulla oblongata at the level of the nucleus of the tractus solitarius)
This also requires low frequency stimulation for producing sleep
iii. Basal forebrain sleep zone
(includes preoptic area and the diagonal band of Broca)
This can produce sleep by both low as well as high frequency stimulation

Control of posture and movement

Posture control

Stretch reflex is fundamental to posture control. The major factor in posture control is by a change in the threshold of the stretch reflex. This can be achieved

- Directly by a change in the excitability of the motor neuron
- Indirectly by change in the rate of discharge of gamma efferent nerve to muscle spindle

There are 6 supraspinal influences on the stretch reflex viz

Cortex =inhibits gamma motor neuron
Basal ganglia=inhibits gamma motor neuron
Cerebellum= inhibits gamma motor neuron
Reticular formation (facilitatory area tonic ally active)= stimulates gamma motor neuron
Reticular formation (inhibitory area)= inhibits gamma motor neuron
vestibular nuclei = stimulates alpha motor neuron

Stretch reflex can be made hyperactive either by increasing gamma stimulation or by increasing alpha stimulation

Transection at various levels helps to find out the role of each structure

SPINAL COMPONENTS -(only the spinal cord intact , transection above the spinal cord) there is initially a period of **spinal shock** during which all spinal reflexes are profound depressed

Features after the spinal shock is over

hyperactive stretch reflexes
presence of positive supporting reaction (magnet reaction)and negative supporting reaction
when suitably stimulated , spinal animals can even produce walking movements indicating the presence of ***loco- motor pattern generators*** .However the spinal locomotor pattern generator needs to be turned on by the mesencephalic locomotor region
Automatic reflexes
- Reflex contraction of the urinary bladder and rectum can occur
- BP is generally normal at rest but there are wide swings
- Bouts of sweating and blanching of the skin occur

Sexual responses -Erection and ejaculation is possible by local stimulation
Mass reflex -Irradiation from one reflex center to another can occur . Minor stimulation of skin can cause evacuation of the urinary bladder rectum, sweating , pallor , BP swings, in addition to withdrawal response

MEDULLARY COMPONENTS - transection at the superior border of the pons causes decerbration. It leaves the following components intact , the spinal cord, medulla , pons and cerebellum

Features

No stage of spinal shock
decerebrate rigidity immediately occurs. The reason for this is

Increased general excitability of the motor neuron pool
Increased discharge of gamma motor neurons (because the inhibitory influence of the cerebral cortex and basal ganglia on the gamma motor neuron is removed)

(Although the cerebellum also has an inhibitory influence on gamma motor neuron , removal of the cerebellum in humans causes hypotonia)

The decerebrate rigidity in animals is most marked in the antigravity muscle. However, in humans the pattern of decerebrate rigidity is extensor in all the 4 limbs

(note that in decorticate rigidity, there is extensor rigidity in the legs and moderate flexion in arms)

tonic labyrinthine and tonic neck reflexes are present: these reflexes are responsible for the change in the pattern of rigidity with change in the position. They are not righting reflexes

righting reflexes are absent

MID BRAIN COMPONENTS Here , the transection is made at the superior border of the mid brain

Features

extensor rigidity is seen only when the animal lies quietly on its back

the animal can rise to standing position walk , and right itself

righting reflexes are present. All the righting reflexes (except the optical righting reflex, which is cortical) are integrated at the mid brain (the rightly reflexes operate to maintain the normal standing position and keep an animals head upright)

grasp reflex present

pupillary light reflex present (if the optic nerves or intact)

nystagmus present

vestibular placing reaction present

CORTICAL COMPONENTS: decortication in many species of animals causes little motor deficiency.In primates , the deficit is more severe but movement in still possible

Features

i) because the hypothalamus is present , temperature regulation and other visceral and homeostatic functions are present

ii) inability to react in terms of past experience

iii) Decorticate rigidity: this is because of loss of cortical inhibition of gamma motor neuron

iv) As in mid brain , the rigidity is present only when the animals is at rest

v) Hopping and placing reaction absent

V B Control of movement

Some general schemes

Commands for voluntary movement *originates in the cortical association* areas (this is any area in the brain that is lying between and connecting on sensory projection area with another)

- The movements are planned in the cortex , basal ganglia and neocerebellum
- From the basal ganglia and neocerebellum (via the thalamus), there is projection to Premotor and motor cortex
- From the motor cortex (via the corticospinal tract and corticobulbar tract) there is Projection to spinal motor neurons and homologous cranial nerve nuclei and there is movement
- There is feedback information of the movement (via the sensory input)
- The spinocerebellum in turn projects to the brain stem (via the rubro spinal , reticulospinal , tecto spinal and vestibulo spinal) for posture & coordination

In the brains stem and the spinal cord,

- The medial (or ventral , pathways / neurons subserve the muscles of the trunk and proximal portions of limbs)
- The lateral pathways / neurons subserve the distal portions of the limbs

Thus,

- The medial portions of anterior horns
- The ventral corticospinal tract and
- The medial descending pathways of brain stem (viz the tectospinal , retciulospinal and vestibulo spinal tracts)

Are concerned with adjustment of proximal muscles and posture

Whereas

- The lateral corticospinal tract and
- The rubrospinal tarct

Are concerned with distal limb muscles (for skilled voluntary movements)

The pyramidal tracts are the corticospinal tracts; strictly speaking it is only the *lateral* corticospinal tract, which should be called the pyramidal tract because it is only the lateral corticospinal tract that forms pyramids in the medulla. The extra pyramidal tracts are the rest of the descending pathways from the brainstem

Cortical motor areas

Motor cortex (the primary motor cortex) this is in the precentral gyrus (area 4)

premotor cortex (area 6)

Supplementary motor area (in the medial side of the hemisphere on and above the superior bank of the cingulated sulcus)

Somatic sensory area I (in post – central gyrus)

Somatic sensory area II (in the wall of the sylvian fissure)

i) Representation In the precentral gyrus

There is a point for point representation in the precentral gyrus. The arrangement is such that the feet is represented at the top and the face at the bottom. Except the face area (which has bilateral representation), the rest of the representation is unilateral to the opposite side musculature)

The size of the representation is proportional to the skill involved in voluntary movement e.g the speech and hand has a large area of representation.

ii) The premotor cortex may be concerned with setting posture at the start of planned movement

iii) Supplementary motor area
This is involved primarily in programming motor sequences
iv) The posterior – parietal cortex (somatic sensory areas)
This provides the origin of 40% of corticospinal and corticobulbar tracts. It also projects to premotor area . Its lesion results in inability to execute learned sequence of movements
(Lesions of the left motor cortex causes motor dysfunction of left and right hand whereas lesions of right motor cortex has little effect on right hand)
[Function of area 5: aiming of hands towards an object and manipulating it]
[Function of area 7 : hand - eye coordination]

3. **Corticospinal / corticobulbar tracts**

Origin:
30% from motor cortex
30% from premotor cortex
40% from parietal lobe , especially somatic sensory ones
(The corticospinal fibres from parietal lobe is presumably concerned with direct sensory motor coordination)
Functions: - the corticospinal and corticobulbar tracts are the primary pathway for initiation of skilled voluntary movement

Lesions:

1) Lesion of lateral corticospinal tract
a. LOSS of control of distal muscles of limbs (which is concerned with fine, skilled movements)
b. Hypotonia
c. Extensor plantar response (Babinski's sign)
2) Lesions of ventral corticospinal tract this causes axial muscle deficits (difficulty with balance , walking and climbing)
3) Lesion of extrapyramidal (posture – regulating pathways) causes spastic paralysis

Rubrospinal tract:

Origin: Red nucleus (of the midbrain)
Crossed pathway
Afferents to red nucleus come from:
- Cerebral cortex
- Inhibits antigravity muscles (or extensors)
- For fine, skilled movement

Tectospinal tract

Origin: superior colliculus of the midbrain
Crossed pathway
Afferents to superior colliculus
- Cerebral cortex (especially from occipital lobe)
- Superior colliculus

Function

Reflex movement of the head and arms in response to visual and exteroceptive stimuli

Vestibulospinal tract

Uncrossed pathway
2 'types'
1. Lateral vestibulospinal tract
2. Medial vestibulospinal tract

Lateral vestibulospinal tract

Origin: Lateral vestibular nucleus (also called Deiter's nucleus)
Afferents to lateral vestibular nucleus come from
- Vestibular nerve – Fastigial nucleus of the cerebellum

Medial vestibulospinal tract

Origin: Medial vestibular nucleus
Function of vestibulospinal tract
Excitatory to antigravity muscles (stimulates the extensors and inhibits the flexors) of neck and back muscles.

Reticulospinal tract

It is a rely station for descending motor commands
Origin: from reticular formation
Afferents to reticular formation come from
- Cerebral cortex
- Intermediate nuclei of cerebellum

2 'types'
1. Lateral reticulospinal tract
2. Medial reticulospinal tract

Lateral reticulospinal tract

Both crossed and uncrossed pathway
Origin: reticular formation in medulla
Function
Facilitatory influence on flexors; inhibitory influence on extensors

Medial reticulospinal tract:
Crossed pathway
Origin: from reticular formation in pons

Function

Inhibitory influence on flexors, facilitatory influence on extensors

VI <u>Basal ganglia</u>
(There is one on each side)
It consist of

1. Caudate nucleus
2. Putamen
3. Globus pallidus

Plus the functionally related

4. Subthalamic nucleus (body of Luys)
5. Substantia nigra

The caudate nucleus and putamen is referred to as the striatum and the putamen and the globus pallidus as the lenticular nucleus

Connections of the basal ganglia

1. Afferents
   i. From cerebral cortex (all parts)to striatum
   ii. From the centromedian nucleus of thalamus to striatum
   so the afferents to the basal ganglia end in the striatum
2. Efferent
   i. Mainly from the internal segment of globus pallidus to the ventro lateral , ventroanterior and centromedian nuclei of thalamus
   ii. From substantia nigra to the thalamus
3. Inside connection

(dopaminergic)

Substantia nigra (pars compacta) → Striatum

this is the nigro striatal pathway . The neurotransmitter is dopamine

ii. Striatum —GABA ergic→ Substantia nigra (pars reticulata)

iii. striatum → globus pallidus (internal and external segment)

iv. external segment globus pallidus

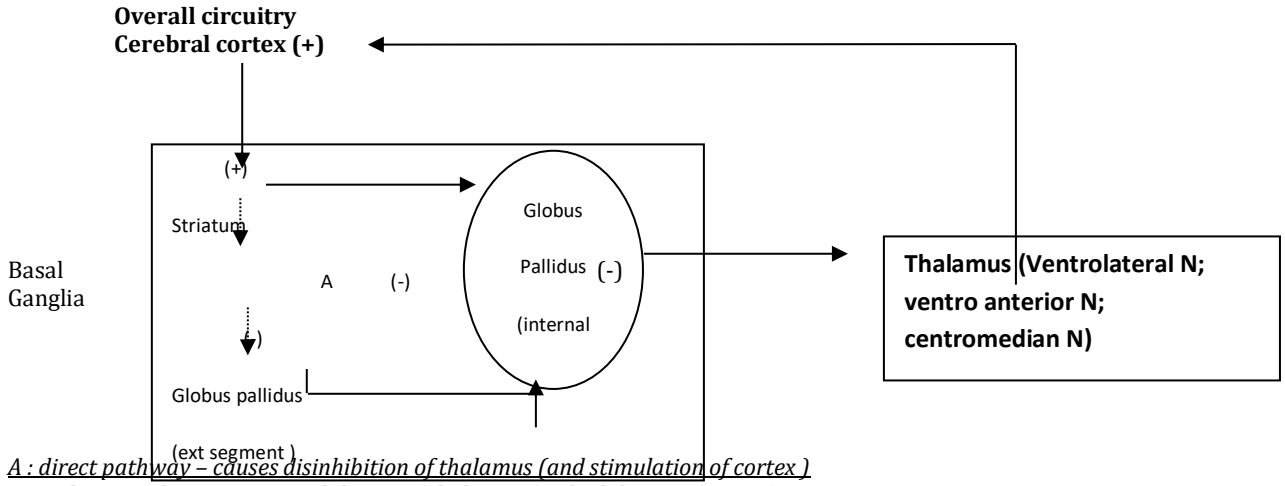
↓

subthalamic nucleus

↓

globus pallidus (GP) (both segments) | substantia nigra

Overall circuitry



Basal Ganglia

<u>A : direct pathway – causes disinhibition of thalamus (and stimulation of cortex)</u>
<u>B:- Indirect pathway : causes inhibition of thalamus (and inhibition of cortex)</u>
<u>(dopamine (nigro striatal pathway) stimulates A and inhibits B)</u>

The appropriate balance between the direct and indirect pathway maintains a suitable excitatory tone within the cortical motor pathway . The additive effect of the nigro striatal pathway provides an excitatory bias to the basal ganglia loop (note that there is a *closed – loop connection* between the cerebral cortex and basal ganglia)

(Also note that in the basal ganglia, the circuits through the subthalamic nucleus is an important regulator of basal ganglia output that normally maintains movement in a smooth and appropriate state)

Functions of basal ganglia

1. Planning and programming of movements

basal ganglia → via thalamus → motor cortex → cortico – spinal tract → motor neurons

2. Role in cognitive processes (especially that of the caudate nucleus)

VII. Cerebellum

1. Divisions (anatomical)

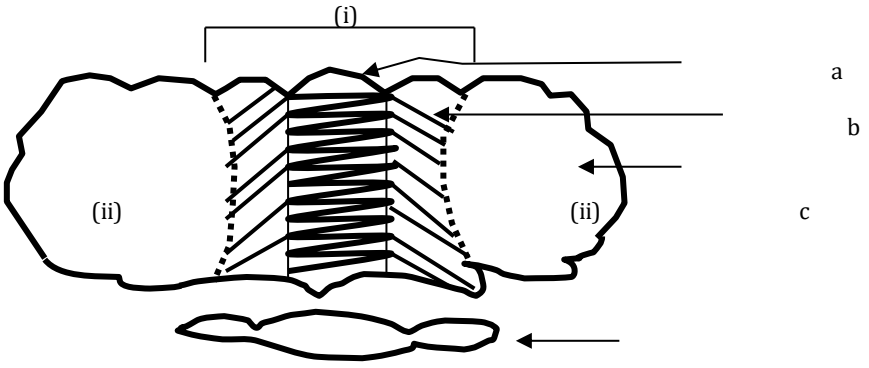
i) It has a central vermis (made up of 10 lobules)

ii) 2 lateral cerebellar hemispheres- these have many foldings and therefore have a large surface area.

The 10 lobules of the vermis are:

I : Lingula
II & III : Centralis
IV & V : culmen
VI : Lobulus simplex
VII : Folium, tuber
VIII : Pyramis
IX : uvula
X : Nodulus

2. Functional divisions
   i) Spinocerebellum
   ii) Cerebrocerebellum (or neocerebellum)
   iii) Vestibulocerebellum



a. To medial descending systems
b. To lateral descending system
   } for motor execution
c. To motor and premotor cortex – for motor planning
d. To vestibular nuclei – for balance and eye movements

The constituents of 3 parts of the cerebellum are:

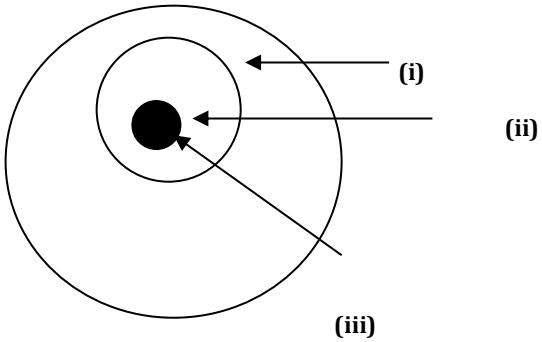
Part	Constituents	Connections	Functions
Spinocerebellum	Vermis (except the nodulus) and the adjacent medial portions of the hemispheres	Afferent • Proprioceptive input from body • Copy of the motor plan Efferent • From vermis ↓ to Brains stem area (for axial and proximal limb muscles) • From the hemispheres ↓ to brain stem area (For distal muscles)	By comparing plan with performance, it smoothens and coordinates movements

Cerebro cerebellum (or neocerebellum)	The lateral portions of hemispheres	Intract with motor cortex	Planning and programming movements
Vestibulo cerebellum (or the floculo- nodular lobe)	The nodulus and flocculus	Vestibular	* Equilibrium * Learning induced change in vestibulo ocular reflex.

3. Structure

The cerebellum is organized as

i) An outer cerebellum cortex, separated by
ii) White matter from the
iii) Deep cerebellar nuclear



The cerebellar cortex has 3 layers and 5 types of cells :

The 3 layers are

- The outer molecular
- Middle purkinje
- Inner granular

The 5 cells are:

- Purkinje
- Granular
- Golgi
- Stellate
- Basket

Location of the cell bodies of the cells:

Stellate, Basket : Outer molecular layers

Purkinje : Middle Purkinje layer

Golgi, Granular : Inner granular

(also, the 'glomeruli' lie in the inner granular)

The deep nuclei are (4 on each side)

Dentate

Emboliform

Fastigial

Globose

(the emboliform and globose are together referred to as the Inter positus)

4. Connections

i) Afferent

There are 2 main primary afferent inputs

a. Mossy fibres

b. *climbing fibres*

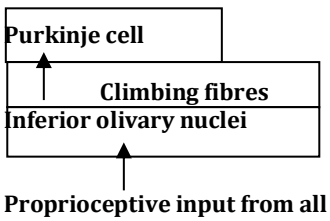
Both of these are excitatory; they send collateral to the deep nuclei & pass to the cerebellar cortex.

The climbing fibres ends on the Purkinje cell; the mossy fibres also end on the Purkinje cell, but through the granule cell.

The input to the Purkinje cell from the climbing fibre is 1:1; it is a stong excitatory input and produces a complex spike whereas the input to the Purkinje cell from the mossy fibre is 1 million : 1; it is a weak input and produces a simple spike.

What do the mossy and climbing fibres convey ?

Climbing Fibres = They come from one single source viz the inferior olivary nuclei. The climbing fibres convey proprioceptive inputs from all over the body



Proprioceptive input from all over the body

Mossy fibres: They come from many sources. The fibres first end on the dendrites of the granule cells in "glomeruli". The mossy fibres conveys proprioceptive input from all parts of the body and also input from the cerebral cortex via pontine nuclei to the cerebellar cortex.

The various tracts carried by the climbing and mossy fibres are:

1. Vestibulo- cerebellar	Vestibular impulses from labyrinth. Direct and via vestibular nuclei (Ipsilateral)
2. Dorsal spinocerebellar	Proprioceptive and exteroceptive impulses from body (trunk/ leg) (Ipsilateral)
3. Ventral spinocerebellar	Proprioceptive and exteroceptive impulses from body (trunk/ leg) (Contralateral)
4. Cuneo cerebellar	Proprioceptive impulses from head and neck (Ipsilateral)
5. Olivo cerebellar	Proprioceptive impulses from all over body through relay in inferior olive
6. Tecto – Cerebellar	Auditory and visual impulses via inferior and superior colliculi
7. Ponto- cerebellar	Impulses from motor and other parts of cerebral cortex via pontine nuclei (From Opposite cerebral cortex)
8. Rubro- cerebellar	Impulses from opposite red. Nucleus
9. Reticulo- cerebellar	Impulses from brain stem reticular formation

- The olivo cerebellar pathway projects to cerebellar cortex via climbing fibres.
- The rest of the listed pathways project via mossy fibres.

[The sensory input to the cerebellum is mostly ipsilateral]

[the dentatethalamo– cortical pathway crosses to the opposite side; further; the corticospinal tract also crosses to the opposite side. Therefore, the cerebellum regulates the activity of the **SAME side** of the body. In cerebellar lesions, there is a ↓ in muscle tone on the same side and the patient tends to fall on same side.

ii) Efferent (output) cerebellum

a. From vestibulo cerebellum – directly to the brain stem (not via the deep nuclei)

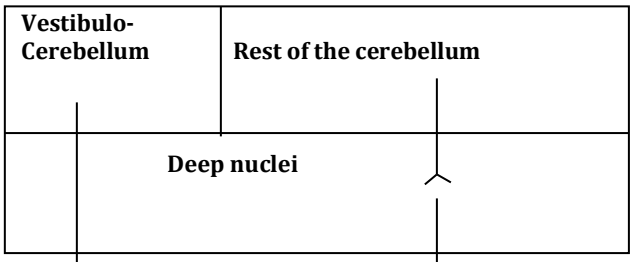
b. From spinocerebellum

- From the medial portions of the spinocerebellum to Fastigial nuclei → Then to Brainstem
- From adjacent hemispheric portions of the spinocerebellum to Emboliform and globose nuclei → Then to Brainstem

iii) From neocerebellum – to the denatate nucleus → Then to (directly / indirectly by) Ventrolateral nucleus of Thalamus → Cortex

(the dentato thalamocortical pathway)

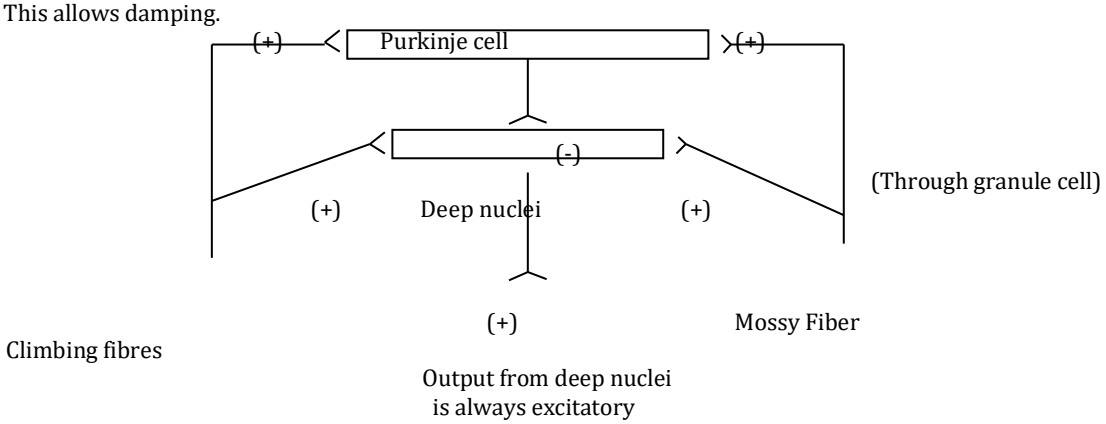
(Note that only the output from the vestibulo cerebellum does not go via the deep nuclei)



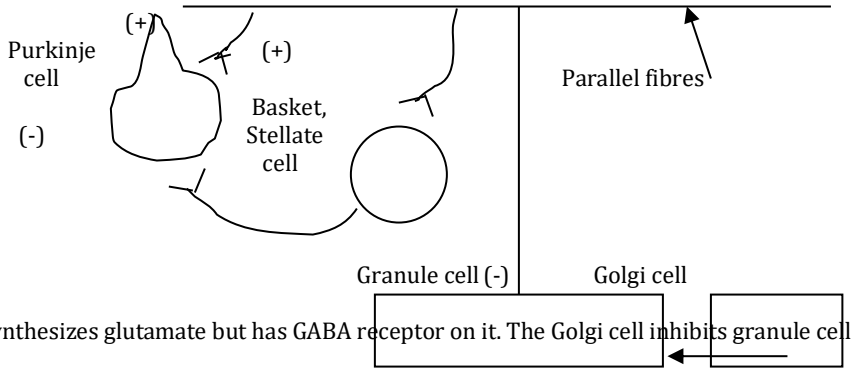
[Note that the *afferent inputs* go both to the cerebellar cortex and to the deep nuclei. In other words, deep nuclei receive input from the cerebellar cortex (except vestibulocerebellum) as well (as via the collateral) from the afferent inputs of the cerebellum]

iii. Inside connections

a) Purkinje cell – (recall that the climbing fibres end directly on the Purkinje cell; the mossy fibres end on the Purkinje cell through the granular cell.) The Purkinje cell projects to the deep nuclei; the deep nuclei then gives its output out of the cerebellum. The input from the Purkinje cell to the deep nuclei is inhibitory; however, the deep nuclei output is always excitatory. Even at rest deep nuclei continuously discharge excitatory inputs. When movement occurs, the deep nuclei discharge increase at first; within a few milliseconds, inhibition of this discharge occurs by the Purkinje cell. This allows damping.



b) Granule cell : - output from the granule cell axons bifurcate and give rise to parallel fibres. The granule cell stimulates the Purkinje cell; however, the granule cell also ends at basket/ stellate cells and stimulates them. But the basket and stellate cells in turn inhibit the Purkinje cell (this inhibition by the basket/ stellate cell is an example of feed forward inhibition). The granule cell itself is inhibited by the Golgi cell

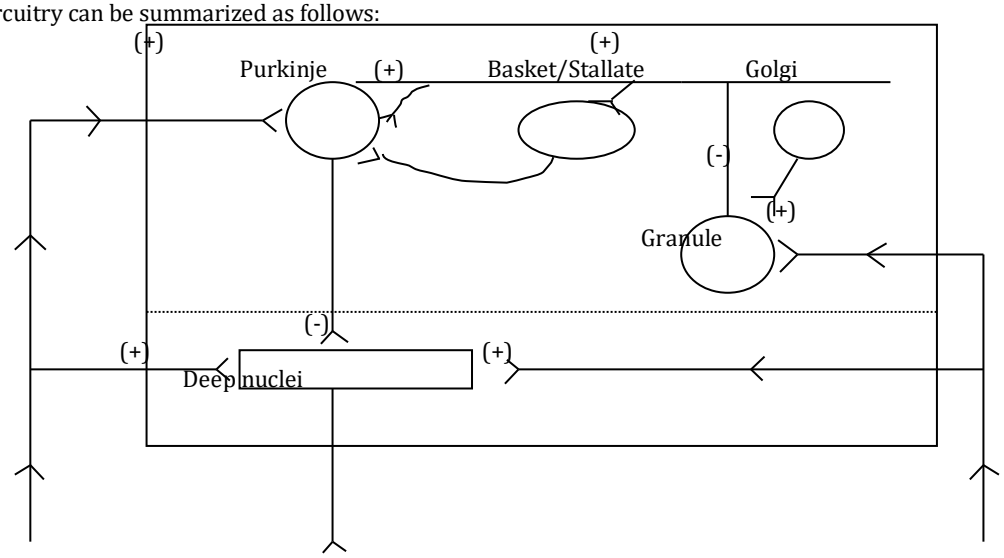


The granule cell synthesizes glutamate but has GABA receptor on it. The Golgi cell inhibits granule cell via the GABA receptors.

(Note that out of the 5 cells in the cerebellar cortex only the output from the granule cell is excitatory the output from the rest of the cells is inhibitory.

Granule cell	Stimulates the Purkinje, Basket and stellate cells
Purkinje cell	Inhibits deep nuclei
Golgi cell	Inhibits granule cell
Basket cell	Inhibits Purkinje cell
Stellate cell	Inhibits Purkinje cell

Thus, the overall circuitry can be summarized as follows:



Climbing fibres

Mossy fibres

(+)

(Note: the synaptic connections in the granule cell from the 'glomeruli')

5. Functions

i) Maintenance of equilibrium – this is the function of the vestibulo cerebellum (i.e. the flocculonodular lobe). There is inter connection between the vestibular apparatus and the flocculonodular lobe.

ii) Role in regulation of tone/ posture – the effects of the cerebellum on the stretch reflex are complex. With cerebellar disease one would expect an increased in tone. But in humans, hypotonia occurs in cerebellar disease. The spinocerebellum projects on

- The alpha motor neurons (through efferent output to vestibular nuclei)
- The gamma motor neurons (through efferent output to reticular formation)

There is a perfect co ordination between the alpha and gamma motor neuron discharge (the alpha- gamma linkage). The linkage exists at the level of the spinal cord; the 'switch' for the linkage is in the cerebellum.

iii) Error control function / effects on movement- By comparing plan with performance, (the cerebellum gets input from the cortex as well as various sensory inputs) the cerebellum makes anticipatory corrections.

iv) Planning functions – This is the function of the neocerebellum

v) Role in learning: The cerebellum is concerned with learned adjustments to repetitive tasks.

6. Cerebellar lesions/ disease

i) Features

a. No paralysis
b. No sensory deficit
c. No abnormalities at rest (except the changes in stretch reflexes)
d. Ataxia (drunken gait)
e. Slurred/ scanning speech
f. Dysmetria (past- pointing)
g. Intention tremor
h. Rebound phenomenon
i. Adiadokodinesia
j. Decomposition of movement

[Electrical activity in cerebellum: the basic electrical of frequency rhythm of the cerebellar cortex is of frequency 150-300/ S and 200μv amplitude. Superimposed on this basic rhythm is a 1000-2000/s component of smaller amplitude.

BRODMANN'S AREAS

S. No.	Area		
1.	Primary sensory area (Post central gyrus)	=	3, 1, 2
2.	Primary Motor area (Pre – central gyrus)	=	4
3.	Premotor area	=	6
4.	Frontal eye field	=	8
5.	Sensory association area	=	5, 7
6.	Primary visual area (Visual association area)	= =	17 18,19
7.	Primary auditory area Auditory association area	= =	41 41, 42
8.	Broca's area Wernicke's area	= =	44 22
9.	Cingulete gyrus Angular gyrus	= =	24 39

Hypothalamic Nuclei / Areas

1. Circadian rhythm : Suprachiasmatic nuclei
2. Temperature
    - Heat response : mediated by anterior hypothalamus
    - Cold response: mediated by posterior hypothalamus

3. Thirst

Lateral preoptic area

4. Hunger
    - Feeding center: lateral hypothalamus
    - Satiety center: ventromedial hypothalamus
    - Leptin receptors: especially in arcuate nuclei and paraventricular nuclei

5. Sexual behavior : Anterior ventral hypothalamus, piriform cortex (in male)
6. Catecholamines: dorsal and posterior hypothalamus
7. Control of pituitary hormones

i) Anterior
- CRH: Paraventricular nuclei
- GnRH : preoptic area
- PIH/PRH (Prolactin)

ii) Posterior
- ADH/ Oxytocin: supraoptic and paraventricular nucleus
  - Both nuclei secrete both hormones; however,
  - Paraventricular: mainly oxytocin
  - Supraoptic: mainly ADH

8. Osmoreceptors : Anterior hypothalamus
9. Pyrogens

These release cytokines from macrophages etc. → act on preoptic area of hypothalamus → release local prostaglandins → fever

10. Autonomic nervous system

Stimulation of
- The anterior hypothalamus
  Causes parasympathetic response like contraction of the urinary bladder
- Lateral areas of the hypothalamus
  Produces sympathetic responses such as rise in BP, pupillary dilation, piloerection, increased adrenal medullary secretion etc. this is the kind of response seen in animals exposed to stress (the fight or the flight reaction)
- Mid-dorsal area of the hypothalamus
  Causes cholinergic sympathetic vasodilatation
- Dorsomedial nuclei and posterior hypothalamic areas

Produces increased adrenal medullary secretion which is one of the physical changes associated with rage and fear.

11. Papez circuit

Mammillary bodies of the hypothalamus

EPSP

Type	Timing	Cause	Site
1. EPSP	Latency : 0.5 ms Peak : 0.5 – 1.5 ms Time Constant : 3 ms	Na/Ca influx	
2. Slow	Latency : 100 – 500 ms Lasts : Several Seconds	↓ K efflux	Aton. Ganglca crdiac muscle, smooth muscle, cortical neurons
3. Late slow	Latency : 1-5 Sec Lasts : 10 – 30 min	↓ Kefflix	Symph. Gangli

IPSP

Type	Timing	Cause	Site
IPSP	Latency 0.5 ms Peaks: 0.5 –1.5 ms Time consistent: 3 ms	Cl influx ↑ K efflux Na/Ca closure	
Slow	Latency 100 – 00 ms Lasts : Several seconds	↑K efflux	Aut. Ganagia, CM, SM, critical neurons

Aid to memory
- Timing f PSP & IPSP : Same
- Slow EPSP & IPSP : cause is K+
- No late slow IPSP.

Fast & slow responses & post ganglionic neurons in sympathetic ganglia:

EPSP Type	Duration	NT	Receptor
1. Fast	30ms	Ach	Nicotinic
2. Slow	30 S	Ach	M2
3. Late slow	4 min	GnRH	GnRH
IPSP Slow	2 S	Dopamine	D 2

Postural reflexes

Reflexes	Integrated in
Antigravity reflexes, attitudinal reflexes, (ie. Tonic labyrinthine & tonic neck reflexes)	Medulla
Locomotor	Med brain, thalamus
Righting reflexes (except optical righting reflex)	Mid brain
Optical righting reflex	Cortex

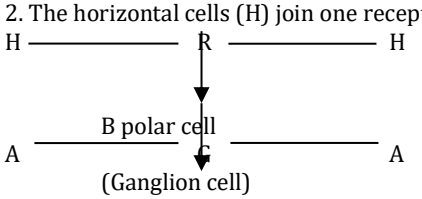
Visuo spinal reflex	Mid brain
Conditioned reflex	Cortex

VISION

1. The function of the 3 layers:
   i) Sclera: Protective
   ii) Uvea : Vascular (nutritive)
   iii) Retina : Light- sensitive

The retina lines the post 2/3rd of the choroids. The lens ligament (zonule) is attached to the lens and to the ciliary body. The aqueous humour is formed in the ciliary body. The normal intraocular pressure is 10-20 mmHg. There are 10 layers in the retina. The neural cells in the retina are the receptor cells (rods & cones), the bipolar cells, the ganglion cells, the horizontal and the amacrine cells. The glial cells are the Muller cells. There are gap junctions from one retinal neuron to another.

2. The horizontal cells (H) join one receptor(R) cell to another; the amacrine (A) cells join one ganglion cell to another.



The rods have connection with bipolar cell. Which in turn has connection with ganglion cell. The axons of the ganglion cell form the optic nerve. Many receptor (R) cells converge an one bipolar cell and many bipolar cells converge on one ganglion cell; there is *overall convergence from the receptor cell to the ganglion cell.*

(Note that the direction of the light rays is from that
ganglion cell ⟶ bipolar cell ⟶ receptor cell

At the posterior pole of the eye, the macula lutea (with fovea centralis) is present. The unique features of the fovea centralis are

   i) It is rod- free; only cones present
   ii) The cones here are densely packed there are very few other cells
   iii) There are no blood vessels *overlying* the receptors
   iv) It is the point of highest visual acuity.

Note that action potentials are formed only in the ganglion cells; in the other retinal neural cells only local potentials are formed.

The primary visual area (area 17) lies on the sides of the calcarine fissure in the occipital lobe.

The visual pathway has connections, which subserve

   i) Vision
   ii) Papillary reflex
   iii) Superior colliculus
   iv) Suprachiasmatic nucleus of the hypothalamus

The rods are more sensitive (lower threshold) than the cones. The visual spectrum is from 393nm to 727 nm. The refractory power is expressed in diopters

$$\text{No. of diopters} = \frac{1}{\text{Focal length in meters}}$$

Accomodation- In accommodation, only the anterior curvature of the lens changes.

Near response consists of

   i) Accommodation
   ii) Convergence of the eyes
   iii) Papillary constriction

The pupils can constrict as a part of the near response; the pupils also constrict as a part of the light reflex)

Reduced or Schematic eye- Since there are many places in the eye where refraction of the light rays takes place, for **simplicity**, (to make ray diagrams) we can assume that all refraction takes place at the anterior surface of the cornea. (Most of the refraction occurs at the cornea)

Photoreceptor mechanism – All or none action potentials are seen only in the ganglion cells. In all others, there are local, graded potentials.

i) Rods/ cones/ horizontal cells: Hyperpolarising potentials
ii) Bipolar cells : Hyper or hypopolarising
iii) Amacrine: Depolarizing.

The sodium channels in the outer segment of the receptor cell are open in the dark; in the dark; there is a steady release of neurotransmitter. When light falls, the sodium channels close. Causing hyperpolarisation and a decrease in the neurotransmitter release. One photon of light is enough to stimulate the rods. The retina has 2 types of ganglion cells:

i) Magno: for movement, stereopsis

ii) Parvo: for color, texture and shape.

The primary colors are blue, red and green. For any color, there is a complementary color that when properly mixed with it, produces a sensation of white. Blobs are cells in the visual cortex associated with colour vision.

Color defects

Weakness- is called anomally
Blindness- is called anopia
'Prot' refers to red
'Deuter' refers to green
'Tri' refers to blue

Trichromats have all the 3 types of cones
Dichromats have a 2-cone system
If 'red' absent- Protanopia
If 'green' absent- Deuteranopia
If 'blue' absent- Tritanopia

Monochromats have only 1-cone system.

Retina	LGB	Visual cortex	Function
P(or parvocellular cell)	Parvo portion (Layers 3-6) Interlaminar region	Layer Deep & C Layer 2,3 (blobs)	Colour, texture, shape Colour
M (or magnocellular cell)	Magnocellular portion (Layers 1 and 2)	Layer superficial 4 C	Movement depth & spatial organization

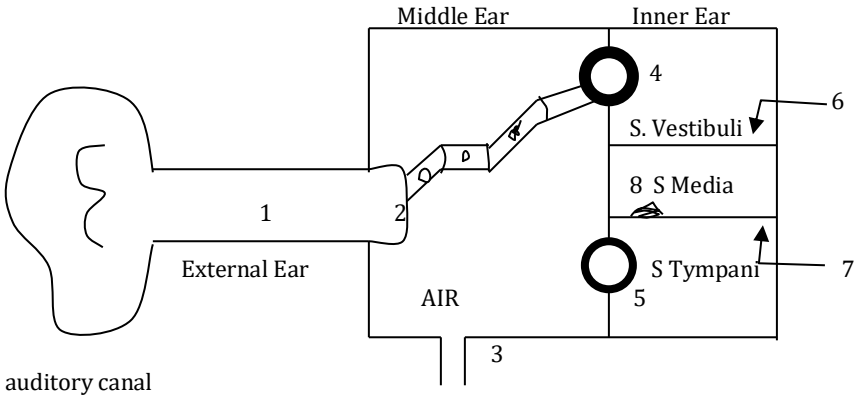
HEARING / EQUILIBRIUM

For hearing- the external, middle and inner ear.
For equilibrium- the semicircular canals (SC), the utricle and saccule of the inner ear

i) Semicircular canals sense rotational acceleration
ii) The utricle senses linear (horizontal) acceleration

iii) The saccule senses linear (vertical) acceleration.

The receptors for both hearing as well as equilibrium are the hair cells. There are 6 groups of hair cells in each ear viz 3 in semicircular cells, 1 each in the utricles saccule and cochlea.



1. Ext. auditory canal
2. Tymp. Membrane
3. Eustachean tube/ Auditory tube/ Pharyngotympanic tube
4. Oval window
5. Round window
6. Reissner's membrane
7. Basilar membrane
8. Organ of corti

Features of middle ear

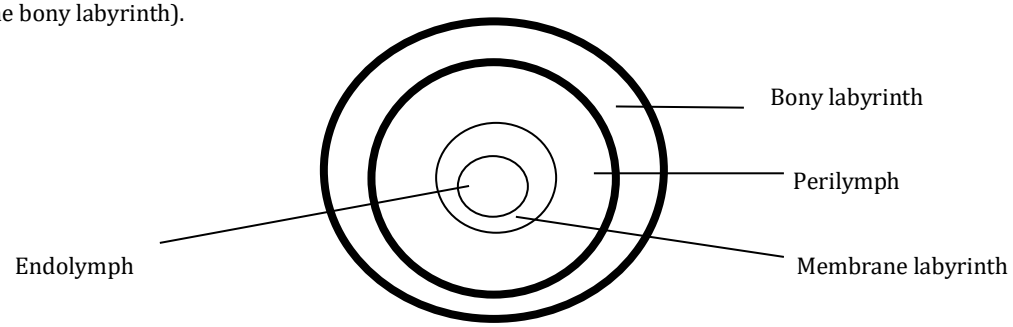
i) It is air- filled space in the temporal bone

ii) The auditory tube (also called eustachean tube, pharyngotympanic tube) connects the middle ear cavity (also called cavity) with the nasophanynx. The auditory tube in usually closed; it opens during swallowing, chewing, yawning. When the tube opens, there is equalization of pressures on the two sides of the tympanic membrane.

iii) There are 3 bones- malleus, incus and stapes.

iv) There are 2 muscles – tensor tympani and stapedius.

Inner ear (Labyrinth) – the inner ear is designed in the form of a tube (membranous labyrinth) encased in a bony tube (the bony labyrinth).



There is endolymph within the membranous labyrnith and perilymph surrounding the membranous labyrinth. There is no communication between endo and perilymph. 3 parts of the bony labyrinth house (contain) 3 parts of the membranous labyrinth;

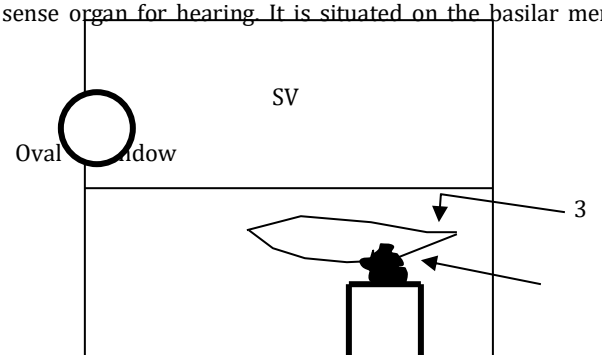
Bony labyrinth	***Membranous labyrinth***
i) Bony cochlea	Membranous cochlea (also called cochlear duct, scala media)
ii) Vestibule	Saccule, utricle
iii) Semicircular canals	Semicircular ducts

Cochlea- Its length in 35mm. It has 2 ¾ turns. The membranous cochlea splits the bony cochlea into scala vestibuli & scala tympani. The membranous cochlea (or the scala media) has endolymph whereas the scala vestibuli and scala tympani have perilymph.

The perilymph resembles ECF (high Na^+, less K^+)

Whereas the endolymph resembles ICF (More K^+, less Na^+)

Organ of corti – This is the sense organ for hearing. It is situated on the basilar membrane. The receptor for hearing are the hair cells .



2

1

Round window

ST

1. *Hair Cell*
2. *Hair cell processes*
3. *tectorial membrane*

The hair cell processes are bathed in endolymph. Whereas the hair cell bases are bathed in perilymph. There are 4 rows of hair cells – 3 outer and 1 inner. 90 to 95% of the afferent neurons arise from the inner hair cells; only 5-10% arise from the outer hair cells (In contrast, most efferent neurons [the olivocochlear bundle] end on the outer hair cells). The cell bodies of the afferent neurons are in the spiral ganglion.

Auditory pathway

Auditory (cochlear) division of vestibulo cochlear nerve
↓
Cochlear nuclei in the medulla
↓
Inferior colliculi (the centers for auditory reflexes)
↓
Medial geniculate body
↓
Auditory cortex (Area 41) (In superior portion of the temporal lobe in the sylvian fissure).

The efferent olivocochlear bundle arises from the superior olivary complex and ends primarily in the outer hair cells of the organ of cortex.

Mechanotransduction – is by the bending of the stereocilia which has ' tiplinks'.

(Note that the scala media is electropositive with respect to the scala vestibuli and scala tympani)

Loudness/ pitch/ timbre

Loudness is related to the amplitude
Pitch is related to frequency
Timbre (quality) is related to overtones (the number of harmonic vibrations)
Loudness is measured in decibels (dB)

$$dB = 10 \log \frac{\text{Intensity of sound}}{\text{Intensity of standard sound}}$$

Or,

$$dB = 20 \log \frac{\text{Pressure of sound}}{\text{Pressure of standard sound}}$$

Note that the average auditory threshold for humans is zero decibel.

The frequency range for hearing is from 20-20000 Hz. The greatest sensitivity lies between 1000- 4000 Hz. The pitch discrimination is between 1000-3000Hz

Tympanic reflex (attenuation reflex) – Loud sounds cause reflex contraction of the tensor tympani and stapedius muscles, decreasing sound transmission.

Theories of Hearing

i) **Place theory –** Frequency discrimination is dependent on the **exact place** on the basilar membrane. Which is most stimulated. (It has been known from Von Be' Ke's ys travelling wave theory that high- pitched sounds reach maximum height near the base of the cochlea and low- pitched sounds reach maximum height near the apex of the cochlea) Place theory helps to explain high frequency discrimination.
ii) For explaining pitch discrimination in the low- frequency range (say 20 to 2000), there is the volley or the frequency principle. That is, low frequency sounds can cause volleys of impulses synchronised at the same frequencies and these volleys are transmitted by the cochlear nerve into the cochlear nuclei of the brain.

Tuning fork tests / types of deafness

There are 2 types of deafness
i) Conductive : Problem in conduction (e.g wax, destruction of ossicles, thickening of tympanic membrane etc.) from external ear up to inner ear.
ii) Neural : due Hair cell degeneration, nerve damage.

Tuning fork test:

i) Rinne's test

a. Normal: Air conduction is more than bone conduction
b. Conduction deafness: BC> AC
c. Neural deafness: AC>BC (as long as the nerve deafness is partial)

ii) Weber's test

a. In nerve deafness: Lateralisation towards normal side (i.e. the subject hears better on the normal side ear during the test)
b. In conduction deafness: Lateralisation is towards damaged side

iii) Schwabach's test (Absolute bone conduction test)

a. Conductive deafness: >normal
b. Neural deafness: < normal

Vestibular apparatus consists of

i) Semicircular canals
ii) Utricle
iii) Saccule

The receptor structure of the semicircular canals is the *crista ampullaris* in the ampulla. Each crista has hair cells and sustentacular cells surmounted by a gelatinous partition (cupula) that closes off the ampula. The utricle and saccule have otoliti organ or macula. The macula has hair cells surmounted by an stolithic membrane in which are embedded crystals of calcium carbonate (otoliths)

Position of macula in utricle and saccule:

i) In utricle: Floor of the utricle
ii) In saccule: wall of the saccule in a semi vertical position.

Pathway

i) The cell bodies of the neurons supplying the cristae and maculas on each side located in the vestibular ganglion. Each vestibular nerve terminates in the
a. Ipsilateral 4- part vestibular nucleus and in the
b. Flocculonodular lobe of the cerebellum.
ii) The 2nd order neurons from the vestibular nuclei
a. Pass down the spinal cord in the vestibulo spinal tracts (concerned primarily with postural adjustments)
b. Ascend through the medial longitudinal fasciculi to the motor nuclei of the cranial nerves concerned with control of eye movements viz 3rd, 4th and 6th cranial nerves (largely concerned with eye movements)

Nystagmus – It is actually reflex; it helps in visual fixation. It has a slow component (labyrinth) and a quick component (brain stem) the direction of nystagmus is given by the quick component.

GIT

Carbohydrates

Dietary carbohydrates

These are :

i) Monosaccharides : fructose, glucose
ii) Disaccharides : lactose (milk sugar), sucrose (cane sugar or table sugar)
iii) Polysaccharides :

The only digestible polysaccharides in humans are the starches (starches are polymers of glucose). Dietary starches can be of :

- **Animal origin :**
- Glycogen :

Glycogen is ***mostly straight*** in structure (with glucose molecules attached to each other by ***1:4 alpha*** linkage); there is some ***side-branching*** also (here the linkage is by ***1:6 alpha*** linkage)

- **Plant origin :**

- Amylopectin :
  This is the ***main dietary starch*** (constituting more than 80 to 90%).This is just like glycogen, with even fewer side branches.
- Amylose :
  This has no side branches.
- Cellulose :
  This cannot be digested in humans.

Digestion

Final end products :

The end products of carbohydrate digestion are the monosaccharides fructose, glucose and galactose. Only monosaccharides can be absorbed from the GIT.

Site :

Although starch digestion begins in the mouth (by salivary alpha amylase), almost all starch digestion occurs in small intestine.

Enzymes :

i) Salivary alpha amylase (ptyalin)
ii) Pancreatic alpha amylase
iii) Small intestine brush border enzymes :

Alpha-dextrinase (also called isomaltase), sucrase, maltase, lactase, trehalase

(Note : alpha-dextrinase and sucrase are separate subunits of a single protein)

Alpha amylase (salivary and pancreatic) digestion :

The alpha amylase acting on starch can break ***only*** the ***1:4 alpha*** linkages;

They cannot break 1:6 alpha linkages, terminal 1:4 alpha linkages and 1:4 alpha linkages next to branching points.

Thus, the end products of amylase digestion are not monosaccharides; the end products are :

- Oligosaccharides
- Maltose (a disaccharide)
- Maltriose (a trisaccharide)
- Alpha-dextrins (these are glucose polymers containing on an average 8 glucose molecules containing 1:6 alpha linkages)

The above end products are further digested by the brush border enzymes.

Note : the *activator* for salivary alpha amylase is *chloride ion*.

Brush border enzyme digestion

This is shown in the table below :

Enzyme	Acts on	End products
Alpha dextrinase or isomaltase (this is the main enzyme for breaking 1:6 alpha linkages)	Alpha dextrins, maltose, maltriose	Glucose
Sucrase	Sucrose, maltose, maltriose	Sucrose : glucose and fructose Maltose : 2 glucose Maltriose : 3 glucose
Maltase	Maltose, maltriose, alpha dextrins	Glucose
Lactase	Lactose	Glucose, galactose
Trehalase	Trehalose (this is a 1:1 alpha linkage ***dimer*** of glucose	2 glucose

Absorption

Site :

Absorption of the monosaccharides occurs in the small intestine.

Amount of monosaccharides that can be absorbed:

Absorption is not regulated. The intestine can absorb more than 5 kg of dietary sucrose/day. Almost all the glucose and galactose present in the intestine can be absorbed. The maximal rate of glucose absorption from intestine is about 120 gram/hr.

Mechanism

i) Glucose/galactose (hexoses)

a) From lumen to enterocyte

These are absorbed by sodium-dependent secondary active transport (the transporter is a symport and is called SGLT or sodium linked glucose transport)

Salient features of SGLT:

- Just like the GLUT series of transporters, SGLT also crosses the membrane 12 times (with its COOH and NH2 terminals on the cytoplasmic side of the membrane)
- It is present in the kidney and intestine
- It is not affected by insulin

- It transports glucose and galactose
- It has 3 binding sites :

- 2 for sodium and
- 1 for glucose or galactose

b) From enterocyte to the interstitium

This is by GLUT 2. From the interstitium, it diffuses into blood.

ii) Fructose (hexose)

Its absorption is independent of sodium. It is transported by ***facilitated diffusion*** by GLUT series of transporters. 2 GLUT series of transporters are involved :

- from lumen to enterocyte : GLUT 5
- from enterocyte to interstitium : GLUT 2

Fructose absorption occurs rapidly because most of the fructose is converted into glucose and lactic acid within the enterocyte; this maintains a high concentration gradient for diffusion.

iii) Pentoses

These are absorbed by simple diffusion.

Proteins

I. Digestion

Generally, proteins must be digested into small polypeptides before being absorbed.

Enzymes responsible for protein digestion

1. Gastric enzyme : viz pepsins

The pepsin precursors are pepsinogens. Pepsinogens are converted into pepsins ***by gastric HCl***. Pepsinogens are ssecreted by the ***chief cells*** of the stomach.

Pepsins break peptide bonds adjacent to aromatic amino acids (e.g. next to phenylalanine, tyrosine); their break down products are polypeptides of different sizes.

Importance of protein digestion in stomach :

Although only 10-15% of the protein digestion occurs in stomach, these protein digestion products act as secretogogues; these secretogogues stimulate secretion of proteases by the pancreas.

2. Pancreatic and intestinal enzymes

The pancreatic and intestinal enzymes involved in protein digestion are shown below; the table also shows the site of break down of the peptide bonds by these enzymes:

Enzymes	**Site of break down of peptide bonds**
Pancreatic enzymes	
i) Trypsin	Carboxyl side of basic amino acids (arginine or lysine)
ii) Chymotrypsins	Carboxyl side of aromatic amino acids
iii) Elastase	Carboxyl side of aliphatic amino acids
iv)Carboxypeptidase A	Carboxyl terminal amino acids that have aromatic or branched aliphatic side chains
v) Carboxypeptidase B	Carboxyl terminal amino acids that have basic side chains
Intestinal brush border enzymes	
i) Aminopeptidases	Amino terminal amino acid
ii) Carboxypeptidases	Carboxy terminal amino acid
iii) Endopeptidases	Midportion of peptide molecules
iv) Dipeptidases	Two amino acids

The pancreatic protein digestion enzymes mentioned above exist as their inactive precursors :

Inactive precursor	Active enzyme
Trypsinogen	Trypsin
Chymotrypsinogens	Chymotrypsins
Proelastase	Elastase
Procarboxypeptidase A	Carboxypeptidase A
Procarboxypeptidase B	Carboxypeptidase B

Activators :

i) Trypsinogen is converted into trypsin by ***enteropeptidase*** (previously called ***enterokinase***)

ii) ***Trypsin*** in turn converts :

- more trypsinogen into trypsin (autocatalysis)
- the other inactive precursors mentioned above into their active form

Endo- and exopeptidases

i) Endopeptidases

Trypsin, chymotrypsins and elastase are called endopeptidases; this is because they break the interior peptide bonds in the peptide molecules.

ii) Exopeptidases

The carboxypeptidases and aminopeptidases are called exopeptidases; this is because they break the terminal amino acids.

II. Absorption

Mechanisms

From lumen to enterocyte

1. For amino acids

i) Na^+ - amino acid secondary active transport

ii) $Na^+ Cl^-$ - amino acid secondary active transport

iii) Na^+ - independent transport of amino acid

2. For di-and tripeptides

H – dependent transport mechanism

3. Proteins

Although polypeptides with greater than 3 peptides are poorly absorbed, some proteins can still be absorbed, especially in infants. For instance, the secretory immunoglobulins (IgAs) in the maternal colustrum are absorbed by endocytosis from the intestine and then into circulation by exocytosis. Protein absorption decreases with age but still it persists in adults. Absorption of certain food protein antigens from the intestine can cause allergy. Absorption of ***protein antigens*** (especially bacterial/viral proteins) occurs in ***M or microfold cells***; M cells are specialized intestinal epithelial cells that ***overlie the Peyer's patches*** (Peyer's patches are aggregates of lymphoid tissue in the intestine)

Secretory immunity

Antigen → from the M cells go to → lymphoid cells and activate the lymphoblasts → these enter the circulation → and reach the intestinal mucosa and other epithelia. Now, if these lymphoblasts are exposed again to the same antigen, IgA is secreted.

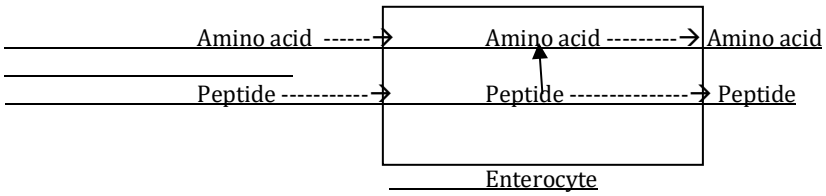
Protein in stools

All the ingested protein is absorbed (95 to 97 % in the small intestine and the remaining 2 to 5 % is digested by bacterial action in colon and then absorbed). Thus, there is ***no ingested protein in stool***. The protein in stool is thus derived from :

- bacteria within the colon
- cellular debris

Absorption from the enterocyte to interstitium

The amino acids and peptides are transported across the basolateral membrane of the enterocytes by facilitated diffusion or by simple diffusion. They they enter the capillaries of the villus by simple diffusion



Absorption of amino acids is rapid in duodenum/jejunum but slow in ileum.

Source of proteins

i) Exogenous (or dietary) proteins : 50%

ii) Endogenous proteins : 50%

- From secretory proteins in digestive juices (25%)
- From desquamated cells (25%)

Is protein absorption from intestine regulated

Unlike absorption of carbohydrate, absorption of proteins from the intestine seems to be regulated. For example, in starvation (or if the intestine is partly resected), the brush border enzyme activity increases.

Nucleic Acids

Nucleic acids are digested by the pancreatic nucleases (viz. ribonuclease and deoxyribonuclease) into nucleotides. The nucleotides are further split into nucleosides and phosphoric acid by intestinal enzymes. In turn, nucleosides are split into their sugars and purine/pyrimidine bases. The purine/pyridmidine bases are absorbed by active transport.

Fats and lipids

I. Digestion

Fat digestion starts primarily in the duodenum. Digestion is by lipase; lipase comes from three sources

1. Lingual lipase

This is secreted by ***Ebner's glands*** present on the dorsal surface of the tongue; lingual lipase can digest up to 30% of the dietary triglycerides. Lingual lipase acts on triglycerides to give fatty acids and 1,2 – diacylglycerols.

2. Pancreatic lipase

This is the most important enzyme for lipid digestion; it acts on triglycerides to give fatty acids and monoglycerides.

3. Gastric lipase

This is not important in humans except in pancreatic insufficiency; it acts on triglycerides to give fatty acids and glycerol.

Pancreatic lipase

Types of pancreatic lipase

1. Colipase-activated pancreatic lipase

Colipase is a ***pancreatic*** enzyme; it ***activates pancreatic lipase***. Colipase itself is secreted as procolipase; trypsin activates procolipase to colipase.

This type of pancreatic lipase can only split triglycerides.

2. Bile salt-activated pancreatic lipase

This is less active (about 10 to 60 times) than colipase-activated pancreatic lipase. However, it can split triglycerides, cholesterol esters, esters of fat-soluble vitamins and phospholipids.

Action

Pancreatic lipase splits the fatty acids in position 1 and 3 of the triglycerides but not the fatty acid in position 2. Thus, it splits triglycerides into 2 fatty acids and 2-monoglyceride.

Emulsification :

Meaning :

The process of break down of fat into small fat droplets (less than 1 micrometer in diameter) is called emulsification.

Carried out by :

Bile salts, lecithin and monoglycerides.

Importance :

Fats must first be emulsified before pancreatic lipase can act on them.

Other pancreatic enzymes for fat digestion

2.Cholesteryl ester hydrolase :

This acts on dietary cholesteryl esters and splits it into cholesterol.

3.Phospholipase A_2

This exists as pro-phospholipase A_2; it gets activated by trypsin into phospholipase A_2. It acts on phospholipids to liberate fatty acids and lysophospholipids.

End products of fat digestion in the intestinal lumen

Fatty acids, monoglycerides, cholesterol and lysophospholipids.

Micelle formation

What is a micelle ?

A micelle (approx. 5 nm in diameter) is a spherical aggregate consisting of 2 'parts'

i) A central lipid phase (hydrophobic) :

The center of the micelle has digested end products of fat (viz. fatty acids, monoglycerides, cholesterol, lysophospholipids); it also has the fat-soluble vitamins.

The fat products have their hydrophobic chains facing the interior and their polar ends facing the water phase outside.

ii) A peripheral water phase (hydrophilic):

The center is surrounded by a peripheral water phase consisting of bile salts.

(Thus, micelle is formed by digested end products of fat in the center and bile salts in the periphery).

Importance of micelle formation

There is a water layer called the unstirred water (USW) layer in between the intestinal lumen and the intestinal cell. Since fats do not dissolve in water, micelle formation helps in passing through the USW layer to reach the enterocyte. This is because the fat products are kept in the center of the micelle and the water-soluble bile salt is in the periphery. The micelle moves down its concentration gradient to reach the surface of the enterocyte; here, the fat products are released from the micelle. Since the fat products are released close to the cell membrane, they can diffuse into the cell. The bile salt is released into the lumen; here, it helps in forming more micelle formation. Finally, the bile salt is absorbed only in the terminal ileum by a sodium-dependent active transport and thus re-used.

The rate-limiting step in lipid absorption is the migration of micelles from the intestinal lumen to the intestinal cell surface.

II. Absorption

For the end products of fat digestion to cross the unstirred water layer, they must first be made soluble in water; this is done by micelle formation with the help of bile salts (see above)

Micelles help in crossing the unstirred water layer to reach the cell surface; here, micelles break into :

i) Digested lipid end products.

ii) Bile salts

i) Lipid end products

Site :

Almost all the digested lipids are ***totally absorbed*** by the time the chyme reaches the mid-jejunum; ***most*** of the absorption occurs in the ***duodenum***.. Lipids enter the enterocyte by ***passive diffusion***.

ii) Bile salts

Site :

Bile salt absorption does not occur much in the jejunum. It remains in the intestinal lumen (this is an advantage because here it helps in forming new micelles) till it reaches the terminal ileum; absorption occurs in the ***terminal ileum*** by a sodium-dependent active transport.

Fat in stools

Normally, almost all (95%)of the ingested lipid is absorbed; thus, fat present in the stool is ***mostly*** derived from the ***intestinal flora***.

Fate of the digested end products of lipid in the enterocyte

Once inside the enterocyte, the digested lipids enter the ***smooth*** endoplasmic reticulum (SER) where they are ***re-constituted***. Only fatty acids with less than 10-12 carbon atoms pass from the mucosal cell directly into the portal blood where they are transported as free (unesterified) fatty acids.

Reconstitution in SER

i) fatty acids (with more than 12 carbon atoms) : are re-esterified to triglycerides.

How?

MGT

2-monoglyceride ----------→ 1-2 diglyceride

Fatty acid
(acylation)

DGT

1-2 diglyceride ----------→ 1-2, 3 triglyceride

Fatty acid
(acylation)

MGT : monoacyl glycerol acyl transferase

DGT : diacylglycerol acyl transferase

ester

ii) Cholesterol ----------→ cholesteryl ester

fatty acids

ii) lysophospholipids ----------→ phospholipids

Note :

Some of the triglycerides in the cell is formed from glycerophosphate (which is a product of glucose metabolism); this occurs in ***rough*** endoplasmic reticulum (RER).

acylation

Glucose ----→ glycerophosphate----------→ triglycerides

The reconstitution inside the enterocyte helps in maintaining the concentration gradient for diffusion from lumen to cell.

Chylomicrons

Formation :

Site : enterocyte

How formed :

i) The reconstituted triglycerides and cholesteryl esters coalesce within the SER to from small ***lipid droplets*** (approx. 1mm diameter).
ii) They are then ***coated with*** a layer of proteins (***beta lipoproteins) and phospholipids*** to form chylomicrons.
iii) The chylomicrons formed in RER move to Golgi apparatus, where carbohydrate moieties are added there.

Transport

The chylomicrons are transported out of the cell by exocytosis.

Importance of beta lipoproteins

Beta lipoproteins (which are synthesized by the enterocyte in the RER) covers the surface of the chylomicrons. In the absence of beta lipoproteins, exocytosis will not occur and the enterocyte becomes engorged with lipids.

(Note : The acylation of glycerophosphate and the formation of lipoproteins occurs in the RER).

Transport of lipids in circulation

After coming out of the cell, the chylomicrons merge into larger droplets that vary in size from 50 to 500 nm, depending on the amount of lipids being absorbed. The larger lipid droplets then diffuse into the lacteals, from which they enter the lymphatic circulation.

Long chain and short chain fatty acids

Long chain fatty acids :

Their absorption is greatest in the upper parts of the small intestine; significant absorption also occurs in the ileum.

Short chain fatty acids (SCFA)

What are they ?

These fatty acids are made up of 2 to 5 carbon chains.

Content

Their average concentration in lumen is 80 mmol/L.

Consist of

They consist of acetate (60%), propionate (25%) and butyrate (15%). Formation

They are formed by the action of ***colonic bacteria on dietary fibre***.

Dietary fiber is the material that escapes digestion in the upper GIT and enters the colon; it consists of complex carbohydrates, resisitant starches etc. Colonic bacteria act on dietary fibre to give rise to SCFAs.

Importance/functions of SCFAs

i) the ***absorbed*** SCFAs from ***colon*** are metabolized and contribute significantly to the total calorie intake.
ii) The SCFAs are trophic to the colonic epithelial cells
iii) They fight inflammation
iv) Acid-base balance : since a part of the SCFA is absorbed in exchange for hydrogen, it helps in acid-base balance

v) Helps sodium absorption by an unknown mechanism.

Absorption of cholesterol and other sterols

This occurs in the small intestine. (Sterols of plant origin are poorly absorbed; further, they decrease absorption of cholesterol). The reconstituted cholesterol in the cell is converted into chylomicrons and enters the circulation via the lymphatics.

Electrolytes

1. Sodium transport

Site : this occurs ***throughout*** the small and the large intestine.

Mechanisms

i) diffusion : some sodium diffuses into (or out of) the small intestine, depending on its concentration gradient.

ii) Secondary active transport :

- The basolateral membrane of the enterocyte has Na^+ - K^+ ATPase
- The luminal membrane has the following secondary active co-transport mechanisms
  - SGLT (Sodium-glucose)
  - Sodium-amino acid
  - Sodium-(di or tri) peptide
  - Sodium- chloride

2.Chloride transport

Chloride gets absorbed mostly by passive diffusion down its electrochemical gradient; the electrochemical gradient is established secondary to the active transport of sodium.

3.Potassium

Potassium is absorbed from the small intestine; it is ***secreted*** into the ***colon*** when the luminal potassium concentration is low. Most of the potassium movement in GIT is due to diffusion.

In the distal colon, there is a H^+ - K^+ - ATPase in the luminal membrane of cells; it moves K^+ from lumen into the cell and H^+ from cell into the lumen. In spite of the H^+ - K^+ - ATPase in the distal colon, loss of colonic or ileal fluids in chronic diarrhoea can cause severe hypokalaemia.

What happens when dietary K^+ is high for a long time?

High K^+ in the diet ----→ aldosterone gets secreted --→ inserts more Na^+ – K^+ ATPase in the basolateral membrane of the intestinal cell ---→ more K^+ moves into the cell from the interstitium ---→ K^+ moves out of the cell into the lumen by passive diffusion --→ more K^+ enters the colon

Water

Water movement in the intestine is passive, moving down its osmotic gradient.

Tonicity of chyme in GIT

i) Duodenum : Hypo- or hypertonic (depending upon the type of food taken)

ii) Rest of the intestine: ***isotonic***. There is an active absorption of electrolytes and nutrients ; this creates an osmotic gradient due to which water moves rapidly, resulting in osmotic equilibrium. Thus, fluid in the ***intestine is always isotonic*** to plasma. In other words, there is iso-osmotic reabsorption of electrolytes/nutrients in the intestine.

Mechanism of action of saline cathartics (e.g. magnesium sulphate) as laxatives :

Unlike sodium chloride, these salts are poorly absorbed from GIT; thus, .they retain water in the intestine and act as laxatives.

Mechanism of diarrhoea in cholera

Basic facts regarding the enterocyte

- the basolateral membrane has Na^+ – K^+ – Cl^- cotransporter (note : in the renal tubules, Na^+ – K^+ – Cl^- is in the luminal membrane)
- the luminal membrane has various Cl^- channels which are regulated by protein kinases
- from the Na^+ – K^+ – Cl^- in the basolateral membrane, Cl^- enters the cell from the interstitium; from the cell, Cl^- enters the lumen by Cl^- channels

In cholera, one type of Cl^- channel in luminal membrane is activated by protein kinase A and therefore by c AMP.

Reasons for diarrohoea in cholera :

1. Increased chloride secretion into the lumen :

In cholera, the c AMP concentration in the cell is increased (and therefore, many of the chloride channels remain open and chloride moves into the lumen). Although the vibrio cholerae as such stays in the lumen, a part of its toxin moves into the cell and increases the c AMP concentration in the cell. How? This can be explained in the following steps :

i) the cholera toxin binds to a receptor (called GM-1 ganglioside receptor) on the enterocyte

ii) due to this, an activated subunit of the toxin (called A^1 peptide) moves into the cell

iii) this A^1 subunit transfers ADP ribose to the alpha-subunit of G_s protein; this results in inhibition of the inherent GTPase activity of the G_s protein

iv) thus, once the G_s protein is activated, it remains active for a long time (because of inhibition of its inherent GTPase) activity

v) this causes continuous stimulation of adenylyl cyclase and thus marked increase in intracellular concentration of c AMP

2. Decreased absorption of sodium from the lumen

This occurs due to increase in c AMP.

Because of the above reasons, there is an increased sodium chloride content in lumen, which results in diarrhoea.

How is ORS (oral rehydration solution) helpful in cholera ?

The cholera toxin does ***not*** affect either the ***Na^+-K^+-ATPase or the SGLT.*** Thus, ORS (which contains sodium and glucose and uses the SGLT secondary active cotransport) is effective.

Vitamins

1.Fat soluble vitamins (i.e. A, D, E and K)

Along with the lipids, these are absorbed as a part of micelles (see above) in the upper small intestine.

2.Water soluble vitamins

Most are absorbed in the upper small intestine; ***vitamin B12*** is absorbed in the ***ileum***.

Vitamin B12 and folate absorption is ***sodium-independent*** ; other water soluble vitamins are absorbed by a sodium-dependent mechanism.

Vitamin B12

The gastric ***parietal*** cells secrete a vitamin B12- binding protein called ***intrinsic factor*** (IF). The IF-vitamin B12 complex binds to a receptor on ileal enterocyte and the complex is absorbed.

Calcium

Calcium absorption in the small intestine is ***regulated*** to maintain calcium balance. For example, absorption is increased in calcium deficiency and decreased in calcium excess. This regulation is mediated ***by 1,25 DHCC*** (this is the active derivative of vitamin D). Normally, the dietary intake of calcium is about 1000 mg; normally, about 25 to 80 % of this is absorbed.

Mechanism

Calcium absorption occurs via a membrane-bound carrier; the carrier is activated by 1, 25 DHCC

Factors affecting calcium absorption

i) 1, 25 DHCC :
   1.25 DHCC enters the enterocyte, where it inserts the calcium carrier in the luminal membrane of the enterocyte.
ii) calcium (and also magnesium) absorption is increased by protein
iii) calcium absorption is inhibited by phosphates and oxalates (because these form insoluble salts with calcium)

Iron

Site of absorption :

Almost all of iron absorption occurs in the ***duodenum***.

Forms in which iron is absorbed :

Iron can be absorbed as :

i) Haeme (as present in meat)
ii) Free ion

Ferrous ion (Fe++) is absorbed much more efficiently than ferric ion (Fe+++). Most of the dietary iron is in the ferric form. Thus, it needs to be converted into ferrous form for absorption.

Conversion of ferric to ferrous : This occurs in

- **stomach :** The stomach acid tends to break the insoluble iron complexes within the chyme and thus releases the iron from the complexes. Once the iron is free, it is converted from ferric to ferrous in the presence of ascorbic acid (***vitamin C***)
- **intestine :** In the enterocyte brush border, the transporter for iron (called DMT 1) has ferric reductase activity.

Mechanism of iron absorption

i) from lumen to cell :

- haeme is absorbed by a haeme transporter called HT
- ferrous ion is absorbed by a iron transporter called ***DMT 1*** transporter.

ii) inside the cell :

- haeme oxidase acts on haeme to release ferrous ion and porphyrin
- ferrous ion

- some ferrous ion is converted to ferric ion; the ferric ion 'combines with' an iron-binding protein called apoferritin to form ferritin (see below).

iii) from cell to interstitium :

The ferrous ion which is not converted into ferric ion is transported across the basolateral membrane by a transporter called ***ferroportin 1***; a protein called ***hephaestin (or Hp)*** helps ferroportin 1 in the basolateral transport of ferrous ion.

iv) In the plasma :

Here, ferrous ion is converted into ferric ion and is bound to the transport protein called ***transferrin***; transferrin is a beta-1 globulin.

MCQ tip

Ferrous form :

Only this form can get across the cell membrane ; the iron in haeme is in ferrous form

Ferric form :

This forms most of the dietary protein, present in ferritin, hemosiderin, transferrin.

Regulation of iron absorption

Normal absorption :

Iron absorption is necessary for maintaining normal iron balance. Very little (0.75 mg in males and 1.5 mg in females) of the 15-25 mg of iron ingested each day is actively absorbed (approximately 3 to 6% of the ingested iron is absorbed).

Iron absorption from intestine is regulated :

In iron deficiency, more iron is absorbed; in iron excess, less is absorbed. There is a close association between iron levels and the amount of ferritin and transferrin.as shown below:

- High iron levels cause ferritin to increase and transferrin to decrease.
- Low iron levels cause ferritin to decrease and transferrin to increase.

Dietary factors affecting iron absorption :

Phytic acid (which is found in cereals), phosphates and oxalates form insoluble compounds with iron in the intestine; thus, they ***decrease*** iron absorption.

Ferritin micelle :

Ferritin is the ***tissue storage form*** of iron; it is present in enterocytes and other cells.

The ferric ion and the protein apoferritin together form ***ferritin micelles***; ferritin micelles consist of ferric ion (in the form of ferric hydroxyphosphate) in the center surrounded by ***24*** subunits of apoferritin. Each ferritin micelle contains some 3000 to 4500 ferric atoms.

Significance of ferritin

i) Normally, there is very little ferritin in the plasma. However, in patients with excess iron, the amount of ferritin in the plasma increases. The amount of ***ferritin in the plasma*** can be used as an ***index of body iron stores***.
ii) Ferritin can be easily seen under electron microscope; thus, it can also be used as a ***marker*** for phagocytosis etc.

Hemosiderin molecule

This consists of aggregated deposits of partly degraded ferritin molecules in lysosomal membranes. It contains much more iron than ferritin molecule.

Ferritin molecule contains ***23% iron*** whereas the ***haemosiderin*** molecule may contain ***50%*** iron.

MCQ

Q. Enzymes from which one of the following can digest carbohydrate, lipid, protein and nucleic acids?

a. Salivary glands
b. Stomach
c. Pancreas
d. Intestine

Ans. 'c'

Enzymes from	**Help in digestion of**
Salivary and lingual glands	Carbohydrates and fats
Stomach	Proteins and fats
Exocrine pancreas	All
Cell membrane of enterocytes	Carbohydrates and proteins
Cytoplasm of enterocytes (has peptidases)	Di- and tri- and tetrapeptides.

From the lumen of the small intestine to the small intestinal cell (called enterocyte), the barriers to diffusion is/are

a. Brush border
b. Glycocalyx
c. Unstirred water layer
d. Mucous coat
e. All

Ans. 'e'

The luminal side of enterocyte is lined by brush border (made up of microvilli);
in turn, the microvilli is 'covered' by 2 layers (from lumen towards the cell) viz. :

- unstirred water layer
- glycocalyx layer (this is rich in neutral and amino sugars)

Thus, for a substance to enter the cell from the lumen, it has to cross the unstirred water layer, glycocalyx, brush border and the mucous layer.

Main enzyme for digestion of alpha-dextrin is

a. isomaltase
b. maltase
c. sucrase
d. lactase

Ans. 'a'

Isomaltase is also known as alpha-dextrinase

Substrate	Digested by (bracket shows % contribution to digestion by the enzyme)
Alpha dextrins	Alpha dextrinase (95), maltase (5)
Maltose	Alpha dextrinase (50), maltase (25), sucrase (25)
Maltriose	Alpha dextrinase (50), maltase (25), sucrase (25)

All are true of glucose absorption in the intestine except

a. It is dependent on insulin
b. It does not require phosphorylation

c. It is competitively inhibited by the drug phlorhizin
d. It occurs via SGLT

Ans. 'a'

Glucose absorption in intestine and kidney have the features mentioned above; further, they are insulin-independent.

The acid-secreting regions of the stomach secrete

b. Pepsinogen I
c. Pepsinogen II
d. Both
e. None

Ans. 'a'

Two types of pepsinogen are secreted by the stomach viz. pepsinogen I and II.
Pepsinogen I is secreted by acid-secreting regions of the stomach;
Pepsinogen II is secreted by acid-secreting regions as well as pyloric regions.
Maximum acid secretion correlates with pepsinogen I levels.

The optimum pH for pepsin action is

a. 1.6 to 3.2
b. 2 to 4
c. 6.5
d. 8

Ans. 'a';

Thus, pepsins get inactivated when the gastric contents mix with the alkaline pancreatic juice in the duodenum/jejunum.
The pH of intestinal contents
- in the duodenal cap : 2 to 4
- rest of the duodenum : 6.5 (approx.)

All the following enzymes are found in the human stomach except

a. Pepsins
b. Gelatinase
c. Lipase
d. Chymosin (also called rennin)

Ans. 'd'

Chymosin is a milk-clotting enzyme found in young animals but is not present in humans.

The final digestion of proteins to amino acids can occur in

a. Intestinal lumen
b. Brush border
c. Inside the intestinal mucosal cell
d. All

Ans. 'd'

Absorption of proteins can occur as

- Amino acids
- Di- and tripeptides; inside the enterocyte, they are then broken down to amino acids by the intracellular peptidases
- (note : protein can be absorbed as such also)

Q. Passive absorption is for

a. Carbohydrate b. Lipids
c. Proteins d. All

Ans. 'b'

Q. The maximum contribution to the total endogenous water secretion in GIT is from

a) Salivary glands b) Stomach
c) Bile d.) Pancreas e) Intestine

Ans. : 'b'

Salivary glands (1500 ml), stomach (2500 ml), bile (500 ml), pancreas (1500 ml), intestine (1000 ml), Total endogenous secretions (7000ml); exogenous i.e. ingested water (2000 ml)

Maximum water is absorbed from

a)jejunum b)ileum
c)colon d)stomach

Ans. 'a'

Jejunum (5500 ml), ileum (2000 ml), colon (1300 ml); total (8800 ml)
Very small movement of water occurs in the stomach.
Thus, out of the total input of 9000 ml of water, 8800 is absorbed; 200 ml is lost in stools. In other words, nearly 98% of the total input is absorbed. About 7500 ml gets absorbed in small intestine and only 1500 ml goes to the colon; out of this 1500 ml, 1300 ml gets absorbed in the colon.

Q. Which of the following is absorbed from colon?

a) Long-chain fatty acids
b) Bile salts

c) Sugars
d) Sodium

Ans. 'd'
Small intestine
Most substances are absorbed from small intestine.
Colon
Substances absorbed from colon :
- Sodium is absorbed in significant amounts in colon; in fact sodium (and also chloride) is absorbed throughout the small intestine and colon
- Chloride is absorbed to some extent
- ***Short-chain*** fatty acids are absorbed from colon
  (Note : ***long-chain*** fatty acids are absorbed from ***small intestine***)
  Substance secreted into colon
- Potassium : this is secreted into the colon when the luminal K^+ is low.

Q. Substances absorbed *mostly* from *lower* small intestine include
a) Bile salts
b) Vitamin b_{12}
c) Antibodies in the new born
d) All
Ans. 'd'

Q. Which substance is not absorbed from lower small intestine?
a) Sugars
b) Vitamins (except vitamin b_{12}) and sulphate
c) Amino acids
d) Sodium
Ans. 'b'
- All vitamins (***except vitamin B_{12}***) (and also sulphate) are absorbed in the upper and mid small intestine.
- Calcium, ferrous and chloride are absorbed to some extent in the lower small intestine

Q. The duodenum differs from the jejunum in that the duodenum
a. Does not absorb sugars
b. Does not absorb amino acids
c. Secretes bicarbonate
d. Does not absorb vitamins
Ans. 'c'
Another difference is that there is very little absorption of NaCl in the duodenum

Most of the iron in the body is in
a. Ferritin
b. Haemoglobin
c. Myoglobin
d. Transferrin
Ans. 'b'

	Percentage of total body iron
Haemoglobin	70
Myoglobin	3
Ferritin	27

Gastrointestinal Motility

Peristalsis
This is a reflex contraction of the gut wall to stretch (e.g. by food). It is present throughout the GIT (from the oesophagus to the rectum). Stretching the gut wall causes a wave of contraction and relaxation viz. an area of circular contraction behind the stretch and an area of relaxation in front of it. The wave moves from an oral to caudal direction and helps in moving the contents of the GIT (at a rate of 2 to 25 cm/s).

Cause/mechanism :
Peristalsis occurs due to the integrated activity of the intrinsic i.e. the enteric nervous system; however, the input from the extrinsic autonomic nervous system can increase/decrease it. If a segment of intestine is removed and the cut ends are joined in their original position, peristalsis still occurs. However, if the ends are reversed and then joined, peristalsis does not occur.

Possible sequence of events
Stretch → releases ***serotonin*** → stimulates the myenteric plexus → from the myenteric plexus, cholinergic neurons go two directions :
i) in a retrograde direction to activate neurons that release ***substance P and acetylcholine*** → these cause the ***contraction***.

ii) In an anterograde direction to activate neurons that release ***NO, VIP and ATP*** → these cause the ***relaxation*** in front of the stimulus.

BER (Basic Electric Rhythm)

Definition :

The smooth muscle of the GIT show a spontaneous, rhythmic ***fluctuations in*** their ***membrane potentials*** (between –65 mV to –45 mV); this is called ***basic electrical rhythm*** or ***BER***.

Site :

BER is present throughout GIT ***except*** the ***oesophagus*** and ***proximal*** portion of the ***stomach***.

Cause :

BER is caused by pacemaker cells called the ***interstitial cells of Cajal***.

Location of the cells of Cajal :

- stomach and small intestine → outer circular muscle layer near the myenteric plexus
- colon → submucosal border of the outer circular muscle layer

Rate of BER:

Stomach : 4/min
Duodenum : 12/min
Distal ileum : 8/min
Caecum : 9/min
Sigmoid : 16/min

Note : The rate decreases in the stomach and small intestine and increases in the large intestine.

Function

Coordination of peristalsis and other motor activity of the GIT. Proof : vagotomy or transection of the stomach wall causes the peristalsis in the stomach to become irregular.

The BER by itself rarely causes muscle contraction; however, the spike potentials superimposed on the most depolarizing portions of the BER waves cause contraction and increases muscle tension. The depolarizing phase of these spike potentials is due to calcium influx and their repolarisation phase is due to potassium efflux.

Factors affecting BER

Acetylcholine increases the number of spike potentials (and thus ***increases muscle tension***) whereas ***epinephrine*** decreases the number of spike potentials (and thus ***decreases muscle tension***)

Migrating motor complex

Definition

The motor and electrical activity of smooth muscle in GIT that ***occur*** during ***fasting*** (between periods of digestion) are called ***migrating motor complex*** or ***MMC***. They are so called because the motor activity starts from the ***stomach*** and migrates ***to*** the ***distal ileum***.

Rate

During the period of ***fasting***, MMCs move down the GIT at a regular rate of approximately ***5 cm/min***. They are completely ***inhibited*** by a ***meal;*** they ***resume 90 to 120 minutes*** after the meal.and occur at ***intervals*** of about ***90 minutes*** till the next meal.

Phases of the MMCs

Phase I : This is the first phase; it is the ***quiescent*** period with no spike potentials and no contractions
Phase II : this is a period of ***irregular*** spike potentials and contractions
Phase III : this is the last phase; it is a period of ***regular*** spike potentials and contractions

Function

This is not fully clear. There is an increase in pancreatic and gastric secretion as well as bile flow during each MMC. The function of MMC may be to ***clear the contents*** of the stomach and small intestine in between the meals. On taking ***food***, ***MMC stops*** immediately and is replaced by peristalsis and other forms of BER and spike potentials.

Gastrointestinal hormones

Classification

The GI peptides can be classified as below :

1. **Gastrin family :**
   The primary hormones in this group are gastrin and cholecystokinin (CCK)
2. **Secretin family :**
   The primary hormones in this group are secretin, glucagon, glicentin (GLI), VIP, and gastrin inhibitory peptide (GIP).
3. **Others**
   Many of the GI peptides do not belong to the above two groups e.g. somatostatin, motilin, substance P, guanylin, neuropeptide YY etc.

The GI cells secreting the GI peptides can be classfied as

1. **Enterochromaffin (or ECL)cells :**
   These cells secrete ***serotonin*** also (in addtion to secreting polypeptides)
2. **APUD (or *a*mine *p*recursor *u*ptake and *d*ecarboxylase) cells :**
   These cells secrete ***amines*** also (in addition to secreting polypeptides). Apart from the GIT, APUD cells can also be found in other organs e.g. lungs. ***Carcinoid*** tumors arise from APUD cells.

The important GI hormones are discussed below :

Gastrin

Site of production :

G cells present in ***antral*** portion of stomach.

Other sites where gastrin is found :

Foetal islets of pancreas, pituitary gland (anterior and intermediate lobes), hypothalamus, medulla oblongata, vagus and sciatic nerves

Actions

i) Stimulation of gastric acid and pepsin secretion
ii) Trophic action : gastrin stimulates the growth of mucosa of stomach, small and large intestines
iii) Stimulation of gastric motility
iv) Stimulation of insulin secretion; a protein meal (but not a carbohydrate meal) releases the amount of gastrin that is required to stimulate insulin secretion

Factors affecting gastrin secretion

1. Factors stimulating gastrin secretion

i) Gastric distension e.g. by food
ii) Protein digestion products in the stomach viz. peptides and amino acids (the amino acids phenylalanine and tryptophan are very effective stimulants)
iii) Vagal stimulation; note that in the ***G cell***, ***vagus*** releases the neurotransmitter ***GRP*** (or gastrin releasing peptide) and not acetylcholine; hence, the gastrin response to vagal stimulation is not abolished by atropine.
iv) Calcium, epinephrine

2. Factors inhibiting gastrin secretion

i) Acid :

Acid in the antrum inhibits gastrin secretion; this is another example of ***negative feedback control*** as shown below :
Gastrin → increases acid production → but, acid feeds back to inhibit further gastrin secretion

In ***pernicious anemia***, there is damage to the acid-secreting cells of the stomach. Hence, the negative feedback inhibition of gastrin by acid is not there; thus, the ***gastrin*** levels are ***increased*** in such cases.

Acid inhibits gastrin secretion in two ways :

- directly, by acting on G cells
- indirectly, by releasing ***somatostatin*** (which is a potent ***inhibitor of gastrin*** secretion)

ii) secretin, GIP, VIP, glucagons, calcitonin

Cholecystokinin-Pancreozymin (CCK-PZ)

CCK-PZ (or more commomly called CCK) is a ***single*** hormone. It is called so because, initially, it was thought that CCK and PZ were two separate hormones having two different actions; later on, it was found that both the hormones were one and the same.

Site of production

I cells of the ***upper small*** intestine.

Other sites where CCK is found

i) nerves in distal ileum and colon (and also in nerves in other parts of the body)
ii) neurons in the brain (particularly in the cerebral cortex)

Actions

i) contraction of the gall bladder
ii) secretion of pancreatic juice rich in enzymes
iii) augments the action of secretin in producing secretion of an alkaline pancreatic juice
iv) inhibits gastric emptying
v) has a trophic effect on the pancreas
vi) increases the secretion of enterokinase
vii) may increase motility of small intestine and colon
viii) together with secretin, it may increase the contraction of the pyloric sphincter (thus, preventing the reflux of duodenal contents into the stomach
ix) CCK (and gastrin) stimulate glucagons secretion (note that the secretion of both CCK and gastrin increases after a protein meal.
x) CCK in the brain may have a role in regulation of food intake; it may also have a role in the production of anxiety and analgesia.

CCK receptors

Types :

CCK-A and CCK-B receptors.

Site :

CCK-A receptors are mainly located in the periphery, whereas both CCK-A and CCK-B are found in the brain.

Mechanism of action :

Both activate phospholipase C (PLC), causing increased production of IP_3 and DAG.

Food digestion products and CCK secretion

Products of food digestion, ***particularly peptides*** and ***amino acids***, increase CCK secretion. Fatty acids (with more than 10 carbon atoms) also increase CCK secretion.

Positive feedback mechanism

CCK → increases bile and pancreatic juice secretion → more digestion of protein and fat → further increases CCK secretion

This positive feedback mechanism stops when the products of food digestion move on to the lower portions of the GIT

Secretin

Secretin was the *first hormone* to be discovered (by *Bayliss* and *Starling* in the year 1902; *Starling* coined the term *'hormone'*).

3Structure :

It is a polypeptide; M.W. : 5000, consists of 27 amino acids. Its structure is different from that of gastrin and CCK but similar to that of glucagon, VIP, GLI, and GIP. There is only one form of secretin (in other words, it does not show macroheterogeneity). It is secreted as prosecretin (inactive); it gets converted by gastric HCl and salts of fatty acids (soaps) into secretin (active).

Site of secretion:

Secretin is secreted by *S* cells present in the upper small intestine. The half-life of secretin is 5 minutes.

Actions

1. It acts on the ***duct cells*** of the pancreas and that of the biliary tract to increase bicarbonate secretion. Thus, it produces a ***watery alkaline*** pancreatic juice, but ***poor in enzymes***. Its effect on the pancreas is mediated by cAMP.
   The volume of the flow of juice is directly proportional to the dose of secretin given intravenously. As the ***volume*** of pancreatic secretion ***increases***, its ***chloride*** concentration ***falls*** and ***bicarbonate*** concentration ***rises***. This is because, bicarbonate is secreted in the small ducts but is reabsorbed in the large ducts in exchange for chloride. The magnitude of this exchange is inversely proportional to the rate of flow.
2. It potentiates the action of CCK (thus, helping in production of pancreatic secretion rich in enzymes)
3. It ***decreases*** gastric ***acid*** secretion (secretin is the body's natural antacid)
4. It may cause contraction of the pyloric sphincter and thus delay gastric emptying. This may prevent the reflux of duodenal contents into the stomach.

Factors increasing secretin secretion

1. Products of protein digestion
2. Acid in the upper small intestine

Acid released from the stomach reaches the upper small intestine and causes increased secretion of secretin; this is another example of negative feedback control as shown below :

Acid → increases secretin secretion → which causes secretion of alkaline pancreatic juice → this neutralizes the acid → decreases secretin secretion

Note :

CCK-PZ acts on acinar cells of pancreas and stimulates secretion of enzyme-rich pancreatic juice

Secretin acts on the duct cells of the pancreas and stimulates secretion of alkaline (bicarbonate-rich), watery pancreatic juice.

Vasoactive Intestinal Peptide (VIP)

Structure

It is a peptide having 28 amino acids. It is formed from its precursor prepro-VIP. Prepro-VIP has VIP and another peptide resembling VIP called PHM-27.

Site

VIP is found in the ***nerves*** in the ***GIT***, blood (where its T/2 is 2 minutes), brain and autonomic nerves. In the brain and autonomic nerves, ***VIP*** is often found along ***with acetylcholine***.

Actions

i) markedly increases the intestinal secretion of electrolytes and water
ii) relaxes the intestinal smooth muscle, including the sphincters
iii) inhibits gastric acid secretion
iv) increases action of acetylcholine on ***salivary*** glands. VIP and acetylcholine co-exist in the nerves to the salivary glands; they do not exist together in other nerves of the GIT.
v) dilates peripheral blood vessels
vi) VIP secreting tumours (called as VIPomas) cause severe diarrhoea

Enterogasterone

This is a putative (meaning as yet chemically unidentified) hormone; it could be the same as peptide YY.

Actions

It inhibits gastric acid secretion and motility; it inhibits gastrin-stimulated acid secretion.

Fat causes its release from the jejunum.

GIP (Gastric Inhibitory Polypeptide)

Structure

Like VIP, GIP is a peptide having 43 amino acids.

Site

It is produced by ***K*** cells in the duodenum and jejunum in the presence of glucose and fat.

Actions

i) inhibits gastric juice secretion and motility; hence called GIP. However, this action of GIP is seen only in high (supraphysiological) doses
ii) stimulates insulin secretion.

Response to oral glucose

- On giving oral glucose, GIP gets secreted and in turn causes release of insulin from the beta cells of the pancreas. For this reason, ***GIP*** is ***also called*** as ***glucose-dependent insulinotropic polypeptide***
- the hormones gastrin, CCK, secretin, and glucagons) are also known to release insulin; however, on giving oral glucose, they do not get secreted in enough amounts to cause insulin release
- the hormone called GLP –1 (7 –36) is a glucagon derivative. In response to oral glucose, it gets secreted from GIT; in turn it causes release of insulin. Its action in releasing insulin is more potent than that of GIP.

MCQ tip

The GIT hormones, which release ***significant insulin*** on giving ***oral glucose*** are ***GIP*** and ***GLP-1 (7-36)***

Motilin

Structure

Motilin is a polypeptide having 22 amino acids.

Site

It is secreted by ***enterochromaffin*** cells and ***Mo*** cells in the ***stomach, small intestine and colon***.

Actions

i) causes contraction of the smooth muscles of the stomach and intestine
ii) it is the ***main regulator*** of the migrating motor complexes (***MMCs***); MMCs control the gastrointestinal motility between meals (i.e. in the inter-digestive phase). The blood level of motilin increases at intervals of about 100 minutes in the inter-digestive phase.

zechanism of action

Motilin acts on *G protein*-coupled receptors present on the neurons in the duodenum and colon. rythromycin binds to these motilin receptors; thus, it may be useful in patients with decreased

gastrointestinal motility.

Neurotensin

Structure

Neurotensin is a polypeptide having 13 amino acids.

Site

It is secreted from neurons and cells in ***ileum***; its release is stimulated by fatty acids

Actions

i) inhibits GI motility
ii) increases blood flow in ileum

Somatostatin

Structure

There are two forms : somatostatin 14 and somatostatin 28.

Site

It is secreted by D cells in the islets of pancreas and by similar D cells in the GI mucosa.
(Somatostatin, which ***is the growth hormone-inhibiting hormone*** was originally isolated from the hypothalamus).
Somatostatin is secreted more into the GI lumen than into the bloodstream; this is true of other GI hormones also.

Actions

Inhibits

i) the secretion of gastrin, VIP, GIP, secretin, and motilin
ii) pancreatic exocrine secretion
iii) gastric acid secretion and motility
iv) gall bladder contraction
v) the absorption of glucose, amino acids and triglycerides
vi) as mentioned under gastrin, acid inhibits gastrin secretion; one of the ways may be as follows :

Acid → stimulates somatostatin secretion → this in turn inhibits gastrin secretion Ghrelin

Structure

It is a polypeptide having 28 amino acids.

Site

It is secreted primarily from the ***stomach***.

Actions

i) it may play an important role in the central ***control of food intake***
ii) stimulates growth hormone secretion (by a direct action on the receptors in the pituitary)

Peptide YY

Structure

It is a polypeptide having 36 amino acids. It is closely related to pancreatic polypeptide and to neuropeptide Y (which is found in the brain and autonomic nervous system). All these peptides end in tyrosine and are amidated at their carboxyl terminal.

Site

It is secreted from the jejunum; its secretion is stimulated by fat

Actions

i) it inhibits food intake
ii) it inhibits gastric acid secretion and motility

Guanylin

Structure

It is a peptide having 15 amino acids. It is so named because it binds to guanylyl cyclase. Certain strains of ***E. coli*** which produce diarrohoea secrete an ***enterotoxin*** which has a structure close to ***guanlyin***; this toxin acts on the intestinal guanylin receptor (see below) to produce diarrhoea.

Site

It is secreted by intestinal cells, from the pylorus to the rectum.

Mechanism of action

Guanylin acts on guanylin receptors. It stimulates guanylyl cyclase → this increases the concentration of intracellular cGMP → this increases the activity of the cystic fibrosis-regulated chloride channel → which causes increased secretion of chloride into the intestinal lumen

Actions

i) it increases chloride secretion into the intestinal lumen and thus may regulate fluid movement. It acts in the GIT in a paracrine fashion.
ii) Guanylin receptors are also found in the kidneys, the liver, and the female reproductive tract; here, it may be act in an endocrine fashion to regulated fluid movement in these tissues.

More text through MCQs

In the GIT, skeletal muscle is present in

a. Stomach
b. Oesophagus
c. Small intestine
d. Large intestine

Ans. 'b'

Upper 1/4th of oesophagus : has striated muscle
Middle portion : has both striated and smooth muscle
Distal portion : has only smooth muscle

Q. The innervation of the intestinal blood vessels is from

a. The intrinsic enteric nervous system
b. The extrinsic sympathetic nervous system
c. Both
d. None

Ans. 'c'

The extrinsic sympathetic fibres :
These secrete norepinephrine and cause vasoconstriction.
The intrinsic enteric nervous system fibres :
These secrete many different substances. For example, many of them secrete ***VIP and NO***; these cause the ***hyperemia*** that occurs during digestion of food.

Q. What is true regarding gastrin ?

a) It shows macroheterogeneity
b) It shows microheterogenity
c) It is mainly inactivated in the kidney and small intestine
d) It is formed from its precursor, preprogastrin
e) All

Ans. 'e'

Macroheterogeneity :

This general term refers to a polypeptide hormone that is secreted in different forms due to the difference in the ***number*** of amino acids in them . For example, gastrin is secreted in many forms (all these forms have the same carboxyl terminal configuration) :

- G 14, G 17 and G 34 are the main forms (the number refers to the number of amino acid residues in the gastrin molecule); ***G 17*** is the ***main*** form with respect to gastric ***acid*** secretion.
  T/2 of
  G 14 and G 17 : 2 to 3 minutes
  G 34 : 15 minutes
- One form has more than 45 amino acids

- Another form is the carboxyl terminal tetrapeptide (this has all the actions of gastrin; however, it is only 1/10th as potent as G 17)

Microheterogeneity

This general term refers to a polypeptide hormone that is secreted in different forms due to derivatisation (e.g. addition of a sulphate) of a single amino acid residue; thus the number of amino acids is the same in these different forms. For example, there are two groups of gastrins : one in which the tyrosine (in the 6th position from the carboxyl terminal) is sulphated and the other in which it is not . In other words, there are sulphated and non-sulphated gastrins. In the case of gastrins, the sulphated and the non-sulphated forms are in equal amounts and they are equally active.

Q. Which of the following is/are true regarding CCK?

b. Like gastrin, it shows micro- and macroheterogeneity
c. Its T/2 is about 5 minutes
d. It is secreted by I cells in the upper small intestine
e. All

Ans. 'd'

CCK is formed from its precursor prepro-CCK. The various forms of CCK are :
CCK 58, CCK 39, CCK 33, CCK 12, CCK 8, CCK 4 (the numbers indicate the number of amino acids);
Unlike gastrin, the non-sulphated form of CCK is not found in the tissues.
The CCK secreted in the duodenum and jejunum is mostly CCK 8 and CCK 12.
The enteric and pancreatic nerves contain primarily CCK.
CCK 58 and CCK 8 are found in the brain.

Q. Vagal stimulation increases gastrin secretion. This is mediated by

a. GRP or gastrin-releasing peptide
b. Acetylcholine
c. Glucagon
d. Substance P

Ans. 'a'

The vagal endings on the gastrin-producing G cells secrete ***GRP*** and ***not acetylcholine***; the GRP mediates the gastrin release from the G cells. GRP has 27 amino acids; out of this, the 10 amino acids at the carboxyl terminal are almost same as ***bombesin*** (a peptide found in amphibians).

Substance P is found in cells and neurons of the GIT; it increases the motility of the small intestine.
(Both GRP and substance P may enter the circulation)
Apart from the pancreas, glucagon is secreted by the GIT; this may be partly responsible for the hyperglycemia that occurs after pancreatectomy.

Pancreas

The pancreas has portions : exocrine and endocrine. In this section, the exocrine portion is discussed.
The exocrine portion secretes the pancreatic juice which contains enzymes important in digestion .

Functional anatomy

The exocrine cells have abundant rough endoplasmic reticulum and ***zymogen granules*** at the apexes of the cells. The zymogen granules contain the enzymes. Secretion from them is emptied (by exocytosis) into small ducts; these small ducts join to form the pancreatic duct of ***Wirsung***. The duct of Wirsung joins the common bile duct to form the ***ampulla of Vater***. The ampulla of Vater opens into the duodenum through the duodenal papilla. The opening of ampulla of Vater is surrounded by a sphincter called the sphincter of ***Oddi***. Some individuals have an accessory pancreatic duct (called the duct of ***Santorini***); the duct of Santorini opens into the duodenum proximal to the opening of the ampulla of Vater.

Pancreatic juice

It is a colourless, odourless watery secretion isotonic with plasma. It is alkaline with a high bicarbonate content of about 113 meq/L. (plasma bicarbonate content is about 24 meq/L). About 1500 mL of pancreatic juice is secreted per day. The alkaline pancreatic juice, along with bile and intestinal juice (which are also neutral or alkaline), helps in neutralizing the gastric acid and raising the pH of the duodenal contents to about 6.0 to 7.0. Thus, by the time the chyme reaches the jejunum, its reaction is nearly neutral, but the intestinal contents are rarely alkaline.

Composition of the pancreatic juice

1. Inorganic constituents :

i) Cations : Na^+, K^+, Ca^{2+}, Mg^{2+}
ii) Anions : $HCO3^-$, Cl^-, $SO4^{2-}$, $HPO4^{2-}$

2. Organic constituents

i) mucous
ii) enzymes (refer chapter)
iii) trypsin inhibitor

Conversion of the inactive proenzymes into active enzymes

The enzymes of the pancreatic juice are secreted as inactive proenzymes as follows :

i) Trypsinogen → to tryspin

Trypsinogen is converted to the active enzyme trypsin by the brush border enzyme ***enteropeptidase (enterokinase)*** when the pancreatic juice enters the ***duodenum***. Enteropeptidase has a high polysaccharide content (of about 40%); this high polysaccharide content apparently prevents it from being digested itself before it can exert its effect.

ii) Conversation of other inactive pancreatic proteases into active forms

All the other inactive forms (e.g. chymotrypsinogens, proelastase, procarboxypeptidases) are converted into their active forms by ***trypsin***. Trypsin can also activate trypsinogen; therefore, once some trypsin is formed, there is an auto-catalytic chain reaction.

Enteropeptidase deficiency occurs as a congenital abnormality and leads to protein malnutrition.

Trypsin inhibitor

This is secreted by the pancreas in the pancreatic juice. It is a polypeptide with a molecular weight of about 5000 to 6000.

Action : It inhibits both trypsin and chymotrypsin.

Function

Trypsin is a very powerful enzyme by itself and also converts the other inactive pancreatic enzymes into their powerful active forms. The conversion of trypsinogen to trypsin occurs in the duodenum by enteropeptidase. However, it is possible that some trypsin may get activated within the pancreas itself. This would lead to autodigestion of the pancreas. Trypsin inhibitor ***prevents*** this ***autodigestion*** by trypsin.

Trypsin and acute pancreatitis

One of the enzymes activated by trypsin is phospholipase A_2. Phospholipase A_2 converts lecithin to lyso-lecithin (by removing a fatty acid). ***Lysolecithin damages*** cell membranes.

Lecithin is a normal constituent of bile. It is possible that acute pancreatitis, phospholipase A_2 is activated in the pancreatic ducts; this in turn forms lysolecithin from lecithin. Lysolecithin damages the pancreatic tissue.

Small amounts of pancreatic digestive enzymes normally leak into the circulation, but in acute pancreatitis, the circulating levels of the digestive enzymes rise markedly. Measurement of the plasma amylase or lipase concentration is therefore of value in diagnosing the disease.

Regulation of pancreatic secretion

Secretion of pancreatic juice is ***primarily*** under the ***hormonal*** control of ***secretin and CCK-PZ***.

i) Actions of secretin :

- Acts on the pancreatic ***ducts*** to cause ***copious*** secretion of a very ***alkaline*** pancreatic juice that is rich in HC03 and ***poor in enzymes***; its effect is mediated by cAMP.
- Stimulates bile secretion.

ii) Actions of CCK-PZ

- Acts on the ***acinar cells*** and causes discharge of the zymogen granules; it causes ***low volume*** secretion of pancreatic juice that is ***rich in enzymes***; its effect is mediated by phospholipase C

Other hormones/factors

i) Gastrin

This plays a minor role in pancreatic secretion. It acts in two ways :

- **Direct action :** it stimulates the pancreatic acinar cells directly and increases acinar secretion
- **Indirect action :** it stimulates the parietal cells and increases HCl secretion; HCl in turn enters the duodenum and releases both secretin and CCK-PZ. This causes increase in enzymes, bicarbonate and water output.

ii) VIP

VIP stimulates pancreatic secretion mainly rich in enzymes. It also stimulates intestinal secretion of electrolytes and water.

iii) Vagal stimulation

This causes secretion of a small amount of pancreatic juice rich in enzymes. The acetylcholine released acts directly on the acinar cells to cause discharge of the zymogen granules; like CCK, acetylcholine acts on via phospholipase-C. There is evidence for vagally mediated conditioned reflex secretion of pancreatic juice in response to the sight or smell of food.

More text through MCQs

Q. Intravenous injection of secretin will cause the following changes in the pancreatic juice secretion except

a. Secretion of copious volume of pancreatic secretion
b. Bicarbonate content increased markedly
c. Chloride content decreases markedly
d. Amylase content increases markedly
e. Potassium content does not change much

Ans. 'd'

As the volume of pancreatic secretion increases, its Cl^- concentration falls and its HC03 concentration increases. Why? This is because although HC03 is secreted in the small ducts, it is reabsorbed in the large ducts in exchange for Cl^-. The magnitude of the exchange is inversely proportionate to the rate of flow.

The enzyme content in the pancreatic juice decreases with secretin.

Salivary Secretion

This is the first juice coming in contact with food. It is secreted by the salivary glands. The salivary glands are located outside the GIT. Food mixes with the saliva on chewing (or ***mastication***).

The main salivary glands are the parotid, ***submaxillary*** (***also called submandibular***) and sublingual glands. The minor salivary glands are lingual, labial, buccal and palatine glands.

Depending on the secretion and histological appearance, there are two types of acini in the salivary glands. These are

Serous acini:

Their cells have round nuclei with collection of secretory (***zymogen***) granules at their apexes; these secrete thin watery saliva rich in ***enzymes*** (ptyalin) .

Mucous acini :

Their cells have flattened basal nuclei; these secrete thick viscous saliva rich in mucin

Demilunes : sometimes, the mucous acini have caps of serous acini over them; these ***caps*** (crescentic in shape) ***of serous acini over the mucous acini*** are called ***demilunes***.

Table showing the histological type and the percentage contribution of the different salivary glands to total saliva

Gland	Histological type	Secretion	% contribution of total saliva
Submaxillary	Mixed	Viscous	***70***
Parotid	Serous	Watery	20
Sublingual	Mucous	Viscous	***5***
Other glands			5

Composition of saliva

Volume

This is about ***1.5 litres/24 hours*** at a rate of about ***1ml/min***. The rate of secretion is maximum during meals and minimum during sleep

pH

Resting salivary glands : slightly ***less than 7***

During ***active*** secretion : approaches ***8***

Osmolality

Hypotonic to plasma

Constituents

Water : 99.5%
Solids : 0.5%
Organic : 0.3 %
Inorganic : 0.2%

Ductal modification

The salivary juice formed in the acini first drains into ducts called intercalated ducts. The intercalated ducts drain the salivary juice into another type of ducts called striated ducts; these finally open into the oral cavity. As the saliva flows through these ducts, its composition gets modified.

The ***saliva first*** formed in the acini (also called as primary secretion) is ***isotonic*** with plasma and its ionic composition is approximately same as that of plasma. However, as this saliva flows through the ducts,

i) ***Na*** and ***Cl*** gets ***absorbed***
ii) ***K*** and ***HCO3-*** is ***added***
iii) It becomes ***hypotonic*** (this is because the ducts are relatively impermeable to water)

Thus, the final composition of the saliva secreted in the oral cavity depends on the rate of salivary flow through the ducts. More the rate of flow, less will be the ductal modification.

At low rates

The saliva is hypotonic, slightly acidic, and rich in K; but has less Na and Cl

At high rates

The saliva is still hypotonic (but closer to isotonic), with higher concentrations of Na and Cl.

Effect of aldosterone on ductal modification

Its action on the salivary ducts is similar to its action on the collecting ducts of the kidney i.e. it increases Na absorption and increases K secretion. Thus aldosterone increases the K concentration and decreases the Na concentration of saliva. In ***Addison's*** disease (where aldosterone is less), there is a high ***Na/K*** ratio in the ***saliva***.

Enzymes in the saliva

1. **Salivary alpha amylase or ptyalin :**
   This is produced by the salivary glands; it acts on starch and converts it into alpha limit dextrins and maltase. Its optimum pH is ***6.8*** and it is activated by chloride ions.
2. **Lingual lipase**
   This is produced by the ***Ebners glands*** present on the ***dorsum*** of the ***tongue***. It becomes active in the stomach and can digest as much as 30% of ingested triglycerides.

Other constituents of the saliva

i) Mucins :
These are glycoproteins produced by the mucous acini of the salivary glands. Their function is to lubricate the food and help in food bolus formation; they also bind bacteria and protect the oral mucosa.

ii) IgA
The secretory immunoglobulin IgA is present in the saliva; it helps to fight against bacteria and viruses.

iii) Lysozymes :
These are groups of enzymes which attack the walls of bacteria and destroy them

iv) Lactoferrin :
This binds ***iron*** and is bacteriostatic

v) proline-rich proteins
These protect tooth enamel and bind toxic tannins

vi) Kallikrein
This enzyme present in the saliva acts on alpha 2 globulin to produce bradykinin; bradykinin is a polypeptide which causes vasodilatation.

vii) Nerve growth factor
This is a polypeptide produced by the submaxillary salivary gland. It is useful for the growth and maintenance of the sympathetic and sensory nerves.

viii) Sialogastrin
This is a gastrin-like substance present in the saliva

Functions of saliva

i) Preparation of the food for swallowing (bolus formation) :
Saliva mixes well with the food and the mucus present in the saliva acts as a lubricant. Food is made into a bolus, which can be easily swallowed.

ii) Solvent
To appreciate the sensation of taste, food has to be dissolved. Saliva acts as a Solvent which dissolves the food materials and helps in stimulating the taste buds.

iii) Speech
Saliva keeps the oral cavity moist; it helps in the movements of the lips and tongue. These factors help in speech.

iv) cleansing action
Continuous secretion of saliva washes off the food residues, bacteria and desquamated epithelial cells. Lysozymes present in the saliva destroy bacteria. Thus, saliva cleans the oral cavity/teeth and helps in oral hygiene. Patients suffering from ***xerostomia or atyalism*** (deficient salivation) have more chances of dental infection than normal people.

v) Digestion
Salivary alpha amylase helps in starch digestion

vi) Excretion
Saliva excretes mercury, lead and KI compounds.

vii) Buffers in saliva
These help to maintain the oral pH at about 7.0. They also help neutralize gastric acid and relieve heartburn when gastric juice is regurgitated into the oesophagus.

Regulation of salivary secretion

Salivary secretion is ***exclusively*** under ***neural*** control; both sympathetic and parasympathetic nerves supply the salivary glands.

Sympathetic nerves

These fibres arise from T_1 to T4 segments of the spinal cord and reach the superior salivary ganglion. Post-ganglionic fibres start here and run along the blood vessels and supply all the salivary glands. The sympathetic fibres supply the blood vessels, the myoepithelial (or basket) cells and acinar cells.

Actions

i) Sympathetic stimulation causes secretion of ***small*** amounts of ***thick, viscous*** saliva ***rich*** in ***organic*** constituents from the ***submandibular*** glands. Increased salivary secretion

Mechanism of action

Sympathetic stimulation /circulating catecholamines stimulate salivary secretion rich in enzymes through alpha and beta receptors. Alpha receptor action is mediated through calcium ions and beta receptor action is mediated through cyclic AMP.

ii) Vasoconstriction
The norepinephrine released brings about vasoconstriction and decreased blood flow; thus, the water content of the secretion is less.

iii) The myoepithelial (or basket) cells contract under the influence of norepinephrine and cause expulsion of the already secreted saliva from the acinus.

Parasympathetic nerve fibers

These come from a nucleus present at the junction of the medulla and pons near the tractus solitarius. The nucleus has got two parts :

i) The caudal part (called *inferior salivary nucleus*) :
This provides parasympathetic nerve fibres to acinar cells and blood vessels of ***parotid gland***. These fibres pass via the ***IX*** (i.e. glossopharyngeal) nerve

ii) The superior part (called *superior salivary nucleus*) :
This provides parasympathetic fibres to the acinar cells and blood vessels of the ***submaxillary and sublingual*** glands. These fibres pass through the ***VII*** (i.e. facial) nerve and the chorda tympani nerve.

Pain afferents from these glands run in the parasympathetic nerves.

Actions

Stimulation of the parasympathetic nerve fibres results in ***profuse*** secretion of ***watery*** saliva with a relatively ***low*** content of ***organic*** material. Along with this secretion, there is a significant ***vasodilation*** in the salivary glands; the vasodilation is likely to be due to ***VIP***. (VIP is a co-transmitter with acetylcholine in some of the post-ganglionic parasympathetic neurons). Atropine and other cholinergic blocking agents reduce salivary secretion.

Mechanism of action of parasympathetic nerves

i) Acetylcholine (Ach) released from the nerve endings directly act on the acinar cells and stimulate enzyme secretion
ii) Ach activates kallikrein; kallikrein in turn activates kininogen and converts it into bradykinin. Bradykinin produces vasodilatation and increases the blood flow to the gland
iii) VIP is a co-transmitter released along with Ach and causes vasodilatation.

Types of salivary secretion

1. Spontaneous or resting salivary secretion
Saliva is secreted continuously even in the absence of any known stimulus; this is called spontaneous or resting salivary secretion. This is possibly due to release of minute amounts of acetylcholine into the gland. However, spontaneous secretion cannot be blocked by atropine. It can, however, be blocked by metabolic poisons like cyanide. This indicates that the spontaneous salivary secretion depends upon the metabolic activity of the salivary glands. This type of secretion is responsible for keeping the oral cavity moist all the time.

2. Reflex secretion
This occurs in response to a stimulus. The reflex secretion can be further subdivided into

i) unconditioned (or inherent)reflex secretion
Food (and other substances) in the mouth causes reflex secretion of saliva (also, stimulation of the vagal afferent fibres at the gastric end of the oesophagus results in reflex secretion of saliva)

Pathway

Food in the mouth → stimulates the trigeminal, glossopharyngeal and vagal nerves → impulses in them are carried to the superior and inferior salivary nucleus → reflex salivation

ii) conditioned (or acquired) reflex secretion
Salivary secretion can be easily conditioned (as shown by Pavlov); the sight, smell or even thought of food causes salivary secretion.

Deglutition or Swallowing

This is the process by which the chewed food is emptied form the mouth into the stomach. It is *initiated voluntarily but* **is** *completed reflexly.*

Pathway

Deglutition is initiated by afferent impulses in V, IX and X cranial nerves → impulses from there are carried and integrated in the nucleus of the tractus solitarius and the nucleus ambiguus → from here, efferent fibres pass to the muscles of the pharynx and tongue via the V, VII and XII cranial nerves.

Mechanism

Swallowing is initiated by the voluntary action of passing the bolus of food with the help of the tongue to the pharynx; thereafter, the process occurs reflexly. When food reaches the pharynx, it starts a wave of involuntary contraction in the pharyngeal muscles; this pushes the food into the oesophagus. Peristalsis in the oesophagus pushes the food down the oesophagus at a rate of about 4 cm/second. However, in the upright position, gravity pulls the liquid/semisolid food to the lower end of the oesophagus faster than the wave of peristalsis.

Other components of the swallowing reflex

i) inhibition of respiration
ii) closure of glottis

Gastro-oesophageal junction

This performs the function of a sphincter. Its functions are

i) to cause orderly flow of food from the oesophagus into the stomach
ii) to prevent reflux of gastric contents into the oesophagus

The gastro-oesophageal junction is made up of 3 components :

i) Intrinsic sphincter or the *lower oesophageal sphincter (LES)* :
This is formed by the oesophageal smooth muscle at its lower end; the LES (unlike the rest of the oesophagus) is ***tonically active***; however, it ***relaxes*** on ***swallowing***. The tonic activity of the LES (in between meals) prevents reflux of gastric contents into the oesophagus.

ii) extrinsic sphincter
This is made up of skeletal muscle fibres of the ***crural*** portion of the ***diaphragm***; these fibres surround the oesophagus (at the point where it enters the diaphragm) and exert a pinchcock-like action on the oesophagus.

iii) Flap valve :
The oblique (or sling) ***fibres*** of the ***stomach*** wall create a flap valve at the gastrooesophageal junction; this valve helps to close the junction whenever the intragastric pressure rises (and thus prevents regurgitation)

Control of the gastro-oesophageal junction

This is under ***neural*** control.

1. Control of internal sphincter i.e. LES

The tone of LES is under neural control from the ***vagus***.

i. the vagal endings which release ***acetylcholine*** → cause ***contraction*** of the internal sphincter
ii. the vagal endings (via interneurons) which release ***NO*** and ***VIP*** → cause ***relaxation*** of the internal sphincter

2. Control of external sphincter i.e. the crural portion of the diaphragm

This is under neural control from the ***phrenic nerves***. The contraction of the crural portion of the diaphragm is coordinated with respiration and contractions of the chest and abdominal muscles.

Clinical correlates

1. Achalasia

This is the name given to the condition in which food accumulates in the oesophagus; due to this, the oesophagus becomes dilated.

Cause :

i) the myenteric plexus of the oesophagus at the LES is deficient
ii) there is defective release of NO and VIP.

Because of the above,

i) there is increased resting tone in the LES
ii) the LES does not relax fully on swallowing

Management

i) pneumatic dilation of the LES
ii) myotomy (incision of the oesophageal muscle)
iii) injection of botulinum toxin into the LES (this acts by inhibiting release of acetylcholine)

2. Gastro-oesophageal reflux disease (GERD)

As the name suggests, in this condition there is reflux of acid gastric contents into the oesophagus. It is due to LES incompetence (thus, it is the opposite condition to achalasia, in which there is increased tone of LES).

Symptoms

i) heart burn and oesophagitis
ii) there can be ulceration and stricture formation (due to scarring of the tissue) in the oesophagus
iii) in severe cases, the internal/external sphincter are weak
iv) in less severe cases, there are intermittent periods where there is less neural drive to these sphincters; the cause of this is not known.

Treatment

i) H2 receptor blockers (omeprazole) : this inhibits acid secretion
ii) Fundoplication : In this surgical procedure, a portion of the fundus of the stomach is wrapped around the lower oesophagus → thus, the oesophagus is made to lie inside a short tunnel of stomach

Pharyngo-oesophageal sphincter

The sphincter at the upper end of the oesophagus is called the pharyngo-oesophageal sphincter. It is formed by the tonic contraction of the ***crico-pharyngeus*** muscle. It is ***normally closed except*** during ***swallowing***. It prevents the entry of air from the mouth into the oesophagus. However, during the act of swallowing (e.g. drinking, eating) some air is swallowed; this is called ***aerophagia*** ('air eating'). Out of the air that is swallowed, some is regurgitated through the mouth during belching, some is absorbed but much of it is passed on to the colon. In the colon, some oxygen from the swallowed air is absorbed; colonic bateria act on carbohydrate and other substances to produce hydrogen, hydrogen sulphide, carbon dioxide, and methane. These latter gases are thus added to the air and passed as flatus. The smell in the flatus is mostly due to the sulphides. Normally, the GIT has about 200 ml of gas; about 500 to 1500 ml of gas is produced/day. In some individuals, gas in the intestine can cause cramps, rumbling noises (these rumbling noises are called as ***borborygmi***) and abdominal discomfort.

More text through MCQs

Q. Regarding swallowing, which is/are true?

a. it is almost impossible to swallow when the mouth is kept open
b. a normal adult swallows about 600 times per day
c. During swallowing, there is cessation of respiration (deglutition apnoea)
d. All

Ans. 'd'

Total number of swallows per day : 600
Out of this,
i) along with eating/drinking : 200
ii) while awake without food : 350
iii) while sleeping : 50

Stomach

Parts of the stomach

Cardia or cardiac orifice :
The part where the oesophagus enters the stomach is called the cardiac orifice or cardia. Fundus :
The portion of stomach which lies above the cardiac orifice is called the fundus.

Body :

The portion of the stomach below he fundus is called the body of the stomach.

Pyloric antrum or antrum/pyloric sphincter

At the end of the body of the stomach is the pyloric antrum or simply called the antrum. The pyloric antrum leads into the pyloric canal. The pyloric canal opens into the duodenum and the opening is guarded by a sphincter called pyloric sphincter.

Incisura angularis

A small notch on the lesser curvature between the body and the pyloric antrum is called incisura angularis.

A straight line from the incisura angularis to the greater curvature separates the pyloric antrum from the body.

Gastric glands

The shape and structure of the gastric glands is different in different parts of the stomach. In the fundus and the body, the glands are long and straight. In the pylorus and in the cardiac area, the glands are short and tortuous.

Four different types of cells are present in the gastric glands; these are :

i) Parietal or oxyntic cells
ii) Chief or zymogen cells
iii) Mucous cells
iv) Argentaffin cells

i) In the cardiac and pyloric regions

Here, the glands secrete mucous

ii) In the body and fundus

Here, the glands ***also*** contain

- ***parietal*** (***or oxyntic*** cells) → which secrete ***HCl*** and ***intrinsic factor*** and
- ***chief*** or ***zymogen*** or ***peptic*** cells → which secrete ***pepsinogens***

These secretions mix with ***mucus*** secreted by the cells in the ***neck*** of the glands. Many such glands open on the gastric pit; the gastric pit in turn opens on the surface of the mucosa.

iii) Surface epithelium

The surface epithelium contains mucous cells; these secrete ***mucous*** and ***bicarbonate***.

Food is stored in the stomach, mixed with acid, mucus and pepsin, and released at a controlled steady rate into the duodenum.

Function of HCl

i) Kills many ingested bacteria
ii) Provides the necessary ph for pepsin to start protein digestion
iii) Stimulates the flow of bile
iv) Activates pepsinogen to pepsin

Blood supply and lymphatic supply

The stomach has a very rich blood and lymphatic supply. Blood is supplied by the cardiac arteries. Lymph drains into the gastro-duodenal group and celiac group of lymph glands.

Nerve supply

Sympathetic

This is from the celiac plexus; the sympathetic supply causes

i) Relaxation of the muscle
ii) Contraction of the sphincters
iii) Vasoconstriction

Parasympathetic

This comes from the dorsal nucleus of the vagi located in the floor of the fourth ventricle. The right vagus supplies the posterior surface and the left vagus supplies the anterior surface. They synapse with the myenteric and Meissner's plexuses. Post-ganglionic fibres start from here and supply the gastric glands.

The parasympathetic supply causes

i) Contraction of the muscle

ii) Relaxation of the sphincter

Local nervous system

These are the myenteric and Meissner's plexuses. Peristalsis is mainly coordinated by the local plexus.

Gastric juice

Amount = about 2500 ml per day;

During meals, the gastric secretion is maximum and during sleep, it is minimum.

pH = about 1.0

Composition

The contents of the normal gastric juice in the fasting state are

i) Inorganic :

Cations are Na, K, Mg, ***H***;

Anions are ***Cl-***, $HPO4^{2-}$ SO_4^{2-}

ii) Organic

Pepsins, lipase, mucus, intrinsic factor

HCl secretion

As mentioned above, HCl is secreted by the parietal cells.

Content of H in parietal cell secretion

Pure parietal secretion has pH of about 0.87 and contains 0.17 N HCl. It is isotonic with plasma (with 150 meq of H and 150 meq of Cl per liter).

Note

The pH of the cytoplasm of the parietal cells is 7.0 to 7.2

Plasma : H concentration = 0.00004 meq/L ; Cl concentration = 100 meq/L

The above-mentioned figures show that there is a very large H gradient against which the parietal cell has to secrete H; thus, the transport mechanism is ***active***. The active transporter is ***H – K ATPase***.

Structure of the parietal cell

The parietal cell has

i) Apical membrane

This faces the lumen of the gastric glands; it contains the H-K ATPase

ii) Canaliculi

The resting cell has intracellular canaliculi, which open on the apical membrane of the cell

iii) Tubulo-vesicular structures

At rest

The parietal cells contain abundant tubulo-vesicular structures; these structures contain H-K ATPase in their walls.

During stimulation of the parietal cells

a) The tubulovesicular structures move to the apical membrane and fuse with it; this helps in inserting many more H-K ATPase molecules into the apical membrane. These H-K ATPase molecules are now exposed to the K in the ECF; this activates the H-K ATPase and the H-K exchange begins.

b) Many microvilli project into the canaliculi; this greatly increases the surface area of the cell membrane in contact with the gastric lumen.

iv) Basolateral membrane

This is in contact with the interstitial fluid.

Mechanism of HCl secretion

1. Secretion of H secretion

As mentioned above, this is done by H-K ATPase.

The H is initially formed inside the parietal cell as follows :

$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO3^-$

The above reaction is catalyzed by carbonic anhydrase; the parietal cells a high content of carbonic anhydrase.

The $HCO3^-$ is extruded from the basolateral membrane into the interstitial fluid in exchange for Cl^- (by $HCO3^- – Cl^-$ antiport).

Because of the efflux of HCO3 into the blood, the stomach has a negative respiratory quotient; in other words, the amount of CO2 in the arterial blood is greater than the amount in gastric venous blood. When gastric acid secretion is elevated after a meal, sufficient H may be secreted to raise the pH of systemic blood and make the urine alkaline ***(post-prandial alkaline tide***)

2. Secretion of Chloride

Chloride is extruded down its electrochemical gradient into the lumen through channels that are activated by cAMP.

In the gastric lumen, the H and Cl combine to form HCl.

Factors affecting HCl secretion

1. HCl stimulants

i) Histamine

This stimulates acid secretion by acting via H_2 receptors → the H2 receptors stimulate G_s protein → increases adenylyl cyclase activity → increases intracellular ***cAMP*** → stimulates protein kinases → stimulates H-K ATPase → increases HCl output

ii) Acetylcholine

This stimulates acid secretion by acting via M_3 muscarinic receptors → this in turn increases intracellular free ***calcium*** → stimulates protein kinases → stimulates H-K ATPase → increases HCl output.

iii) Gastrin

Gastrin increases HCl output in two ways :

- **Direct action :**

via the gastrin receptors on the parietal cells → this in turn increases intracellular free ***calcium*** → stimulates protein kinases → stimulates H-K ATPase → increases HCl output.

- **Indirect action (*via ECL* cells)**

This is the ***main way*** by which gastrin increases HCl secretion.
Gastrin stimulates the gastrin receptors on the enterochromaffin-like (ECL) cells.

ECL cells :

These are the vesicle- and granule containing cells; the ECL cells are the predominant endocrine cell type in the acid-secreting portion of the stomach.
Stimulation of ECL cells → stimulates histamine secretion → which in turn stimulates HCl secretion.
ECL cells undergo hypertrophy when gastric acid secretion is suppressed for prolonged periods.
The different intracellular mediators interact with each other; thus, activation of one receptor type potentiates the response of another receptor type.

2. HCl inhibitors

i) Somatostatin : this inhibits ECL cells.
ii) PGE2 : acts via G_i to decrease adenylyl cyclas222e activity and decrease intracellular cAMP.
iii) EGF and TGF □□□: these also act via G_i.
iv) High acidity, H_2 blockers, and atropine also decrease
HCl secretion.

Organic constituents of the gastric juice

1. Mucous

This is of two types

a) insoluble or visible mucous : it is a polymer of glycoprotein with a high viscosity; it is secreted by the ***surface epithelial cells*** and forms a 0.5 to 2.5 mm thick layer. It protects the gastric mucosa from the acid.
Non-parietal secretion includes the mucous, enzymes, and electrolytes. When HCl combines with either salts or other substances, it gets neutralized and produces neutral chloride.

b) soluble mucous : this is secreted by the ***mucous neck cells*** and acts as a vehicle for HCl and other enzymes secreted by the gastric glands.

2. Intrinsic factor

This is secreted by the parietal cells. It is a glycoprotein required for the absorption of vitamin B12. Its deficiency leads to pernicious anaemia. Its secretion is stimulated by acetylcholine, gastrin and histamine.

3. Enzymes : pepsin, gelatinase, carbonic anhydrase, rennin, lipase, urease

i) **Pepsin :** this is secreted by the chief cells in the inactive form as pepsinogen. Pepsinogen is activated to pepsin by HCl and pepsin itself. Molecular weight = 35000; optimum pH for activity is 1. 5 to 3.5. Beyond 3.5, pepsin is inactivated. Secretion of pepsin is stimulated by vagus, acetylcholine, gastrin, histamine and insulin. Pepsin is an endopeptidase; it acts on denatured proteins and converts them into proteoses, peptones and a few amino acids. It attacks the peptide linkages in which the amino groups are attached to the aromatic amino acids.
ii) **Rennin :** this is important in calves and human infants. Origin is not known. It is suggested to be produced by chief cells. It acts on milk in the presence of calcium and causes its precipitation. It is **absent in adult humans and cows where its function is taken over by HCl and pepsin**
iii) **Gelatinase :** causes digestion of gelatin
iv) **Lipase :** acts chiefly on tributyrin and other low molecular weight triglycerides. Its origin in humans is not known. It is active between 4 to 5 pH and is inactive below pH 2.5. It is a weak fat-splitting enzyme and becomes important for fat digestion only when there is pancreatic insufficiency.
v) **Carbonic anhydrase :** derived from the parietal cells
vi) **Urease :** origin not known; converts urea into ammonia

Note : Salivary amylase can act in the stomach and converts starch into maltose till it is inactivated by gastric acidity. It is inactivated within 30 to 60 minutes.

Gastric mucosal barrier

This protects the stomach from getting damaged by the acid in gastric juice. The mucosal barrier is made by

i) The mucus and
ii) The $HCO3^-$.

i) Mucus :

Source :

- Neck cells of the gastric glands and
- surface mucosal cells.

Composed of Mucus is made up of glycoproteins called mucins; the mucins form a flexible gel on the gastric mucosa.

ii) **HCO3-**

Source :

Surface mucosal cells
HCO3- trapping
Most of the secreted HCO3 is ***trapped*** in the mucus gel.

Because of this, a pH gradient is established at the epithelial cells as follows :

- on the luminal side : the pH is 1.0 to 2.0
- at the surface of the epithelial cells : the pH is 6.0 to 7.0.

HCl secreted by the parietal cells in the gastric glands crosses this barrier in finger-like channels, leaving the rest of the gel layer intact.

Mucus and HCO3- secreted by mucosal cells also play an important role in protecting the duodenum from damage when acid-rich gastric juice is secreted into it.

Factors affecting mucus/HCO3- secretion

Prostaglandins stimulate mucus secretion.

HCO3- secretion is also stimulated by prostaglandins and by local reflexes.

Other factors which protect the gastric mucosa

Trefoil peptides

Some of the resistance of the mucosa of the GIT to autodigest is also provided by ***trefoil peptides*** in the gastric mucosa.

These are of several types and are acid-resistant.

Other places where trefoil peptides are found :

i) Hypothalamus
ii) Pituitaryand
iii) In rapidly proliferating tissues.

Structure

They are characterized by a three-loop structure that looks like a three-leaf clover.

In mice in which the gene for one of these peptides has been knocked out, the gastric and intestinal mucosa are histologically abnormal and there is a high incidence of benign and malignant mucosal tumours.

Factors which tend to damage the mucosal barrier

i) Regurgitated bile salts acting as detergents
ii) Alcohol
iii) Nicotine
iv) Salicylates and other drugs that decrease mucus and hco3- secretion
v) Lyso lecithin in the regurgitated food
vi) Ischaemia of gastric mucosa
vii) ⍰⍰adrenergic agonists like adrenaline and noradrenaline by decreasing HCO3- secretion.

Gastric Motility

Receptive relaxation

When food enters the stomach, the fundus and the upper portion of the body of the stomach relax and accommodate the food (without any increase of pressure). This relaxation of the ***stomach*** is called ***receptive relaxation***.

Mechanism

Receptive relaxation is ***vagally*** mediated; it is triggered by movement of the pharynx and oesophagus.

Peristalsis

This is ***controlled by*** the gastric ***BER***. Peristalsis begins immediately after the receptive relaxation and helps in mixing and grinding the food.

Peristalsis begins in the ***lower portion of the body*** and goes toward the pylorus. The contraction of the ***distal stomach*** caused by each wave is called ***antral*** systole; the contraction waves occur at the rate of ***3 to 4 per minute*** and each contraction wave can last up to 10 seconds.

Regulation of gastric emptying

For this, the antrum, pylorus, and upper duodenum function as a unit. ***First***, there is contraction of the ***antrum***; this is followed by sequential contraction of the pyloric region and then the duodenum.

Importance of the initial antral contraction

The initial contraction of the antrum ***prevents solid masses*** from entering the duodenum; instead of being 'prematurely' pushed into the duodenum, the food particles are allowed to be mixed and crushed. Thus, the more liquid gastric contents are sent in small quantities into the duodenum.

Normally, there is no regurgitation of food from the duodenum; the reasons are :

i) the contraction of the pyloric segment persists slightly longer than that of the duodenum
ii) CCK and secretin may constrict the pyloric sphincter.

Hunger Contractions

These are the gastric contractions that occur between meals; they are presumably associated with the migrating motor complexes (MMCs). Hunger contractions can sometimes be felt and may even be mildly painful. They are so called because they are associated with the sensation of hunger. However, they have ***no role*** in the regulation of food intake.

Regulation of Gastric motility and secretion

This is by neural and humoral mechanisms.

Neural mechanisms :

This is by

i) local autonomic reflexes (involving cholinergic neurons) and
ii) impulses from the CNS by way of the vagus nerves.

Vaga1 stimulation increases gastrin secretion by release of ***GRP*** (see above). Other vagal fibers release acetylcholine; the released acetylcholine acts directly on the cells in the glands in the body and the fundus to increase acid and pepsin secretion. Stimulation of the vagus nerve in the chest or neck increases acid and pepsin secretion, but vagotomy does not abolish the secretory response to local stimuli.

Humoral mechanisms

Discussed above.

Gastric juice is secreted continuously throughout the day. During the resting state, only a small amount is secreted ; during digestion, the secretion increases.

Gastric juice secretion can thus be divided into two main phases :

1. Digestive phase
2. Inter-digestive (or resting) phase

The digestive phase is further sub-divided into

i) Cephalic phase
ii) Gastric phase
iii) Intestinal phase

Both neural and humoral mechanisms regulate the secretion of gastric juice during the digestive phase. Neural control mechanisms dominate in the cephalic phase; humoral control mechanisms dominate in the gastric phase.

i) **Cephalic phase**

This is the initial ***reflex*** phase. These are ***vagally*** mediated responses induced by activity in the ***CNS***.

The presence of food in the mouth reflexively stimulates gastric secretion. The efferent fibers for this reflex are in the vagus nerves. Thus, even before the food enters the stomach, there is stimulation of gastric secretion.

This vagally mediated reflex can be easily ***conditioned***. For example, the sight, smell, and thought of food increase gastric secretion. Cephalic influences are responsible for ***one third to one half*** of the acid secreted in response to a normal meal.

Psychological states

Psychologic states can affect gastric secretion and motility; these changes are mediated principally via the ***vagi***.

William Beaumont made observations on a patient called Alexis St. ***Martin***. Martin (a Canadian) had a permanent gastric fistula resulting from a gunshot wound; thus, William Beaumont could study the stomach in various psychological states of the patient. He noted the following :

- anger and hostility :
  This was associated with turgor, hyperemia, and hypersecretion of the gastric mucosa
- fear and depression :
  This was associated with decrease in gastric secretion, blood flow and gastric motility.

Note : vagotomy abolishes the cephalic phase.

ii) Gastric phase

The gastric phase of secretion begins when the food enters the stomach. Food in the stomach potentiates the increase in gastric secretion produced by the sight and smell of food and the presence of food in the mouth.

Mechanisms

The gastric phase is controlled by both neural and humoral mechanisms.

a) Neural mechanisms

Presence of food in the stomach stretches the gastric mucosa. This leads to stimulation of secretion in two ways :

- long vago-vagal reflex mechanism
  Vagal nerve endings are stimulated → impulses travel via vagal afferents to the vagal nucleus → then relayed through vagal efferents → to stimulate gastric juice secretion
- local gastric reflexes in the intrinsic submucous (or Meissner's) plexus
  Receptors in the gastric mucosa are activated by stretch and chemical stimuli, mainly amino acids and related products of digestion. This in turn activates the submucous (or Meissner's) plexus and causes acid secretion.
  The products of protein digestion also bring about increased secretion of gastrin, and this augments the flow of acid.

Note :

Thus, stretch stimulates gastric secretion by

- long vago-vagal reflex
- local reflex

b) Humoral mechanisms

Discussed above (see the effects of gastrin, histamine and acetylcholine)

iii) Intestinal influences

Although gastrin-containing cells are present in the mucosa of the small intestine as well as in the stomach, instillation of amino acids directly into the duodenum does not increase circulating gastrin levels.

Fats, carbohydrates, and acid in the duodenum ***inhibit*** gastric acid secretion, pepsin secretion and gastric motility via neural and hormonal mechanisms. The hormone involved is probably ***peptide YY***. Gastric acid secretion is increased following removal of large parts of the small intestine. The hypersecretion, which is roughly proportionate in degree to the amount of intestine removed, may be due in part to removal of the source of peptide YY.

Other Influences

i) Hypoglycemia

This acts via the brain and vagal efferents to stimulate acid and pepsin secretion.

ii) Caffeine and alcohol

These act directly on the mucosa to increase gastric secretion.

iii) Smoking

Nicotine present in the smoke stimulates gastric secretion. Light smoking stimulates and heavy smoking inhibits secretion due to excess nicotine.

Regulation of Gastric Motility & Emptying

Rate of gastric emptying

This depends on

i) the type of food ingested :

- Carbohydrate-rich food : leaves the stomach in a few hours.
- Protein-rich food : leaves more slowly
- Fat-rich food : leaves most slowly

ii) **the osmotic pressure of the material entering the duodenum :**

Hyperosmolality of the duodenal contents decreases gastric emptying. The hyperosmolality is sensed by "duodenal osmoreceptors"; the effect is probably neural in origin.

Peptic Ulcer

Localised erosion and destruction of gastric or duodenal mucosa is called peptic ulcer.

Causes

1. Breakdown of gastric mucosal barrier

Peptic ulcer is primarily due to breakdown of the gastric mucosal barrier. The breakdown can be due to

i) Infection with the bacterium Helicobacter pylori

ii) Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs)

These inhibit the production of prostaglandins and consequently decrease mucus and HC03 secretion (see above).

2. Excess acid secretion

E.g. Zollinger-Ellison syndrome**.** This syndrome is seen in patients with gastrinomas. Most of the gastrinomas are found in the pancreas (although they can occur in the stomach and duodenum). The gastrin causes prolonged hypersecretion of acid. Lipids and protein digestion are affected due to the high acidity and there is steatorrhoea and diarrhoea.

3. Chronic stress

4. Ischemia of gastric mucosa

Treatment

1. Inhibition of acid secretion by :

i) H_2 histamine receptors blockers
Drugs e.g. cimetidine block the H_2 histamine receptors on parietal cells.

ii) Omeprazole
This inhibits the H+-K+ ATPase on the parietal cell.

iii) H. pylori can be eradicated with antibiotics

iv) Ulcers which are due to NSAIDs can be treated by stopping the NSAID; if for some reason, this is not advisable, then treatment can be done with the prostaglandin agonist misoprostol.

Functions of the Stomach

1. Storage function : the stomach receives large quantities of food taken in a short time and stores it for 2 to 3 hours.
2. Digestive function : The stomach mainly helps in the digestion of proteins; pepsin in the gastric juice is an important proteolytic enzyme
3. Mechanical churning or grinding action : food is broken into smaller particles and converted into chyme; this facilitates the digestive process
4. Produces intrinsic factor (IF) : IF is 49-kDa glycoprotein ; it binds to cyanocobalamin (vitamin B_{12}) and is necessary for its absorption from the small intestine.
5. Bacteriolytic : The HCl that is produced in the stomach kills bacteria
6. Absorption : water, alcohol, saline are absorbed in the stomach to some extent.
7. Conversion of ferrous to ferric ion : iron present in the colloidal form is liberated from the food. Then it is oxidized to ferric from the ferrous state. This is done by the acid and is later reduced to ferrous by ascorbic acid.

Cyanocobalamin is a ***cobalt***-containing vitamin. Deficiency of this vitamin causes megaloblastic anaemia and deterioration of certain sensory pathways in the CNS. If the deficiency of cyanocobalamin is due to lack of the intrinsic factor, oral administration of cyanacobolamin will not be effective but parenteral administration will be effective.

Deficiency due to an inadequate dietary intake of cyanocobalamin is very rare; this is probably because the minimum daily requirements are quite low and the vitamin is found in most foods of animal origin.

Mechanism of Vitamin B_{12} reabsorption

Vitamin B_{12} normally binds to intrinsic factor and forms a complex with it; this complex is taken up by a protein called ***cubilin*****;** cubulin is a high-affinity apolipoprotein in receptors in the distal ileum. This triggers absorption of the complex by endocytosis.

In the ileal enterocytes, the cyanocobalamin is transferred to ***transcobalamin II***; transcobalamin II is a cyancobalamin transport protein that transports the vitamin in plasma.

Causes of cyanocobalamin deficiency

i) gastrectomy : this removes the intrinsic factor-secreting tissue
ii) pernicious anemia**,**
In this disease, there is autoimmune destruction of the parietal cells.
iii) diseases of the distal ileum.

Effects of gastrectomy

i) ***pernicious anaemia*** develops; as mentioned above, in such cases, the cyanocobalamin deficiency can only be treated by ***parenteral*** injection of cyanocobalamin.
ii) Digestion of food : the gastric juice contains pepsin, which helps in protein digestion; however, the pancreatic enzymes can digest the proteins and thus nutrition can be maintained. Thus, protein digestion is ***not*** affected.
iii) these patients are prone to develop ***iron deficiency anemia*** and other abnormalities, and they must eat frequent small meals.
iv) Dumping syndrome

Patients with gastrectomy or gastrojejunostomy may have symptoms of weakness, dizziness and sweating after meals; this is referred to as the ***dumping syndrome***. The reasons for the symptoms are :

a) hypoglycaemia

This occurs because of the following sequence of events
In gastrectomized patients → there is rapid absorption of glucose from the intestine → the hyperglycemia causes abrupt rise in insulin secretion → thus they may develop ***hypoglycemic*** symptoms about 2 hours after meals.

b) rapid entry of hypertonic meals into the intestine → this cause the movement of a lot of water into the gut → there is significant hypovolemia and hypotension
c) stimulation of the autonomic reflexes : this occurs secondary to distension of the small intestine and release of hormones from the gut due to rapid entry of gastric contents into the duodenum and jejunum
v) small stomach syndrome

This occurs when partial gastrectomy is done. The symptoms are

a) there is distension and discomfort on food intake; thus, food intake decreases with consequent loss of weight
b) vomiting may occur due to entry of bile into the stomach
c) diarrhoea and steatorrhoea may occur due to failure of fat digestion
d) palpitation and flushing

More text through MCQs

Q. Which part of the stomach secretes gastrin?

a. Body
b. Antrum
c. Fundus
d. Cardia

Ans. 'b'

Body (and also fundus)
Have

i) Parietal (or oxyntic) cells which produce HCl and intrinsic factor
ii) Chief (or peptic or zymogen) cells which produce pepsinogens

Mucus is secreted in ***all*** parts of the stomach.

1. From the lumen to the enterocyte, the barrier to diffusion include

A. Glycocalyx B. Brush Border
C. Unstirred Layer D. Mucous Coat
E. Villous membrane F. All of the above

2. Optimum pH for salivary α amylase (ptyalin) is

A. 6.7 B. 7.8
C. 8.6 D. 1.2-2.4

3. Mal triose is

A. 3 glucose B. 2 Glucose + Lactose
C. 2 glucose + fructose D. 3 galactose

4. Salivary α-amylase can hydrolyze (polysaccharides)

A. 1:4 α B. 1:6 α
C. 1:4Bβ D. Terminal 1:4 α
E. 1:4 α next to branching point F. A, D and E

5. Isomalase (α dextrinase) can split

A. α-dextrins B. Maltriose
C. Maltose D. All of the above

6. All are true of carbohydrate absorption except

A. Principal end products of CHO digestion in lumen are oligosaccharides/ disaccharides
B. α-dextrinase an split 1:6 α linkages
C. Trehalase is an enzyme in brush border

D. Some CHO can get absorbed as lactose

7. Fructose is absorbed by

A. Simple Diffusion B. Facilitated Diffusion
C. SGL T-1 D. SGLT-2
E. Simple diffusion only in the presence of insulin

8. Protein digestion begins in

A. Saliva B. Stomach
C. Duodenal Cap D. At the attachment of ligament of Treitz

9. Maximal acid secretion correlates with levels of

A. Pepsinogen 4 B. Pepsinogen 2
C. Pepsinogen 2 D. Pepsinogen 4

10. All the following enzyme are present in stomach except

A. Pepsin B. Chymosin
C. Lipase D. Gelatinase

11. Digestion of proteins occurs at

A. Intestinal lumen B. Brush Border
C. Cytoplasm of mucosal cells D. All of the above.

12. Di- and tripeptides are transported into enterocytes by a system that requires

A. H^+ B. Na^+
C. Cl^- D. Independent of A, B, C

13. Absorption of one of the following can occur without being broken down

A. Protein B. Triglycerides, although this seen only in infants
C. α-Dextrins D. Sucrose

14. Ebner's glands secrete

A. Ptyalin B. Lingual lipase
C. Mucus D. Colipase

15. Most fat digestion begins in

A. Stomach B. Saliva/ Mouth
C. Duodenum D. 1leum

16. Pancreatic lipase acting on triglycerides can split

A. All 3 bonds B. 1 and 3
C. 1 and 2 D. 2 and 3

17. Bile-salt activated pancreatic lipase can split

A. Triglycerides B. Cholesterol esters
C. Esters of fat-soluble vitamins D. Phospholipids
E. All of the above

18. Emulsification of fat is by

A. Bile salts B. Lecithin
C. Monoglycerides D. All of the above

19. Lipids form micelles by interacting with

A. Bile salts B. Lecithin
C. Monoglycerides D. All

20. Bile salts are maximally absorbed in

A. Duodenum B. Jejunum
C. Ileum C. Colon

21. Cholera toxin acts on

A. Cl with channel in luminal membrane
B. Na^+-K^+-2CC with cotransporter in luminal membrane
C. Na^+-K^+ ATP ase
D. SGLT1

22. The contents are <u>essentially isotonic</u> in all the following except

A. Duodenum B. Jejunum
C. Ileum D. Colon

23. One of the following water soluble vitamins does not require Na^+ for its absorption

A. Vit B_{12} B. Thiamine
C. Riboflavin D. Ascorbic acid

24. Most of the iron in the body is in

A. Hemoglobin F. Ferritin
C. Myoglobin D. Transferrin

25. Auerbach's plexus is concerned primarily with

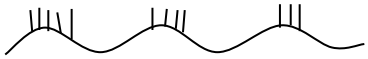
A. Motor control B. Secreting activity
B. Blood flow D. Sensory function

26. True about extrinsic innervation of gut is

A. PS generally (+) SM of wall and (-) sphincters
B. PS generally (-) SM of wall and (+) sphincters

C. S generally (+) SM of wall and (-) sphincters
D. S generally (-) SM of wall and (-) sphincters

27. All are true of peristalsis except
A. It is a reflex response
B. It occurs in all parts of GIT (from oesophagus to rectum)
C. Its activity can be ↑ed or↓ed by extrinsic innervation
D. B.E.R. coordinates peristaltic activity
E. It does not require the enteric nervous system.



28. Basic electrical rhythm (B.E.R.) is seen in all the following except
A. Oesophagus B. Stomach
C. Ileum D. Colon

29. The rate of B.E.R. is minimum in
A. Stomach B. Duodenum
C. Caecum D. Sigmoid

30. All are true of migrating motor complex except
A. These cycles of motor activity migrate from stomach to distal ileum
B. They migrate ab orally at ~ 5 cm/min
C. Occur at intervals of – 90 min
D. Gastric secretion, bile flow, pancreatic secretion increase during each MMC
E. They are present during fasting and are immediately stopped on ingestion of food
F. Gastric may have a role in its generation

31. All the following hormones (G.I) belong to secretion family except
A. Glucagon B. Glicentin
C. V.I.P. D. G.I.P.
E. CCK

32. All are true of gastrin except
A. Secreted by G cells of antrum
B. G cells are APUD cells
C. Gastrin shows micro and microheterogeneity
D. Vagal (+) releases gastrin from G cells, Ach being the mediator
E. The AAS phenylalanine and tryptophan is stomach are potent stimuli for gastric secretion
F. H^+ in antrum (-) gastrin secretion is ↓ed

33. All are true regarding CCK-PZ except
A. Secreted by I cells in upper SI
B. Like gastrin, it shows micro/microheterogeneity
C. Causes contraction of G.B. and secretion of pancreatic juice rich in Enzymes
D. ↑es gastric motility
E. CCK (+)'s glucagon secretion
F. ↑es secretion of enterokinase
G. Its secretion is ↑ ed by peptides, AAS, fatly acids in duodenum

34. Regarding secretin, the following statements are true except.
A. Secreted by S cells of upper small intestine.
B. Only one form of secretin has been isolated, unlike CCK and gastrin
C. ↑es secretion of HCO^-_3 by the duct cells of the pancreas and biliary duct
D. Augments the action of CCK
E. ↑es gastric acid secretion by an action on G cells (via gastrin)
F. Secretion of secretion is ↑ed by products of protein digestion and by acid in duodenum

35. All are true of G.I.P. except
A. Secreted by K cells of Duod. & jejunum
B. (+)ed by glucose, fat in the duodenum
C. In large doses, it (-)s gastric secretion and mobility
D. It stimulates insulin secretion
F. Belongs to gastrin family of G.I. hormones.

36. V.I.P., all are true except.
A. Markedly es intestinal secn. of electrolytes
B. Relaxes intestinal smooth muscle and sphincters
C. Dilates peripheral blood vessel
D. It is found in nerves of GIT
E. (+)s gastric acid secretion
G. Potentiates action of Ach. On salivary glands.

37. All are true of somatostatin except

A. Produced by D cells of GI mucosa
B. Generally, inhibitory in its actions on GI
C. It is (+) ed by acid in stomach
D. Only form of somatostatin is seen in tissue

38. 'Receptive relaxation' is seen in

A. Oesophagus B. Stomach
D. Duodenum D. Caecum

39. Regarding salivary juice, only one of the following is true :

A. The salivary juice output from the duct is always hypotonic
B. Maximum contribution of total saliva is by parotid gland
C. It secretion is controlled by G.I. hormone
C. (PS) (+) ↑ es and (S) (+) ↓ es its secretion
E. Regardless of flow rate, its ionic composition remains the same.
F. Aldosterone does not affect its ionic composition.

40. The cells of the stomach can secrete all the following except

A. Pepsin B. HCE
C. Intrinsic factor D. Mucus
E. HCO_3^-

41. Postprandial alkaline tide can be attributed to

A. Oxyntic Cells B. Peptic Cells
C. Paneth Cells D. M Cells

42. All the following inhibit gastric motility except

A. Hyposmolarity of duodenal contents
B. Products of protein digestion in duodenum
C. H^+ in Duodenum
D. Enterogastric reflex
E. Distension of duodenum
F. Peptide YY
G. Vagotomy

43. Enteropeptidase act on

A. Polypeptides B. Dipeptides
C. Trypsinogen D. Starch

44. The primary bile acids are

A. Deoxycholic acid and lithocholic acid B. Cholic acid and deoxycholic acid
C. Cholic acid and chenodeoxycholic acid D. Cholic acid and lithocholic acid

45. **Critical micelle concentration refers to the critical levels of**

A. Cholesterol B. Bile salts
C. Phospholipids D. Free fatty acids

46. All the following are true of bile secretion except

A. Increased by (+) of vagus
B. Increased by secretin
C. The bile salts reabsorbed from intestine actually inhibit synthesis of new bile acids
D. Bile salts decrease bile flow

47. Valvula conniventes (3), villi (10) and microvilli (20) increase the absorptive surface of SI by above

A. 200 times B. 100 times
C. 600 times D. 1500 times

48. All are true of ileocecal valve except

A. It is normally closed and opens only when a peristaltic wave reacts it
B. It gets opened by gastroileal reflex
C. Sympathetic (+) increase its contraction
D. It is also a part of the gastrocolic reflex where in it relaxes.

49. The following are stimuli for release of CCK except

A. Peptides B. AAS
C. Fatty acid D. Monoglycerides
E. Triglycerides

50. Gastric inhibitory peptide is secreted by

A. Oxyntic cells of stomach B. Chief cells of stomach
C. Surface epithelial cells of stomach D. Upper SI

51. The only G.I. hormone that is released in response to fat, protein and carbohydrate is

A. CCK-PZ B. Secretin
C. G.I.P. D. V.I.P.

52. All the following are contained in micelles except

A. Glycerol B. Cholesterol
C. Monoglycerides D. FAS

Answer Key with Explanation

1. e

To enter the enterocyte (which is the columnar cell on the villous cell membrane), A to D are barriers except E

2. a

For salivary α-amylase, the optimum pH is 6.7. It does not (it cannot) act in the acidic pH of the stomach. For pepsins, optium pH is 1.6 to 3.2

(pH in the duodenal cap = 2- 4, pH of the rest of the duodenum is 6.5 approximately)

3. a

Maltriose = 3 Glucose
Maltose = 2 Glucose
Suerose = Glucose + fructose
Lactose = Glucose + galactose
Trahalose = 2 Glucose (a 1 : 1 α - linked di chain of glucose)

4. a

There are no β-linkage splitting enzyme in humans (β linkages are found in cellulose etc) Salivary and pancreatic α anylase can only hydrolyse 1 : 4 α linkage in the straight chain but they cannot hydrolyse the terminal 1 : 4 linkages, the 1 : 4 linkages next to branching or the 1 : 6 linkage

5. d

Isomaltase (or dextrinase) can split α - dextrins, maltose and maltriose

6. d

In the humen, the lamylar can split carbohydrates only upto oligosaccharides / disacc harides
Lactose cannot be absorbed as such (it has to be split by the lactase enzyme in the membrane)

7. b

Fructose gets absorbed by facilitated diffusion. The transporters involved are

i) E try of fructose from the luminal side into the cell is by GLUT 5 transporter
ii) Exit of fructose from the basolateral membrane to the interstitium is by GLUT 2 transporter

Glucose transporters

There are 2 series of glucose transporters

a) SGLT series (Sodium linked Glucose Transporter) : These are present in the kidney and is the intestine

Features of the SGLT series

i) It is not affected by insulin
ii) No phosphorylation is required
iii) It is inhibited by phlorhizin

b) Glut series (Glucose Transporters)

There are GLUT 1 To GLUT 7 transporters

GLUT 1 and 3 : Found in brain placenta etc. It is for basal glucose uptake
GLUT 2 : Found in β cell of pancrease, liver
GLUT 4 : Found in skeletal muscle, adipose tissue heart It is insulin – dependent*
GLUT 5 : for fructose transport
GLUT 7 : Found in liner

*(Glucose uptake in the liver is also affected insulin but not via GLUT 4. Instead, insulin stimulates glucokinase in the liver (glucokinase converts glucose into glucose – 6 phosphate) and thus favours the diffusion into the liver cell

8. b

Saliva has α-amylase (for stract digestion) and also has lipase; it does no have enzymes for digesting proteins. The duodenal cap or bulb is the first portion of dudenum, it is a common site of peptic ulceration the duodenum becomes the jejunem at the ligament of Treitz.

9. a

Pepsinogens of gastric mucosa is of 2 groups, immuno histochemically viz

Pepsinogens I - found only in acid – secreting regions
Pepsinogens II - It is found in pyloric region as well

10. b

(Chymosin, also known as rennin, is found in the stomach of young animals but is probably absent in human)

11. d

Protein digestion in stomach is up to polypeptides level. In the intestine, the intestinal mucosal enzymes and the pancreatic enzymes further digest the polypeptides. The intestinal rush border has aminopeptidases, carboxypeptidases, endopeptidases and dipeptidases

The pancreatic enzymes for protein digestion are:

Trypsin
Chmotrypsins — Which are endopeptidases (Which act on interior peptide bonds)
Elastase

Carboxypeptidases : Which are exopeptides

Further, they are intracellular peptidases in the mucosal cells

12. a

Aminoacids are transported mostly with Na+ (these are many different transporters). But the di / tripeptides transporter system requires H+ and not Na+

13. a

Absorption of undigested protein can occur, especially in infants. This decreases with age. However, adults can still absorb undigested protein. The M cells (microfold cells) overlying the Payer's patches absorb antigens

14. b

Lingual lipase - is secreted by glands of the tongue (Ebner's glands)
Salvary α amylase - is secreted by salivary glands
Gastric lipase - is not an important enzyme except in pancreatic in sufficiency
But
Lingual lipase is an important enzyme and can digest as much as 30% of diatary triglycerides

15. c

Beginning of digestion of
i) Carbohydrate - in saliva
ii) Protein - in stomach
iii) fat - in duodenum

16. b

Triglyceride = 3 fatty acids + glyecrol (FA = fatty acid)
i.e.

CH_2OH - FA Ist bond
|
CHOH - FA 2nd bond
|
CH_2OH - FA 3rd bond

Pancreatic lipase splits 1st and 3rd bond to give monoglycoride (1 fatty acid + glycerol)
i.e.

CH_2OH
|
CHOH - FA (2 monoglyceride)
|
CH_2OH

In Short,
Triglycerides ⟶ 2 Monoglyceride
Pancreatic lipase and 2 fatty acid

17. e

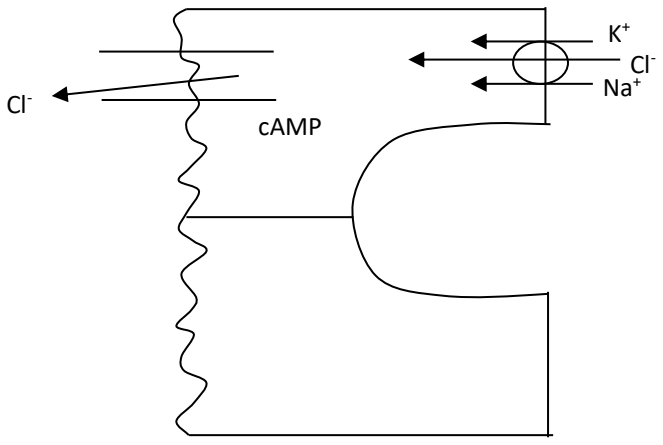
Pancreatic lipase is the enzyme far fat digestion
(But, first the fats have to be emulsified) There are 2 types of pancreatic lipase (depending on how they can get activated / facilitated) :

i) Colipase – Facilitated pancreatic lipase
ii) Bile – salt activated pancreatic lipase

Colipase in obtained from procolipase by action of trypsin
i.e. Procolipase ⟶ (Trypsin) Colipase

Colipase – activated pancreatic lipase	Bile – salt activated pancreatic lipase
i) 10-60 times more active but ii) Can oplit only triglycerides	Can catalyse the hydrolysis of cholesterol esters, esters of fat – soluble vitamins, phosptolipids and triglycerides

18. d
19. a
20. c
21. **a**



Choleratoxin activates CAMP, causing more secretion of CL^-. It also hampers Na+ carrier in mucosa and thus also decreases NaCl absorption

Cl^- enters enterocytes from the basoleteral membrane and gets secreted by Cl- channel in luminal side

22. a

The contents of the duodenum may be hyper or hypotonic but the contents of the jejunum is almost isotonic and this isotonicity of the contents is maintained throughout the small intestine

23. a

Vit B_{12} is absorbed in ileum; most other vitamins are absorbed in upper small intestine

Vit B_{12} and folate absorption are Na^+ - independent; but absorption of all others (options B,C,D,E,F) are by Na+-cotransport mechanism

24. a

70% of iron in body is in Hb

3% ———— in Myoglobin

27% ———— in ferritin

Ferritin is found in enterocytes and other cells. It is the principal tissue storage form of iron

25. a

(i) bmucous (or Meissner's) plexus in the submucosa is concerned with control of intestinal secretion, blood flow of gut and sensory function.

(ii) Myenteric (or Auerbach) plexus is concerned mainly with motor activity (motility)

26. a

I. Sympathetic stimulation : Stimulates sphincters -: inhibits smooth muscle in walls

II. Parasympathetic stimulation : inhibits sphincters; stimulate, smooth muscle in wall

27. e

Peristalsis is a reflex response to stretch. The stretch causes a circular contraction behind the stimulus and an area of relaxation in front of it

28. a

(i) Peristalsis - is seen from oesophagus to rectum

(ii) BER - is seen everywhere in GIT except in oesophagus and proximal portions of stomach

(iii) MMC (Migrating Motor complex) - migrates from the stomach to distal ileum

BER is initiated by the interstitial cells of Cajal (Which are the pacemaker cells)

The 'spikes' on the BER are increased by acetylcholine and decreased by epinephrine

29. a

The rate of BER is in

Stomach : 4 / minute

Duodenum : 12 / minute

Distal ileum : 8 / minute

Caecum : 9 / minute

Sigmoid colon : 16 / minute

30. f

Motilin is responsible for MMC (migrating motor complex). It is secreted by EC cells and Mo cells in stomach, small intestine colon. It causes contraction of smooth muscle in stomach / intestine

31. e

There are 2 families of gastro intestinal hormones:

(i) Gastrin family → includes gastrin, CCK – PZ

(ii) Secretion family → includes secretin, glucagon, glicentin VIP, GIP

32. d,g

Gastrin is also secreted by 'TG' cells which are present throughout the stomach and small intestine Entero endocrine cells are cells of GIT which secrete hormones (peptides). If these cells also secrete serotomin, they are called EC (entero chromaffin) cells; if they secrete amines (in addition to peptide secretion), are called APUD (amine precursor uptake and decarboxylate) cells

i.e. EC cells – secrete peptide plus Serotonin

APUD cells – secrete peptides plus amines

Gastrin has 3 forms : G14, 17 and 34

The principal form with respect to gastric acid secretionis G17

Macroheterogeneity : is varying lengths of amino acids

Microheterogeneity : is same length of amino acid but difference of single amino acid residues

Vagus stimulates gastrin release; the neurotran mitter is gastrin – releasing peptide (GRP) and not acetyecholine

In pernicious anaemia, there is gastric atrophy therefore, there is no acid production. Thus, the negative feedback effect of acid on gastrin secretion is not there, so, there is more gastrin.

33. d

CCK- PZ inhibits gastric motility

34. e

Secretin is "anti – acid" in its actions

35. e

GIP is secreted by K cells of jejunum and duodenum.

Previously, it was called gastric – inhibitory peptide. Now, it is called glucose – dependent insulinotropic polypeptide (the two names indicate its two actions)

36. e

Most of the gastro intestinal hormones inhibit gastric acid motility and secretion

Gastrin is inhibited by : somatostatin, secretin VIP, GIP, glucagon calcitonin

37. d

There are 2 forms of somatostatin in tissues viz somatostatin 14 and 28

38. b

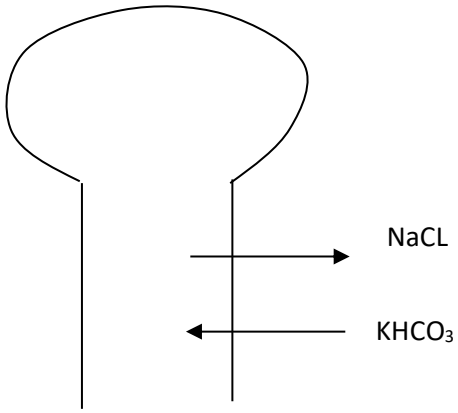
39. a

Maximum contribution to total saliva is by submaxillary gland

i) Submaxillary gland : Mixed secretion
ii) Perotid gland : serous secretion
iii) Sublingual : Mucous secretion

Salivary secretion is controlled by parasympathetic reflexes and not by gastointestime harm ones.

Both sympathetic as well as pasesynpethetic stimulation increase salivary secretion; parasympathetic stimulation causes watery saliva, relatively less in organic constituent and causes vasodiletation (VIP mediated). Sympathetic stimulation*. The salivary juice gets modified as it flows through the salivary ducts. Nacl is absorbed and $KHCO_3$ is seoreted into the duct. With increased flow rate, the ductal modification of the salivary juice decreases. With decreased flow rate, less NaCL and more $KHCO_3$ appears



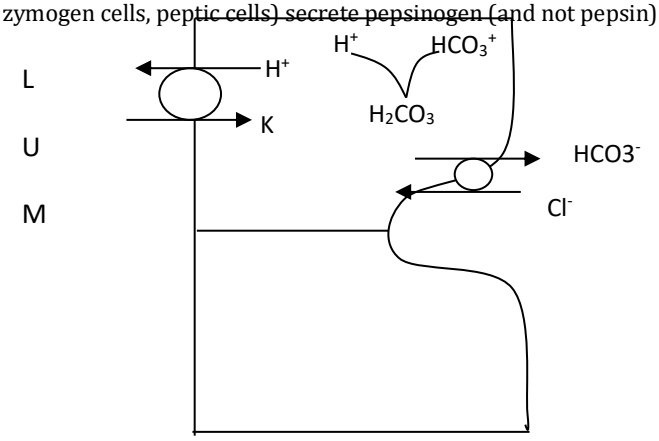
The salivary juice is always hypotonic, because the duct is more permeable to NaCL than it is to water

[*Causes secretion of small amounts of saliva, rich in organic constituents, from the submaxillary glands. It also causes vasoconstriction]

40. a

The body of the stomach has parietal cells (also called oxyntic cells) which secrete HCl and intrinsic factor The chief cells (also called zymogen cells, peptic cells) secrete pepsinogen (and not pepsin)

41. a



When H+ is secreted by the oxyntic (partial cells) is response to food HCO_3^- is added to the blood.

Paneth cells are endocrine cells located in the crypts of Lieberkihn of smell intestine. They may produce guanylin.

Guanylin → (+) guanylyl cyclase → ↑ed CGMP → ↑ed Cl- secretion into lumen → ↑ activity of CFTR Cl^- channel

42. a

Hyperosmolality rather than hypoasmolality of the duodenal contents inhibit gastric motility

43. c

Enteropeptidase has also been known as enterokinase. But eince the enzyme is not a kinase (as was formerly thought) but a peptidase, it is correct to call it entero peptidase

44. c

Primary bile acids	Secondary bite acids
1) cholic acid →	→ Deoxycholic acid
2) Chenideoxycholic acid →	→ Lithocholic acid

45. b

Above a certain concentration called the critical micelle concentration all bile salts added to a solution form micelles

46. d

The bile salts reabsorbed from the intestine actually inhibit the synthesis of new bile acids but they themselves are promptly secreted and they markedly increase bile flow.

47. c

i) Valvulae connivents : increase the absorption surface 3 times
ii) Villi (on the valvulae conniventes) : increase the absorption surface 10 times
iii) Microvilli (on the villi) : increase the absorption surface 20 times

So, the total increase in absorption surface due to all three = 3 X 10 X 20

48. d

Gastrocolic reflex : Distension of the stomach by food initiates contraction of the rectum and frequently a desire to defecate.

49. e

50. d

51. c

52. a

'GLUT' SERIES (Glucose Transporters)

GLUT 1	Blood brain barrier, brain, placenta, kidney etc
GLUT 2	β cells of is lets of pancreas, liver, epithelial cells of small intestinal / renal tubules
GLUT 3	Brain, placenta, kidney etc
GLUT 4	Insulin – stimulated glucose uptake in skeletal muscle / adipose tissue
GLUT 5	Fructose transport in jejunum / sperm
GLUT 6	
GLUT 7	Liver, G-6-P in Endoplasmic reticular

Glucose absorption

Site	Transport mechanism	Insulin
Intestine	SGLT	No effect
Kidney	SGLT	No effect
Muscle (SK muscle / cardiac muscle)	GLUT 4	Favour
Adipose	GLUT 4	Favour
Liver	(Hexokinase)	Favour

Insulin does not affect the absorption of glucose in:
Kidney, intestine, RBC, brain.

Gastro – Intestinal Hormones								
	Gastrin	**CCK – PZ**	**Secretion**	**GIP**	**VIP**	**Somatostatin**	**Motilin**	**Neurotensin**
Structure	Micro and macro heterogenecity	Micro and heterogencity	Only one from					
Site	G – cells,	I – cells –	S cells	K cells –	Ner	D cells of	EC	Ne

	antrum	Upper SI	– upper SI	upper S1	ves	GIT	cells duodenum	rve inileum
Actions	Stimulates acid and pepsin; stimulates gastric motility; stimulates insulin; stimulates glucagons; closure of G-E	Stimulates GB; relaxes sphincter of Oddi; stimulates pancreatic juice (rich in enzymes); inhibits gastric emptying; may stimulate pyloric sphincter; stimulates insulin and glucagons; trophic to pancreas; increases enterokinase; may increase motility of SI and colon; augments secretion	Stimulates secretion of pancreatic juice (alkaline); inhibits gastric acid secretion; may stimulate pyloric A1 sphincter; stimulates insulin; augments CCK; action of secretion is to decrease H^+ in SI	In large dose it inhibits gastric motility and inhibits gastric secretion; stimulates insulin	Stimulates intestinal secretion of electrolytes and water; relaxation of intestinal smooth muscle; dilation of peripheral blood vessels; inhibits gastric acid secretion – stimulated gastric aci	Inhibits secretion of gastrin, VIP, GIP, secretion, motilin; inhibits pancreatic exocrine secretion; inhibits gastric secretion and motility; inhibits gall bladder contraction; inhibits absorption of aminoacids, triglycerides, Increased by acid in lumen; decreased by vagus	Contraction of intestinal smooth muscle; regulator of MMC (migrating motor complex)	Inhibits gastrointestinal motility; increase ileal blood flow

					d sec reti on; pot enti ate s acti on of ace tylc holi ne on sali var y gla nds ; sti mul ate s pan cre atic bic arb ona te sec reti on and inhi bits H sec reti on			
Factors	Increased by: peptides, distensio n, vagus, cold, epinephri ne decrease d by calcitonin , acid, somatost atin, secretion, GIP, VIP	Increased by peptides, aminoacid s, fatty acids (not triglycerid es)	Increas ed by produc ts of food digesti on, acid in duoden um	Increase d by fatty acids, amino acids, glucose	Incr eas ed by fat in jeju nu m	Increased by acid in lumen decreased by vagus		

Gastrointestinal Secretion				
	Saliva	**Gastric secretion**	**Pancreatic secretion**	**Bile**

Main characteristic	Hypotonic; high bicarbonate; high K+; alpha amylase, lingual lipase	HCl; pepsinogen; intrinsic factor	High bicartonate, isotonic, pancreatic lipase, pancreatic amylase, proteases	Bile, salts, bilirubin, phospholipids, cholesterol
Factors stimulating	Stimulated by parasympathetic and sympathetic; by food in stomach	HCl: stimulated by histamine, acetylcholine, gastrin: Pepsinogen: stimulated by parasympathetic	Bicarbonate: stimulated by CCK, secretion and parasympathetic; enzymes: stimulated by CCK, secretion parasympathetic	CCK: stimulates GB; parasympathetic: stimulates GB
Factors inhibiting	By sleep, dehydration, atropine	Inhibited by HCl		Inhibited by iteal resection

	Volume (in L/day)	**Osmolality**	**pH**	**Na^+**	**K^+**	**Cl^-**	**HCO_3**
Plasma	3	300	7.4	150	5	110	24
Saliva	1.5	100	7.5	40	15	25	30
Gastric Juice	3	200	1	50	10	100	0
Pancreatic Juice	1.5	300	7.8	140	10	70	80
Bile	0.5	300	7.5	140	5	80	20
Ref. A.K. Das (TB physiol.)							

At the end of	**Volume (L/day)**	**Na**	**K+**	**Cl-**	**HCO3**
Duodenum	9.2	55	15	55	12
Jejunum	3.2	145	8	95	35
Ileum	1.2	135	7	55	75
Colon	0.2	35	85	10	25

BER	**Rate (per min)**
Stomach	4
Duodenum	12
Proximal Jejunum	12
Distal Ileum	8
Caecum	9
Sigmoid Colon	16
BER: Absent in Oesophagus and proximal colon	

Stimulate Insulin Secretion

1. Gastrin
2. CCK
3. Secretion
4. Glucagon
5. GIP

Reflexes

1. Gastroileal
2. Gastrocolic
3. Enterogastric
4. Intestino – intestinal
5. Rectosphincteric
6. Colono - ileal

BLOOD

Molecular weight = 64450.

Structure

It is a globular protein. Each molecule of Hb has 4 subunits.

Each subunit has :

i) Pigment heme conjugated to

ii) a polypeptide.

Thus, there are 4 polypeptide chains in each Hb molecule; the polypeptide chains are collectively called 'globin'.

Heme

This is an iron-containing porphyrin known as iron-protoporphyrin IX. The porphyrin nucleus consists essentially of 4 pyrrole rings joined together by 4 methine (=CH-) 'bridges'; the porphyrins are thus tetrapyrroles. The iron in heme is in the ***ferrous (Fe^{2+})*** form.

The iron in heme is attached to the

- N of each pyrrole ring
- N of the imidazole group of the associated globin

Synthesis of heme

(Hb appears in the intermediate stage of erythropoiesis in the bone marrow).

Heme is synthesized from glycine and succinyl CoA as shown below :

Steps

i) succinyl CoA + glycine → alpha amino beta keto adipic acid

ii) alpha amino beta adipic acid → delta levulinic acid + CO2

iii) delta levulinic aicd (2 molecules) → porphobilinogen

iv) porphobilinogen (4 molecules) → protoporphyrin

v) protoporphyrin IX + Fe^{2+} + globin → Hb

A single Hb molecule has

- 4 protoporphyrin IX molecules
- 4 ferrous atoms
- 4 polypeptide chains

1 gram of Hb has about 3.34 mg of ferrous ion.

1 gram of Hb, when fully saturated, carries 1.34 ml of oxygen.

Different states of Hb

OxyHb (HbO2)

Oxygen binds loosely and reversibly with Hb; this Hb is called oxyHb. The oxygen attaches to the ferrous ion in the heme.

2-3 DPG and H+ compete with oxygen for binding to the deoxygenated Hb; thus, increase in 2-3 DPG and temperature shift the oxygen-Hb curve to the right.

The affinity of CO to Hb is 210 times the affinity of oxygen for hemoglobin.

DeoxyHb (Hb or HHb)

Hb to which oxygen is not attached is called deoxy Hb. It is also called reduced Hb.

Carbamino compound :

This is a compound of Hb with carbon dioxide

Sulphaemoglobin :

This is a compound of Hb with hydrogen sulphide

CarboxyHb

This is a compound of Hb with CO; it is better called as carbonmonoxy Hb.

Oxidised Hb (HbOH) or Methaemoglobin :

In this form of Hb, the ***ferrous (Fe^{2+})*** ion gets oxidized to ***ferric ion (Fe^{3+})***

When reduced or oxygenated Hb is treated with an oxidizing agent, the ferrous ion gets oxidized to ferric ion; this state of Hb is called as methaemoglobin. The disadvantage of this methaemoglobin is that it cannot unite reversibly with oxygen.

MetHb is represented like 'HBOH'; because, here the ferric ion is attached to OH group

The iron in Hb in the normal state is in the ferrous form. Drugs and oxidizing agents convert the ferrous to ferric form, making it methaemoglobin. Methaemoglobin is dark coloured and when present in large quantities causes a dusky discolouration of skin resembling cyanosis.

Hb (Ferrous ion) -→ oxidized (ferric ion) → gives methaemoglobin

	Hb	**MetHb**
Iron	Ferrous form	Ferric form

State of Hb	Reduced form	Oxidised form
Colour	Red	Darker
Binding to oxygen	reversible	irreversible

Note

Oxygenated Hb = HbO2; oxidized Hb = MetHb (HBOH)

Glycosylated or glycated Hb (HbAic)

When blood glucose enters the RBCs, the glucose gets attached to Hb at various positions ; this Hb is called glycated Hb. One of the glycosylated/glycated Hbs is HbAic. This glycated Hb has a glucose attached to the terminal valine in each beta chain.

The percentage of glycosylated Hb = 50 %. This percentage is directly proportional to blood glucose concentration. Since the half-life of RBC is 60 days, the level of glycated Hb (HbAic) reflects the mean blood glucose concentration over the preceding ***6 to 8 weeks***. So, its estimation is important in management of diabetes mellitus.

Different types of Hb

In the different types of Hb, the heme portion is identical; physical and chemical differences are due to variations in the composition of the peptides of the globinfraction. **HBA (alpha2, beta 2) :**

this is the ***normal and main form of adult Hb***; it has 2 alpha and 2 beta chains. Each alpha chain has 141 amino acids; each beta chain has 146 amino acids.

HbA2 (alpha 2, delta 2)

This constitutes about ***2.5% of the normal adult Hb***. It has 2 alpha and 2 delta chains. Each delta chain has 146 amino acids (but 10 amino acids are different from those of beta chains)

HbF or foetal Hb(alpha 2, gamma 2)

This occurs in foetal RBCs; it usually disappears by 2-3 months after birth. Since 2-3 DPG has less affinity to bind to HbF, HbF has greater affinity for oxygen. So, at a given pO2, the percentage saturation of HbF with oxygen is more than that of HbA.

Importance

This increased affinity helps in uptake of oxygen from maternal to foetal circulation.

HbF is much more resistant to alkali than HbA.

Fate of RBC/Hb

At the end of their life span, RBCs are destroyed in the reticuloendothelial system (nowadays called as tissue macrophage system) and Hb is released from the RBC.

In the tissue macrophage system, the globin and heme portion are split off. The heme is oxidized (by ***heme oxygenase***) to ***biliverdin***. In this process, ***CO*** is formed.

Most of the biliverdin is ***reduced*** (by biliverdin reductase) ***to bilirubin*** and is excreted in the bile. The iron released from the heme is reused for Hb synthesis.

1 gram of Hb gives 35 mg of bilirubin. About 250 to 375 mg of bilirubin is produced per day (mostly from Hb; also from ineffective erythropoiesis and from other heme proteins such as cytochrome P 450)

Exposure of the skin to white light converts bilirubin to lumirubin, which has a shorter half-life than bilirubin.

Other heme containing compounds

Myoglobin

Heme is present in myoglobin also. It is found in the red (slow) muscles.

Neuroglobin

This is an oxygen-binding globin in the brain; its function may be to supply oxygen to neurons.

Cytochrome C

This is a respiratory chain enzyme; it contains heme.

More text through MCQs

Q. HbF is

a) alpha 2, beta 2
b) alpha 2, gamma 2
c) alpha 2, delta 2
d) alpha 2, zeta 2
e) epsilon 2, zeta 2

Ans. : 'b'

Gamma chain has 146 amino acids (like beta chain, which also has 146 amino acids); however, 37 amino acids are different.

Epsilon 2, zeta 2 : Gower 1 Hb

Alpha 2, epsilon 2 : Gower 2 Hb

Gower 1 and Gower 2 Hb present in the young embryo; thus, epsilon and zeta chains are embryonic.

Alpha chain gene is present on chromosome 16; the gene for other chains (beta, gamma, delta, epsilon, zeta) are present on chromosome 11.

Espison, zeta : disappear at approximately 3 months of intrauterine life

Gamma

Maximum percentage (about 45%) occurs at about 3 months of intrauterine life; its percentage starts decreasing just before birth and gets decreased to very low level by about 3 months after birth; it almost completely disappears at 6 months after birth.

Beta chain

The graph for beta chain is almost a mirror image of gamma chain. It starts increasing just before birth; reaches very high level (about 45 %) at about 3 months after birth and almost 50% at 6 months (that is the maximum percentage possible because the other 50% is alpha chain)

Alpha chain
This reaches 50% at about 3 months of intrauterine life and remains so throughout life.
Delta chain
This starts appearing just before birth and becomes maximum (about 2%) at about 6 months after birth.
MCQ round up
At 3 months of intrauterine life
- Zeta, epsilon chains disappear
- Alpha chain percentage becomes maximum (about 50%)
- Gamma chain percentage becomes maximum (about 45%)

At 3 months after birth
- Gamma decreases to very low level
- Beta increases to very high level

At 6 months after birth
- Gamma almost disappears
- Beta becomes almost maximum

Alpha chain
Becomes maximum at about 3 months of intra uterine life; thereafter, it remains so throughout.

Physiology of Hemostasis

Definition of hemostasis
Hemostasis literally means stoppage of bleeding.
Processes
When a blood vessel is cut or damaged, the following 3 basic processes prevent blood loss :

i) Vasoconstriction
This is due to ***serotonin*** and other vasoconstrictors released from the platelets.

ii) Temporary platelet plug formation
This is formed by a loose aggregation of platelets. How? The damaged vessel exposes the collagen; the platelets bind to the exposed collagen. The bound platelets release ADP; ***ADP in turn attracts more platelets*** and helps in platelet aggregation.

iii) Blood coagulation
The clotting mechanism forms fibrin, fibrin reinforces the loose platelet plug. Thus, the loose temporary plug is converted into a definitive plug.

Physiology of coagulation

The process of clotting is called coagulation. The various coagulation factors (also called clotting factors) bring about the coagulation. Many of the coagulation factors are present in the plasma; some are released from the platelets.
Coagulation factors
The following are the coagulation factors in the blood and their synonyms :

Factors (symbol)	Synonyms
I	Fibrinogen
II	Prothrombin
III	Tissue thromboplastin (TPL), Tissue factor
IV	Calcium
V	Proaccelerin, labile factor, accelerator globulin (Ac-globulin, Ac-G)
VII	Proconvertin, Serum Prothromobin Conversion Accelerator (SPCA), stable factor
VIII	Anti-hemophilic factor (AHF), anti-hemophilic factor A, anti-hemophilic globulin (AHG)
IX	Plasma thromboplastin component (PTC), Christmas factor, anti-hemophilic factor B
X	Stuart factor, Stuart Prower factor
XI	Plasma thromboplastin antecedent (PTA), anti-hemophilic factor C
XII	Hageman factor, glass contact factor
XIII	Fibrin-stabilizing factor, Laki-Lorand factor
HMW-K	High-molecular weight kininogen, Fitzgerald factor
Pre-K_a	Prekallikrein, Fletcher factor
Ka	Kallikrein
PL	Platelet phospholipid

Note : there is no factor VI (it is not a separate entity and therefore it is not listed); it was earlier called as accelerin.
Mechanism of blood coagulation
Enzyme cascade mechanism

The ultimate aim of the clotting mechanism is to form ***insoluble fibrin from*** the ***soluble fibrinogen***. The clotting mechanism consists of a cascade of reactions in which inactive enzymes are activated; these activated enzymes in turn activate other inactive enzymes.

Steps involved in conversion of fibrinogen to fibrin

i) Formation of fibrin monomer from fibrinogen

Fibrinogen is made up of three types of polypeptide chains viz. alpha, beta and gamma polypeptide chains.
As a first step, two pairs of polypeptides are released from each fibrinogen molecule; the remaining portion is the fibrin monomer.

ii) Formation of loose fibrin mesh

The fibrin monomer polymerizes with other monomer molecules to form fibrin. This fibrin is initially a loose mesh of interlacing strands.

iii) Formation of tight fibrin mesh

The ***loose*** fibrin mesh is converted ***into*** a ***tight***, dense mesh by the formation of covalent cross-linkages; this process is called ***stabilization***. The stabilization reaction is catalyzed by activated factor ***XIII*** and requires ***calcium***.

Details of conversion of fibrinogen to fibrin

Role of thrombin

i) Thrombin catalyzes the conversion of fibrinogen to fibrin. Thrombin is a serine protease; it is formed from its circulating precursor, prothrombin. Prothrombin is converted to thrombin by the action of activated factor X.

ii) Other actions

Activation of platelets, endothelial cells, and leukocytes via a G protein-coupled receptor.

Factor X activation

There are 2 pathways for activation of factor X

i) intrinsic pathway
ii) extrinsic pathway

Intrinsic pathway for factor X activation

Steps

i) Conversion of ***inactive factor XII to active factor XII*** (i.e. from factor XII factor XIIa (the 'a' stands for activated factor XII)

This is the ***initial reaction*** in the intrinsic pathway.
This activation is ***catalyzed by*** high-molecular-weight (HMW) ***kininogen and kallikrein***. Kallikrein is a protease present in small amounts in the plasma; it is formed from pre-kallikrein. As soon as factor XIIa is produced, it causes the conversion of prekallikrein to kallikrein; kallikrein in turn activates XII. Thus, it is another example of ***positive feedback*** mechanism.

The activation of factor XII in vitro and in vivo occurs as follows :

a) in vitro

Factor XII can be activated in vitro by exposing the blood to electronegativelv charged wettable surfaces such as glass and collagen fibers.

b) in vivo

Activation of factor XII in vivo occurs when blood is exposed to the collagen fibers underlying the endothelium in the damaged blood vessels

ii) Activation of factor XI

Active factor XIl (i.e. XII a) in turn activates factor XI

XII a
XI ----------→ XI a

iii) Activation of factor IX

Active factor XI activates factor IX.

XI a
IX ----------→ IX a

iv) Activated factor IX forms a ***complex with active factor VIII***
Factor ***VIII is activated when*** it is ***separated from von Willebrand factor***.

v) Activation of factor X
- The ***complex of IXa and VIIIa*** activate factor X.
- ***Phospholipids*** from aggregated platelets (PL) and ***calcium*** are necessary ***for full activation*** of factor X.

Extrinsic pathway for factor X activation

Steps

i) The ***initial step*** is the release of ***tissue thromboplastin (TPL)*** (also called ***tissue factor***) from damaged tissue; TPL is a protein-phospholipid mixture containing proteolytic enzymes. tissue thromboplastin activates factor VII.

ii) The tissue thromboplastin forms an ***active complex with factor VII***; this complex ***activates*** factors ***1X and X***. The activation of factor X by this complex of VIIa and TPL requires the presence of calcium and platelet phospholipid (PL).

Common pathway beyond formation of X a

The ultimate aim of both the intrinsic and extrinsic pathway is to activate factor X. Once activated factor Xa is formed, the remaining coagulation pathway is the same for both intrinsic and extrinsic pathways as given below:

i) Activated factor X (i.e. X a) converts prothrombin to thrombin (the activation requires the presence of platelet phospholipid i.e. PL, calcium and factor V

ii) Thrombin
- Converts fibrinogen to fibrin monomer polymerization of fibrin monomer to form loose fibrin mesh
- Activates factor XIII (to form XIII a)

iii) ***Factor XIII a*** causes ***stabilization*** of the loose fibrin mesh to form tight fibrin mesh

The extrinsic pathway is inhibited by a ***tissue factor pathway inhibitor*** by forming a quaternary structure with TPL, factor VIIa, and factor Xa.

Other useful MCQ points

Blood coagulation is an example of ***positive feedback*** mechanism; formation of active factor in one step stimulates its own catalyst. Because of this, very little initiation in the system can produce an immense response.

Most of the coagulation factors in their active state are ***serine proteases*** whose active site contains a hydroxyl group.

Anti clotting Mechanisms

Introduction

Clotting is essential for stopping bleeding due to injury. However, clotting should not occur inside the blood vessels. For preventing clotting inside the blood vessels, there are anti-clotting mechanisms. The anti-clotting mechanisms :

i) prevent clotting inside the blood vessels
ii) if any clot does form, it breaks the clot

The various anti-clotting mechanisms are :

1. Balance between thromboxane A_2 and prostacyclin :
- Thromboxane A_2 causes platelet aggregation
- Prostacyclin inhibits platelet aggregation

The balance between the two allows clots to form at the site of injury but prevents clot within the lumen of the vessel.

2. Antithrombin III (also called heparin cofactor II)

This is a circulating protease inhibitor; it binds to the serine proteases in the coagulation system. As mentioned above, most of the active forms of the clotting factors are serine proteases; thus, anti-thrombin III blocks the activity of these clotting factors.

Anti-thrombin III ***inhibits*** the active forms of factors ***IX, X, XI, and XII***.

Heparin increases the action of anti-thrombin III. How? Heparin increases the binding of anti-thrombin III to the serine proteases. (Heparin is a naturally occurring anticoagulant; it is a mixture of sulphated polysaccharides with molecular weights between 15,000-18,000).

3. The endothelium of the blood vessels

The endothelium is another important anti-clotting mechanism; it plays an active role in preventing the extension of clots into blood vessels.

Thrombomodulin

What is it?

This is a ***thrombin-binding protein***, expressed on the endothelial cells.

Site of production

All endothelial cells ***except*** those in the ***cerebral*** microcirculation produce ***thrombomodulin*** and express it on their surface.

Mechanism of action

In the circulating blood, ***thrombin*** is a ***pro-coagulant*** that activates factors V and VIII; however, ***when thrombin binds to thrombomodulin***, it becomes an ***anticoagulant***. How?

The thrombomodulin-thrombin complex activates protein C. The activated protein C (APC), along with its cofactor protein S:
- inactivates the activated factors V and VIII
- inactivates an inhibitor of t-PA (tissue plasminogen activator); thus, it increases the formation of plasmin from plasminogen.

4. Fibrinolytic system

Clots formed in the tissues have ultimately to be disposed of as healing takes place; the dissolution of the clot is called fibrinolysis and is due to the action of the proteolytic enzyme called plasmin or fibrinolysin.

Plasmin (also called fibrinolysin)

There is no free plasmin in the blood; the blood contains its inactive precursor called plasminogen (also called profibrinolysin).

Plasmin lyses fibrin and fibrinogen; this produces fibrinogen degradation products (FDP); the fibrin degradation products inhibit thrombin.

How is the active plasmin formed from its inactive precursor, plasminogen?

This occurs by the action of
- thrombin
- tissue-type plasminogen activator (t-PA).
- also by urokinase-type plasminogen activator (u-PA).

Evidence

Effect of knock out of either the t-PA gene or the u-PA gene in mice :
- Some fibrin deposition occurs
- and clot lysis is slowed.

Effect of knock out of both the t-PA and u-PA genes :

- there is extensive spontaneous fibrin deposition
- there is delayed wound healing
- there are defects in growth and fertility (this is because the plasminogen system not only lyses clots but also plays a role in cell movement and in ovulation).

Other actions of plasmin

In addition to its fibrinolytic activity, plasmin can form plasma kinins (bradykinin, kallidin) and thus contribute to the vascular and sensory features (pain) of the inflammatory response to injury.

Structure of human plasminogen

It consists of a

- heavy chain (560-amino-acid) and
- a light chain (241-amino-acid)

The heavy chain

- Has glutamate at its amino terminal
- It is folded into five loop structures, each held together by three disulfide bonds. These loops are called ***kringles*** because of their resemblance to a Danish pastry of the same name.

Kringles

The Kringles are lysine-binding sites by which the plasminogen molecule attaches to fibrin and other clot proteins (kringles are also found in prothrombin)

Plasminogen is converted to active plasmin when t-PA hydrolyzes the bond between Arg 560 and Val 561.

Plasminogen receptors :

These are located on the surfaces of many different types of cells and are plentiful on endothelial cells. When plasminogen binds to its receptors, plasminogen becomes activated; thus, clot formation does not occur in the intact blood vessel walls

5. The protein C pathway

Three protein factors – protein C, protein S and thrombomodulin – constitute an important negative feedback pathway to keep the clotting mechanism under control.

Thrombomodulin

As mentioned above, it is a protein present on the vascular endothelium; all endothelial cells except those in the cerebral microcirculation produce thrombomodulin and express them on their surface

Protein C and protein S : these are plasma proteins

How does the system work?

i) thrombin binds to thrombomodulin
ii) the thrombin-thrombomodulin complex activates protein C
iii) In combination with protein S, the activated protein C (APC) inactivates factor V a and VIIIa
iv) Because of the inactivation of factors Va and VIIIa, the clotting process is checked.

Applied aspects

With the help of recombinant DNA techniques, human t-PA is now being produced for clinical use. It lyses clots in the coronary arteries if given to patients soon after the onset of myocardial infarction. Streptokinase, a bacterial enzyme, is also fibrinolvtic and is also used in the treatment of early myocardial infarction

Annexins

These are a group of proteins which are associated with coagulation and fibrinolysis. About 10 annexins have been described in mammals.

Possible role of annexins

Annexin II

This forms a platform on endothelial cells on which components of the fibrinolytic system interact, producing fibrinolysis.

Annexin V

This forms a shield around phospholipids involved in coagulation and exerts an antithrombotic effect.

Plasma Proteins

Composition of plasma

Water : 91.5%

Solutes : 8.5%

The solute fraction consists of

Proteins

The relative percentage of the plasma proteins are

- albumin (55%)
- globulins (38%)
- fibrinogen (7%)

Non-protein nitrogenous substances

- nitrogen, urea, uric acid, creatinine, ammonium salts

Regulatory substances

- enzymes and hormones

Electrolytes

- Na, K, Mg, Ca, Cl, $HPO4^-$, $HCO3^-$

Amino acids, glucose

Total plasma proteins = 6.4 gm to 8.3 gm /dL (average = 7.4 gm /dL)

Albumin = 3.5 to 5.2 gm/dL

Globulins = 1.7 to 3.2 gm/dL

Fibrinogen = 0.2 to 0.4 gm/dL

The normal albumin : globulin ratio (A : G ratio) : about 1.7

Classification of plasma proteins

1. Classical or Howe method

In this method, the plasma proteins are classified into 3 major groups :

albumin, globulins and fibrinogen; the globulin fraction is further subdivided into other components

Some fractions of globulins are :

- Lipoproteins, glycoproteins, interleukins, haptoglobulins, cortisol-binding globulin, ceruloplasmin, transferrin, immunoglobulins

2. Electrophoretic method

By this, the plasma proteins can be separated into 5 fractions viz. albumin, alpha 1, alpha 2, beta and gamma fractio

Functions of plasma proteins

1. Maintenance of colloidal osmotic pressure

The ***osmotic pressure*** exerted ***by*** the ***plasma protein*** colloids is also called as ***oncotic*** pressure. The plasma proteins are able to exert osmotic pressure because the capillary walls are relatively impermeable to plasma proteins.

Value of this oncotic pressure : about ***25 mm Hg***

2. Maintenance of blood pH

The plasma proteins can combine with acids or bases to maintain the pH o f blood. The plasma proteins are also responsible for ***15%*** of the buffering capacity of the blood. How? There is weak ionization of their caroboxyl (COOH) and amino (NH_2) groups; these are capable of combining with acids or bases and buffer them. ***At*** the normal plasma pH of ***7.40***, the proteins are mostly in the ***anionic form***

3. Blood clotting

Plasma proteins contain a large number of proteins called clotting factors (viz. fibrinogen, prothrombin). Fibrinogen is converted into fibrin during the process of blood coagulation.

4. Carriers

Plasma proteins act as carriers of metals, hormones (e.g. thyroid, adrenocortical, gonadal etc.), lipids, fat-soluble vitamins and drugs.

Advantage of the protein binding

i) prevents filtration of the bound hormones through the glomeruli

ii) acts as a reservoir of the hormones

Albumin acts as a ***non-specific transport protein*** for a number of substances e.g. metals, ions, fatty acids, amino acids, steroids, vitamins, hormones, bilirubin, enzymes, and drugs.

5. Defence mechanism

Immunoglobulins (also called gamma-globulins) and complement system are the plasma proteins responsible for body defence mechanism.

<u>Production of plasma proteins</u>

i) plasma cells

Circulating antibodies in the ***gamma globulin*** fraction of the plasma proteins are ***manufactured in*** the ***plasma cells***

ii) Liver

Most of the other plasma proteins are synthesized in the liver.

Properties of the individual plasma proteins

Albumin

Molecular weight = 70,000

Half-life = about 10 days

Synthesis : in liver

Function

It is responsible for the carriage in the plasma of most of the bilirubin and of non-ionized calcium

Metabolism

In normal adult humans,

- the plasma albumin level = 3.5-5.0 g/dL
- the total exchangeable albumin pool = 4.0-5.0 g/kg body weight
- 38-45% of this albumin is intravascular
- Much of the extravascular albumin is in the skin.
- Between 6% and 10% of the exchangeable pool is degraded per day
- the degraded albumin is replaced by hepatic synthesis of 200-400 mg/kg/d.

Regulation

Albumin synthesis is carefully regulated. It is decreased during fasting and increased in conditions such as nephrosis in which there is excessive albumin loss.

Globulins

Molecular weight = 90,000 to 1,56,000

Components

The globulins consist of alpha 1, alpha 2, beta 1, beta 2, gamma 1, and gamma 2 fractions; the gamma globulins consist of the antibodies

Synthesis

Gamma globulin : in plasma cells

Other globulins : liver

Fibrinogen

Molecular weight = 5,00,000

Synthesis : liver

The plasma fibrinogen concentration is raised in almost all diseases in which raised ESR is found, particularly in acute infections and in pregnancy.

Applied aspects

Causes of hypoproteinemia

i) prolonged starvation
ii) malabsorption syndrome
iii) liver disease (because hepatic protein synthesis is decreased)
iv) nephrosis (because of increased loss of albumin in urine)

Because of the decrease in the plasma oncotic pressure, edema tends to develop

Afibrinogenemia

Causes

- Congenital
  This can occur as a rare congenital abnormality; here, there is congenital absence fibrinogen
- severe liver disease
- in pregnancy, as a complication of detachment of placenta

It is characterized by defective blood clotting.

Q. The plasma volume in a 60-kg man will be approximately

a. 3 L
b. 4 L
c. 5 L
d. 1.5 L

Ans. 'a'

Plasma volume = 5 % of body weight

So, in a 60-kg man, it will be 5/100 x 60 = 3 L

Q. All the following are true statements except

a. plasma clots on standing
b. serum = whole blood minus clot
c. serum does not contain fibrinogen, clotting factors II, V and VIII
d. serum has a lower serotonin content than plasma

Ans. 'd'

Plasma remains fluid only if an anticoagulant is added.

Composition of serum and plasma

Serum has the same composition as plasma except

- that serum does not have fibrinogen and clotting factors II, V, and VIII
- it has a ***higher serotonin*** content than plasma; this is because of the breakdown of platelets during clotting.

More text through MCQs

All the following plasma proteins are produced mainly in the liver except

a. Albumin
b. Fibrinogen
c. Haptoglobin
d. Immunoglobulins

Ans. 'd'

Immunoglobulins are produced by the plasma cells. ***Most*** other plasma proteins are produced by the ***liver***.

The Hb transport protein in the plasma is

a. ceruloplasmin
b. haptoglobin
c. hemopexin
d. C-reactive proteins (CRP)
e. Transferrin
f. transthyretin

Ans. 'b'

Haptoglobulin

This binds and transports the cell-free Hb. ***One molecule*** of haptoglobin binds ***one molecule*** of Hb.

Hemopexin

This binds and transports porphyrins, especially ***heme***. ***One molecule*** of hemopexin binds with ***one molecule*** of heme.

Ceruloplasmin

This transports ***copper***. ***One mole*** of ceruloplasmin binds ***6 copper*** atoms

CRP

This is one of the acute phase proteins. It plays a role in tissue inflammation; it binds ***complement C1q***. Its level increases in ***inflammation***.

Transferrin

This transports ***iron***. ***One mole*** of transferring binds ***2 iron*** atoms.

Transthyretin

The other name for this is thyroid-binding prealbumin. It binds and carries thyroid hormones. The other thyroid hormone- binding protein is thyroid-binding globulin.

Q. The following blood clotting factors are produced in the liver except

a. factor 2 b. factor 3
c. factor 7 d. factor 9 e. factor 10

Ans. 'b'

Which of the following plasma proteins is structurally similar to albumin?

a. alpha-fetoprotein b. protein C
c. apolipoprotein B d. alpha2-macroglobulin
e. antithrombin III f. alpha 1-antiprotease

Ans. 'a'

All the above proteins are produced in the liver. The function of alpha-fetoprotein is not exactly known. Like albumin, it may function as an osmotic regulator and as a non-specific carrier protein (for hormones, amino acids etc). It is found normally in fetal blood; hence, the name.

Alpha2-macroglobulin binds and ***inhibits*** serum ***endoproteases***.

Antithrombin III is a ***protease inhibitor*** of the intrinsic clotting system. One molecule of antithrombin III binds one molecule of these proteases.

Protein C (also, anti-thrombin C) inhibit blood clotting.

Apolipoprotein B is a plasma lipid carrying protein.

Alpha1-antiprotease : this is a trypsin and general protease inhibitor.

The plasma or serum concentration of which of the following proteins is maximum?

a. Fibrinogen b. albumin
c. haptoglobin d. C-reactive proteins

Ans. 'b'

The plasma levels of some plasma proteins are :

Plasma protein	**Plasma/serum concentration (mg/dL)**
Albumin	3500 to 5000
Fibrinogen	200 to 450
Globulins (total)	1700 to 3200
Alpha 2 macroglobulin	150 to 420
Haptoglobin	40 to 180
Hemopexin	50 to 100
Ceruloplasmin	15 to 60
Transferrin	3 to 6.5
Antithrombin III	15 to 30
Clotting factors 2, 7, 9 and 10	20
TBG (thyroid-binding globulin)	1.5
TBPA (thyroid-binding prealbumin) or transthyretin	25

Platelets (Thrombocytes)

Structure

These are colourless, non-nucleated, granulated, spherical, oval or rod-shaped bodies.
Diameter : 2 to 4 micrometer
Number : 1.5 to 4 lakhs per cu mm
Half-life : ***4 days***; ***average life span*** : about ***10 days***

Formation

Site : Bone marrow

Development :

Platelets are formed from giant cells called ***megakaryocytes***. The megakaryocytes themselves are formed from stem cells called megakaryoblasts. The megakaryoblasts → become promegakaryocyte, which become → megakaryocyte → which form platelets.

Release into circulation

The platelets are formed in the cytoplasm of the megakaryocytes; bits of cytoplasm get detached and are released into the circulation.
Platelets reside in the spleen for a short period prior to circulation in the blood stream.
Percentage of the released platelets ***in*** the ***circulating blood*** : ***60% and 75%***
Out of the ***rest*** 25 to 40%, ***most of them*** are in the ***spleen***; thus, removal of the spleen increases the platelet count.

Ultrastructure

Platelet membrane
The platelet membrane is highly invaginated and has a canalicular system; the canaliculi are in contact with the ECF

Receptors on the membrane

The platelet membrane contain receptors for collagen, ADP, vessel wall von Willebrand factor and fibrinogen.
Microtubules
A ring of microtubules is present around the periphery of platelets.

Cytoplasm

The platelet cytoplasm contains actin, myosin, glycogen, lysosomes, and granules.
The platelet granules are of 2 types :

i) Dense granules
These contain the ***non-protein*** substances that are secreted in response to platelet activation; the substances include ***serotonin***, ***ADP***, and other adenine nucleotides,

ii) Alpha -granules,
These contain secreted ***proteins other than*** the ***hydrolases*** in lvsosomes. These proteins include clotting factors and platelet-derived growth factor (***PDGF***).

PDGF

Structure
It is a dimer made up of A and B subunit polypeptides. Both homodimers (viz. AA and BB) and heterodimer (viz. AB) are produced.

Function

i) stimulates wound healing
ii) it is a potent mitogen for vascular smooth muscle.

Von Willebrand factor

This is a protein present in the vessel wall and in plasma; it is produced by
- the endothelial cells of blood vessels
- platelets

Function

i) helps the platelets to adhere to damaged vessel wall
ii) regulates circulating levels of factor VIII.

Role of platelets in hemostasis

Steps :

i) Platelet binding

When a blood vessel is injured, platelets bind to
- the exposed collagen
- and to the von Willebrand factor in the wall

The receptors on the platelet membrane help in this binding.

ii) **Platelet activation**

Binding produces platelet activation → this causes release of the contents of their granules; ADP is also one of the released substances

iii) **Platelet aggregation**

This is mediated by :

a) ADP

The released ADP acts on the ADP receptors in the platelet membranes → this produces further accumulation of more platelets (platelet aggregation).

Platelet ADP receptors :

These are ***P2Y₁ , P2Y₂ , and P2X₁***.

b) Platelet activating factor (PAF)

What is PAF?

It is a cytokine secreted by neutrophils, monocytes and platelets. It is an ether phospholipid, 1-alkyl-2-acetylglyceryl-3-phosphorylcholine; it is produced from membrane lipids. It acts via a G protein-coupled receptor to increase the production of arachidonic acid derivatives, including thromboxane A.

Actions of ***PAF*** :

- It helps ***in platelet aggregation***
- It has inflammatory activity.

Factors regulating platelet production :

i) Colony-stimulating factors (CSF): these control the production of megakaryocytes

ii) ***Thrombopoietin*** :

This is a circulating protein factor.

Production

It is produced constitutivelv by the ***liver*** and ***kidneys***,

Role

- It helps in maturation of megakaryocytes
- It helps in ***feedback regulation of platelet production*** :

There are thrombopoietin receptors on platelets.

When the number of platelets is low → the free circulating thrombopoietin is increased (because less thrombopoietin is bound to the platelets) → this increases production of platelets.

When the number of platelets is high → the free circulating thrombopoietin is decreased (because more thrombopoietin is bound to the platelets) → this decreases production of platelets.

- The amino terminal portion of the thrombopoietin molecule has the platelet-stimulating activity
- whereas the carboxyl terminal portion contains many carbohydrate residues and is concerned with the bio-availability of the molecule.

Applied aspects

Thrombocytopenic purpura

This occurs due to low platelet count.

Features :

- clot retraction is deficient
- there is poor constriction of ruptured vessels.
- easy bruisability and multiple subcutaneous hemorrhages.

Thrombasthenic purpura

In this condition, the platelet count is normal but the platelets are abnormal

Q. PDGF (or platelet-derived growth factor) is secreted from

a. alpha granules of platelets
b. dense granules of platelets
c. both
d. none

Ans. 'a'

Note : PDGF is also produced by macrophages and endothelial cells

RBC (Erythrocytes)

The RBCs carry haemoglobin (Hb).
Morphology and dimensions
Shape :
Biconcave, non-nucleated, very elastic and highly flexible when going through capillaries
Diameter :
6.5 to 8.8 micron (average = 7.5 micron)
Thickness :
at the center : 1 micron
at the periphery : 2.2 microns
average thickness : 2 microns.
Surface area :
135 to 140 square microns; the surface area is greatly increased by the biconcave shape (The surface area is much greater than if its volume were contained in a sphere).
Volume : 90 cubic microns.
Advantage of biconcave shape
It is more resistant to fragility
i) it does not get damaged as it passes through capillaries (it assumes a sausage or parachute shape while going through capillaries)
ii) its surface area increases; it helps in more efficient gas exchange.
Average life span in the circulation : 120 days; half-life : 60 days.
Count
Male : 5.4 millions/cumm of blood
Female : 4.8 millions/cumm of blood
(note : 1 cumm = 1 microlitre)
Each RBC has 20 pg of Hb.
In adult man has 3×10^{13} RBCs and about 900 gm of Hb.
Energy supply
Energy to the RBC is provided by :
- glycolysis (80 %)
- pentose phosphate pathway (20%)

Energy is required to maintain the ionic gradient across its membrane and to keep the iron in the ferrous (Fe^{2+}) state.
Permeability of the RBC membrane
The viability of RBC depends on the integrity of its membrane. It is freely permeable to water, sodium, potassium and chloride. But a Na-K pump keeps the intracellular sodium low and potassium high. The energy for the pump is provided by the membrane ATPase which requires magnesium, sodium and potassium for full activation. ATP is formed during glycolysis and its hydrolysis provides the energy for the sodium pump. When RBC metabolism ceases (as in cold-stored blood), the ions move between plasma and cells according to their concentration gradients.
Production of RBC
The production and maturation of RBC is called erythropoiesis.
Site
Foetus
First trimester
In the early embryo, blood formation takes place first in the mesoderm of the ***yolk sac*** (the area vasculosa) and later in the ***body*** of the foetus. It is called as the mesoblastic stage of erythropoiesis.
In the mesoblastic stage, the erythropoiesis takes place ***intravascularly***; the endothelial cells themselves get converted into nucleated RBC and get released in the circulation; in the circulation, they lose their nuclei.
Note :
Mesoblastic stage is the only stage where RBC is formed intravascularly; later, it is extravascular.
Second trimester
This stage of erythropoiesis is called the hepatic stage. In this stage, the sites of production are ***spleen and liver (especially liver***). Nucleated RBCs develop from the mesenchyme between the blood vessels and the tissue cells.
Third trimester
About the middle of foetal life, the bone marrow begins to act as a blood-forming organ. After this, the function of the bone marrow (in RBC production) increases and that of the liver decreases.
Adult
The only site of production is the bone marrow, however, if bone marrow is destroyed, then extramedullary erythropoiesis takes place in the liver and spleen. Before it enters the circulation from the bone marrow, it loses its nucleus. Thus, the peripheral blood has non-nucleated RBCs.
At birth, all the bones are filled throughout their length with red marrow. With increasing age, the marrow becomes more fatty (i.e. red marrow becomes yellow marrow). This process first starts in the distal bones of limbs (tarsus and carpus); then in the intermediate bones (tibia, fibula, radius and ulna); finally, in the proximal bones (femur and humerus).
At age 20 years, all marrow in the long bones is yellow except in the upper end of the femur and humerus.

In adults, red marrow persists mainly in the vertebrae, sternum, ribs, skull and pelvis bones.

Weight for weight, children have more red marrow than adults. If one wishes to study extension of haemopoiesis, one can study the shaft of long bone.

Stages in the development of RBCs or erythrocytes

a) From the pleuripotent hematopoietic stem cell (HSC) (refer) → committed stem cells are formed . The committed stem cells in the RBC series are of 2 types :

i) BFU-E (or burst forming unit –erythrocyte)

ii) CFU-E (or colony forming unit –erythrocyte)

b) BFU-E gives rise to → CFU-E cells

c) CFU-E cells give rise to → proerythroblast (or pronormoblast)

d) The stage from proerythroblast to RBC is shown in the following table :

	Name	**Size of cell (μm)**	**Cytoplasmic staining**	**Mitosis**	**Nucleus**	No. per 100 nucleated cells in the bone marrow
I	Pro-normoblast or proerythroblast	15 to 20	Deep violet blue (Basophilic)	Only during stress	Nucleus is 12 μm; it has many nucleoli; chromatin is fine and stippled; No Hb	1 to 3
II	Early normoblast	Somewhat smaller (10 to 17)	Basophilic	Active	***No nucleoli***; ***Hb appears***, chromatin is fine and shows a few nodes of condensation (Hb is formed from stage II to stage IV)	1 to 3
III	Intermediate normoblast	Still smaller (10 to 14 μm)	Polychromatophil	Active	The resting nucleus shows further condensation of chromatin. Hb increases; its eosinophilic staining gives the cytoplasm a polychramtic appearance	4 to 8
IV	Late normoblast (also called orthochromatic normoblasts)	7 to 10 μm	Eosinophilic	No	Nucleus is small; the condensed chromatin shows '***cart-wheel***' appearance; finally it becomes uniformly deeply condensed and stained (this state of the nucleus is called ***pyknosis;*** pyknosis = thickened and shrunken nucleus). Pyknosis is a stage in the degeneration of the nucleus. The nucleus finally breaks up and is extruded out	8 to 16
	Reticulocyte	Slightly larger than the mature RBCs	Eosinophilic (also basophilic reticulum is present)		No nucleus; Hb synthesis continues in this stage.	
	Mature RBC	7.2 μm	Fully eosinophilic (no reticulum)			

Duration

The entire process of erythropoiesis takes about 7 days. Out of this, time taken for conversion from proerythroblast to reticulocyte is 3 days; time taken for reticulocyte to become matured RBC is 4 days. Out of these 4 days, the last one day is spent in the peripheral circulation by the reticulocytes.

Note :

Maturation of the erythroblasts involves

- a decrease in the size of the cell
- increased condensation and finally pyknosis and disappearance of the nucleus
- accumulation of Hb
- a change in the staining of the cytoplasm from basophil via polychromatophil to eosinophil (initially the cytoplasm is basophilic due to plenty of RNA; later it turns eosinophilic due to accumulation of Hb and also due to decrease in RNA)

Reticulocyte

This is the name given to the young red cell; it is so called because on vital staining with cresyl blue, it shows a network of ***basophilic reticulum*** in the cytoplasm.
All the nucleated precursors of the reticulocyte (i.e. the normoblasts) also give this staining reaction.

The reticulum

This probably consists of ***remnants of the basophil cytoplasm*** of the immature cell (chemically, the reticulum is made up of ***RNA***).
If red cells are stained with eosin and methylene blue, the presence of the reticulum in the young cells (i.e. the reticulocytes) leads to a diffuse mauve staining of the cell; this is called polychramtophilia. (The cytoplasm is stained eosinophilic due to Hb and the reticulum is stained basophilic due to RNA)

Importance

i) In pathological states, this stained basophil material is sometimes present in clumps which appear as discrete blue particles. This finding known as basophil punctation (or ***punctate basophilia***) is especially obvious in ***lead poisoning***.
ii) As the red cell ages, the reticulum disappears. In the ***newborn, 2 to 6 %*** of the red cells in the circulation are reticulated; the number falls during the first week to ***less than 1%,*** at which level it remains ***throughout life***. Their number is increased whenever red cells are being rapidly manufactured. In such cases, 25 to 35 % of the circulating cells can be reticulocytes. An increase in the reticulocyte count (reticulocytosis) is the ***first blood change*** noted when ***pernicious*** anaemia is ***treated*** with vitamin B_{12}.

Spleen as a blood filter

It removes spherocytes and other abnormal RBCs. Abnormal RBCs are removed if they are not as flexible as the normal RBCs; if they are not flexible, they are not able to go between the endothelial cells that line the splenic sinuses. Thus, they get trapped and are removed.
Spleen also contains many platelets; it also plays a significant role in immunity.
RBC membrane fragility

This can be classified as under :

1. Mechanical fragility

When RBCs are shaken with glass beads for one hour, about 2 to 5 % of the cells get lysed. In some hemolytic anaemia, the % is more.

2. Autohemolysis

If normal blood with an anticoagulant is kept at 37 degree centigrade for 24 hours, less than 0.5 % cells get hemolysed. A higher percentage is seen in some hemolytic anaemia.

3. Osmotic fragility

If RBCs are suspended in hypertonic solution, they shrink. If suspended in hypotonic solution, they swell, become spherical (from disc-shaped) and eventually break and lose their Hb (haemolysis). The Hb of the hemolysed cells dissolves in the plasma, colouring it red.
0.9 % NaCl solution is isotonic with plasma
Values of normal RBC osmotic fragility
Haemolysis begins in 0.5% saline; 50 % lysis occurs in 0.40 to 0.42 % solution and complete haemolysis occurs at 0.3 % solution.
In hereditary spherocytosis (also called congenital haemolytic icterus)
The cells are already spherocytic in the normal plasma and not disk-shaped; thus, their osmotic fragility is more (i.e. they start getting hemolysed at less hypotonic or more hypertonic solutions than the normal cells). Therefore, hereditary spherocytosis is one of the most common causes of hereditary hemolytic anaemia.

Why are the cells spherocytic in hereditary spherocytosis
Here, there is defect in the RBC membrane; there is abnormality in the protein network that normally maintains the shape and flexibility of RBC membrane.

The RBC membrane skeleton is normally made up of the following proteins :

- ***spectrin, band 3 protein and ankyrin***

Spectrin is anchored to the trans-membrane protein band 3 by ankyrin.
(the band 3 protein also functions as an anion exchanger)
Hereditary spherocytosis can occur due to defects in spectrin, band 3, or ankyrin.

RBC of ***venous*** blood are slightly ***more fragile*** than those of arterial blood in normal persons.
Osmotic fragility is related to the shape of the RBS; the more spherical it is, the greater the fragility i.e. the higher the concentration of saline at which hemolysis occurs.

4. Drugs and infections

Hemolysis of RBC can occur due to drugs and infections. Deficiency of G-6-P-D increases the susceptibility to hemolysis by these agents. Why? G-6-P-D catalyses the first step in the oxidation of glucose via the hexose monophosphate shunt (HMS) pathway. This pathway generates NADPH; NADPH is required for the integrity of the normal red cell membrane.
Severe G-6-P-D deficiency also inhibits the killing of bacteria by granulocyte (and so predisposes to severe infections)

RBC indices

	Adult men	Adult women	Children 1 year
Direct measures			
1. Red cell count (RCC) (in	5.5	4.8	4.4

millions per cumm)			
2. Hb (gm/dL)	15.5	14	12
3. Mean corpuscular volume (MCV)(in fL)	85	85	85
4. Packed cell volume (PCV) or hematocrit (%)	47	42	40
Derived measures			
MCH (in pg)	29	29	27
MCHC (g/dL)	33	33	33

Note :
1 microlitre = 1 cu mm
1 fl = 10^{-15} litre
1 pg = 10^{-12} gram

MCH = mean corpuscular Hb; it is the average amount of Hb in one RBC

$$MCH = \frac{Hb}{RCC}$$

Formula for calculating MCH

$$MCH = \frac{Hb\ (g/dL)}{RCC\ (\textbf{\textit{as so many}}\ \text{millions})\ \text{per cumm}} \times 10$$

MCV = mean corpuscular volume; it is the average volume of one RBC

$$MCV = \frac{PCV}{RCC}$$

Formula for calculating MCV

$$MCV = \frac{PCV\ (\text{as percentage})}{RCC\ (\textbf{\textit{as so many}}\ \text{millions})\ \text{per cumm}} \times 10$$

MCHC = mean corpuscular hemoglobin concentration
This gives the amount of hemoglobin in one RBC wrt to its volume

$$MCHC = \frac{MCH}{MCV}$$

Since MCH = Hb/RCC and MCV = PCV/RCC,
MCHC can be expressed as =

$$\frac{Hb}{MCV \times RCC}$$

Formula for calculating MCHC

$$MCHC = \frac{Hb\ (\text{in g/dL})}{PCV\ (\%)} \times 100$$

MCV
> 95 f l = macrocytes
< 80 fl = microcytes

MCH
< 25 pg = hypochromic

Q. Which of the stages of the erythroid series can be seen in the peripheral blood?
a. Proerythroblast b. Early normoblast
c. Intermediate normoblast d. Late normoblast
'd'

Leucocytes (White Blood Corpuscles or cells - WBCs)

Introduction

The leucocytes are also called white blood corpuscles (WBS) or simply white cells of the blood but they are not white but colourless. The WBCs defend the body against diseases by fighting infections (bacterial, viral, parasitic, etc.), antigens and also against malignancy.

Types

WBCs can be divided into

i) Granulocytes

These WBCs have granules in their cytoplasm. The granulocyte WBCs are : neutrophils, eosinophils and basophils

ii) **Agranulocytes**

These WBCs do not have granules in their cytoplasm. The agranulocyte WBCs are : monocytes and lymphocytes

Normal values with range

Cell	Absolute value (Cells/cu.mm.)	Range (cells/cu.mm.)	Percentage of the total WBCs
Total WBC	9000	4000 to 11000	
Neutrophils	5400	3000 to 6000	50 to 70
Eosionophils	275	150 to 300	1 to 4
Basophils	35	0 to 100	0.4
Lymphocytes	2750	1500 to 4000	20 to 40
Monocytes	540	300 to 600	2 to 8

Note : 1 cu mm = 1 microlitre

Morphology of the nuclei

Nuclei

Granulocytes

Young granulocytes : horseshoe-shaped nuclei

Older granulocytes : multilobed nuclei

Agranulocytes

Lymphocytes : large round nuclei, scanty cytoplasm

Monocytes : kidney-shaped nuclei, abundant cytoplasm

Development of leucocytes (WBCs)

Leucocytes develop from the same single type of pleuripotent hematopoietic stem cells (HSCs) from which all the blood cells develop. The HSCs give rise to committed stem cells (also called progenitor cells or colony-forming units or CFUs). The committed stem cells are separate for each type of leucocyte except for the neutrophil and monocyte; neutrophil and monocyte develop from a common committed stem cell.

Stages in the development of neutrophil

Pluripotent hematopoietic stem cell → give rise to committed stem cell ; the committed stem cells go through the following stages :

1. Myeloblast

Diameter : 12 to 18 □m;

Nucleus

It is purple-blue, large and round with finely stippled chromatin with several nucleoli.

Cytoplasm

This consists of a narrow blue rim without granules. Protein synthesis is very active, as shown by a highly developed endoplasmic reticulum. The cells show active mitosis.

2. Promyelocytes

These show primary granules in the cytoplasm (azurophilic granules). Nucleoli decrease in number. Nucleus is round, chromatin has started to condense. Mitosis is seen at this stage also.

3. Myelocyte

Diameter : 10 to 15 □m

Cytoplasm

This is more extensive and less basophilic than myeloblast. It has granules; the colour of the granules classifies them as neutrophil , eosinophil or basophil myelocytes. Primary granules are no longer visible; in this stage, the secondary or specific granules (for three different granulocytes i.e. neutrophilic, eosinophilic and basophilic granules) appear. The cytoplasm is still basophilic. Mitosis is observed in this stage also.

Nucleus

Smaller and more basophilic than myeloblast. There are ***no nucleoli***; chromatin is coarser and it is further condensed.

4. Metamyelocyte

These cells have deep indented nuclei. The specific granules are plenty and they cytoplasm is yellow-pink. ***Mitosis is not seen***; chromatin is highly condensed.

5. Band form or juvenile neutrophil

Nucleus becomes ***horse-shoe or crescent shaped***. Specific granules are in plenty. In case of increased production of neutrophils, this form is also released into the circulation.

6. Segmented form or the mature neutrophils

It is a mature stage and the morphology is like a matured neutrophil. The cells have acquired all the properties of a neutrophil i.e. phagocytosis, chemotaxis etc. and also the surface receptors. The cells pass into the sinusoids to go into circulation.

Duration

From the stage of myeloblast to the stage of matured neutrophil it takes about 10 days, out of which half is required for development up to the stage of myelocyte (mitotic pool) and the other half is spent from metamyelocyte to matured neutrophil (maturation pool).

This time period is decreased during an acute infection when more neutrophils are needed. The matured neutrophils stay in the circulation for a short time (half life = 6 hours). Then the cells enter the tissues and die after 3 to 4 days. The neutrophils are destroyed by the RE cells, eliminated via GIT and via the respiratory tract secretions. Bone marrow contains 3 days reserve of matured neutrophils.

Eosinophils and basophils

These develop with their specific granules in the same way as the neutrophils.

Monocytes

These are produced from the same committed stem cells from which the neutrophils develop. The stages of development are :

Pleuripotent hematopoietic stem cell → committed stem cell → monoblast → promonocyte → monocyte. The monocyte after a short stay in the circulation pass to the tissues and are then called macrophages.

Neutrophils

These contain neutrophilic granules. They are the most numerous WBCs.

Diameter : 10 to 15 microns

Lobes in the nuclei

Their nucleus shows variable number of lobes (2 to 7); hence, they are called as polymorphonuclear leucocytes. The number of lobes increases as the neutrophil gets older.

Cytoplasm : pink

Granules :

fine violet (red-brown); amphophilic granules i.e. the granules take up ***both*** acidic and basic stains; thus although they are called neutrophils, their granules are not neutral.

Nucleus : purple blue; chromatin is coarse and ropy

Average ***half-life*** of a neutrophil in the circulation : ***6 hours***.

(thus, in order to maintain the normal circulating blood level, it is necessary to produce more than 100 billion neutrophils per day).

The ***neutrophils*** are ***most numerous*** and are of ***shortest life span***; therefore, their rate of formation is also high. The ***bone marrow*** contains the ***highest*** number of ***neutrophils*** in different stages of development and also the matured ones.

Neutrophil pool

The neutrophils are divided into different ***pools*** or collections, depending on the site.

i) The bone marrow pool

This represents the neutrophils present in bone marrow; it constitutes the largest pool viz. ***90%***

ii) circulation

This represents the neutrophils present in the circulation; it constitutes ***3%***; out of this 3%

- 1.5% are in actual circulation and
- ***1.5%*** are attached to the endothelium; this is called the. ***marginal pool***.

iii) Tissue pool

This represents the neutrophils present in the tissues; it constitutes ***7%***;

Function

Neutrophils are also called as ***microphages***; this is because they engulf small-sized particles (the ***monocytes*** are called ***macrophag\es*** ; this is because they engulf large-sized particles).

Neutrophils are called the body's ***first line of defence***; this is because they are the first to move towards the invading the bacteria.

How do the neutrophils leave the capillaries and enter the tissues?

Many of the neutrophils enter the tissues.

i) attraction towards the endothelium :

At first, the neutrophils get ***attracted to*** the ***endothelial*** surface ***by selectins*** and they roll along the endothelium.

ii) Binding to the endothelium:

Next, they bind to the endothelium with the help of neutrophil adhesion molecules of the integrin family.

iii) Diapedesis:

The neutrophils have contractile proteins e.g. actin, myosin I etc. in their cytoskeleton. With the help of these contractile proteins, they come out of the walls of the capillaries by passing in between the endothelial cells. This process is called ***diapedesis***.

Note :

Many of the neutrophils that come out of the circulation enter the gastrointestinal tract and are lost from the body.

Inflammatory response of the neutrophils to bacterial invasion

Invasion of the body by bacteria triggers the inflammatory response.

i) Stimulation of the bone marrow

The bone marrow is stimulated to produce and release large numbers of neutrophils.

ii) Chemotaxis

Chemical agents move the ***neutrophils*** towards the infected area ; such movement of neutrophils is called ***chemotaxis***. The chemical agents responsible for chemotaxis are called as chemotactic agents.

Chemotactic agents

Bacterial products interact with plasma factors and cells to produce these agents The chemotactic agents are a part of a large family of ***chemokines*** .

The chemotactic agents include :

- A component of the complement system (***C5a***);
- Leukotrienes;
- Polypeptides (from lvmphocytes, mast cells, and basophils).

G_c- globulin

This is a plasma protein that increases the effect of C5a; the neutrophil membranes also contain this protein.

It also binds and transports vitamin D in the plasma.

iii) Opsonization

Coating of the bacteria by certain plasma factors helps the neutrophils in attacking the bacteria. The coating makes the bacteria "***tasty***" for the neutrophils. This process of coating of the bacteria is called ***opsonization***. The factors used for coating are called ***opsonins***. The principal opsonins are the ***IgG*** immunoglobulins and ***complement proteins***.

iv) Phagocytosis

- The opsonized bacteria bind to the receptors on the neutrophil cell membrane
- This binding to increases the motor activity of the neutrophil via a hetero trimeric G protein .
- The increased motor activity leads to prompt ingestion of the bacteria by the neutrophil (phagocytosis) forming a phagocytic vacuole containing the bacteria

v) Degranulation

The neutrophil granules discharge their contents into the phagocytic vacuoles (and also into the interstitial space); this process is called as degranulation.

The granules release

- various proteolytic enzymes and
- ***defensins*** : these are anti-microbial proteins; the defensins are of two types - alpha and beta.

vi) **Activation of NADPH oxidase**

The neutrophil cell membrane-bound enzyme NADPH oxidase is also activated; this leads to production of ***toxic oxygen metabolites***.

The combination of proteolytic enzymes from the granules and the toxic oxygen metabolites help in killing and digestion of the bacteria.

vii) Respiratory burst

Activation of NADPH oxidase (present on the neutrophil cell membrane) results in :

- a sharp ***increase in O_2 uptake*** and metabolism in the neutrophil; this is called as ***respiratory burst***)
- generation of O_2^- by the following reaction:

$NADPH + H^+ + 2O_2 \rightarrow NADP^+ + 2H^+ + 2O_2^-$

viii) Killing and digestion of the bacteria by :

a) Oxidants : These are

- O_2^- (also called ***superoxide***):
  This is s a free radical formed by the addition of one electron to O_2.
- H_2O_2
  2 O_2^- react with two H^+ to form H_2O_2; this reaction catalyzed by the cytoplasmic form of superoxide dismutase (SOD-1):

$$O_2^- + O_2^- + H^+ + H^+ \xrightarrow{\text{SOD-1}} H_2O_2 + O_2$$

Both the oxidant O_2^- and H_2O_2 are effective bactericidal agents; however, H_2O_2 is converted to H_2O and O_2, by the enzyme ***catalase***.

SOD-1

The cytoplasmic form of SOD contains both ***Zn*** and ***Cu***. It is found in many parts of the body.

Defective SOD

This can occur due a gene mutation; the defective SOD is the cause of a familial form of amyotrophic lateral sclerosis (ALS).

Because of the deficiency of SOD, it is possible that O_2^- accumulates in motor neurons and kills them in at least one form ALS.

Two other forms of SOD encoded by at least one different gene are also found in humans.

- **HOCl, HOBr**

These are also effective oxidants.How are they produced?

Neutrophils have an enzyme called ***myeloperoxidase***; this enzyme catalyzes the conversion of CI-, Br, I-, and SCN- to the corresponding acids (HOCI, HOBr, etc). These acids are also potent oxidants. Since CI- is present in greatest abundance in body fluids, the principal product is HOCI.

b) Other agents in neutrophils that destroy bacteria :

Neutrophil granules have defensins, an elastase and two metalloproteinases that attack collagen, and a variety of other proteases; all these help in destroying the invading organisms. These enzymes act in a cooperative fashion with the oxidants mentioned above to kill the bacteria.

Note:

In certain diseases, e.g. rheumatoid arthritis, the neutrophils may also cause local destruction of host tissue.

Role of microtubules and microfilaments

These play a role in

- movement of the cell in phagocytosis
- migration of the cell to the site of infection

Proper function of the microfilaments involves the interaction of the actin they contain with ***myosin-I*** on the ***inside of the cell membrane***.

Eosinophils

They are called so because they have eosinophilic granules; these get stained with acidic dyes.

Characteristic features :

Eosinophils show many of the features of neutrophils. For example, they a short half-life in the circulation; they are attracted to the surface of endothelial cells by selectins; they bind to integrins which attach them to the vessel wall; they enter the tissues by diapedesis. Like neutrophils, eosinophils also show chemotaxis.

Sites

Eosinophils are especially abundant in

- the mucosa of the gastrointestinal tract; here, they defend against parasites.
- and in the mucosa of the respiratory and urinary tracts.

Functions

i) Phagocytic function

Like neutrophil,eosinophils are also phagocytic; however, eosinophils are ***less motile*** than neutrophils. Like neutrophil granules, eosinophil granules are also lysosomal in nature and contain most of the enzymes found in neutrophil granules. Eosinophil granules have a very high peroxidase content which partly accounts for their parasiticidal action e.g. versus schistosomes.

ii) Allergic reactions

Eosinophils collect at the site of ***allergic*** reactions. It has been suggested that they limit the effects of mediators (e.g. histamine, bradykinin) of some types of antigen-antibody reaction. The ***aryl-sulphatase-B*** present in the eosinophil inactivates the slow reacting substance (SRS) released from mast cells and prevents anaphylaxis (anti-allergic reaction). Furthermore, histaminase etc. from eosinophils destroy the substances released from mast cells. Because of its phagocytic action, it takes up antigen-antibody complexes.

iii) Eosinophils contain a ***major basic protein*** (MBP) which damages the larvae of parasites.

iv) There is one eosinophilic cation protein which probably neutralizes heparin..

v) Eosinophils also contains peroxidase.

Factors and conditions affecting eosinophil activation

i) Their maturation and activation in tissues is particularly stimulated ***by IL-3***, ***IL-5***, and ***GM-CSF***.

ii) The level of circulating eosinophils is ***reduced by*** adrenal ***corticosteroids*** and hence by secretion of ACTH. The eosinopenia is ***caused by sequestration*** of eosinophils in the lungs and spleen ***and*** by their ***destruction*** in the circulating blood.

iii) Circulating eosinophils are ***increased in***

- ***allergic*** diseases such as ***asthma*** and
- in various other ***respiratory*** and ***gastrointestinal diseases***.

Basophils

Basophils also enter tissues and release proteins and cytokines. They are also ***motile*** and ***phagocytic***. They ***resemble*** but are not identical to ***mast cells***. Like mast cells, basophils contain ***histamine and heparin***. They release histamine and other inflammatory mediators when activated by a histamine releasing factor secreted by T lymphocytes; they are essential for ***immediate-type hypersensitivity*** reactions. These reactions range from mild urticaria and rhinitis to severe anaphylactic shock.

Mast Cells

What are they?

Mast cells are heavily ***granulated wandering*** cells

Sites where found

They are found in areas rich in connective tissue, and they are abundant beneath epithelial surfaces.

Contents of their granules

Their granules contain ***heparin***, ***histamine***, and many ***proteases***. The heparin appears to play a role in granule formation.

Role

i) in acquired immunity

Mast cells have ***IgE receptors*** on their cell membranes; like basophils, they degranulate when IgE-coated antigens bind to their surface. They are involved in ***inflammatory*** responses ***initiated by immunoglobulins IgE and IgG***. The inflammation fights invading parasites.

ii) in natural immunity

Mast cells ***release TNF-alpha*** in response to bacterial products by an antibody-independent mechanism; thus they participate in the nonspecific natural immunity that fights infections. Marked mast cell degranulation produces clinical manifestations ranging from allergy to anaphylaxis.

iii) histamine released from the mast cells of the GIT(and from other gastrointestinal immune cells) stimulates GIT secretion of water and electrolytes

iv) primed mast cells play a central role in the gastrointestinal response to antigen. A primed mast cell is one that carries antibody on its surface. When the antibody "recognizes" its particular antigen, the mast cells degranulate and release many different mediators. Several of these mediators induce hypersecretion of salts and water by the epithelial cells as well as hypermotility. Mast cells also release cytokines that recruit other mucosal immune cells to the response. These cells may then also release secretogogues.

Monocytes

Life span of monocytes

i) in the circulation

Monocytes enter the blood from the bone marrow and ***circulate*** for about ***72 hours***.

ii) in the tissues

After about 72 hours in the circulation, monocytes enter the tissues and become ***tissue macrophages***

Their life span in the tissues is unknown; studies suggest that they persist for about ***3 months***. It appears that they do not reenter the circulation.

Some monocytes become the ***multinucleated giant cells*** seen in chronic inflammatory diseases such as tuberculosis.

Monocyte- macrophage system

As mentioned above, monocytes after a short stay in the circulation enter the tissues and becomes tissue macrophages. These tissue macrophages are found in many organs and are known by different names :

Tissue macrophage in	**Known as**
Liver	Kupffer cells
Connective tissue	Histiocytes
Lymph nodes	Dendritic cells
Spleen	Dendritic cells
Bone marrow	Dendritic cells
Adrenal glands	Endothelial cells
Pituitary	Endothelial cells
CNS	Microglia
Alveoli	Pulmonary alveolar macrophages (PAMS)
Skin	Langerhans cells
Bone	Osteoclasts

The monocyte-macrophage system was ***previously known as reticuloendothelial system.***

Functions of tissue macrophage system

i) Phagocytic

The macrophages become activated by lymphokines from T lymphocytes. The activated macrophages migrate in response to chemotactic stimuli phagocytose invading bacteria. The steps in phagocytosis is similar to that in neutrophils.

ii) they play a key role in immunity.

iii) They secrete many different substances e.g.

- substances that affect lymphocytes and other cells
- prostaglandins of the E series
- clot promoting factors etc.

Factors stimulating/activating the cells of the bone marrow

The hematopoietic stem cells (HSC) in the bone marrow (refer page) are the pleuripotent uncommitted stem cells; they give rise to committed stem cells (also called progenitor cells). As the name suggests, committed stem cells produce one type of blood cell.

i) Interleukins

Interleukins IL-1 and IL-6 followed by IL-3 act in sequence to convert pluripotential uncommitted stem cells to committed progenitor cells .***IL-3*** is also known as ***multi-CSF***. (CSF = colony stimulating factor)

ii) Colony-stimulating factors (CSF)

CSFs are factors which stimulate/activate a particular committed stem cell. They are so called because these factors forms colonies of the committed stem cell in soft agar culture medium.

The various CSFs are

- granulocyte-macrophage CSF (GM-CSF)
- granulocyte CSF (G-CSF)
- macrophage CSF (M-CSF).

Function of interleukins and CSFs

i) Each of the CSFs stimulates mainly one type of stem cell
ii) In addition, each of the CSFs (as well as the interleukins) are capable of stimulating other stem cells as well.
iii) The interleukins and CSFs also they activate and sustain mature blood cells.

The genes for many of these factors are located together on the ***long arm*** of ***chromosome 5***. Basal hematopoiesis is normal in mice in which the GM-CSF gene is knocked out; this indicates that loss of one factor can be compensated for by others. However, the absence of GM-CSF causes accumulation of surfactant in the lungs.

Source of these factors

The factors are produced by macrophages, activated T cells, fibroblasts, and endothelial cells. Mostly, the factors act locally in the bone marrow.

(Note : The RBC stimulating hormone, erythropoietin, is produced in part by kidney cells and is a circulating hormone).

Applied aspects

To fight invading bacteria, the phagocytic mechanism has to be intact.. If there is a defect in this mechanism, it can make the person prone to infections. The various defects in the phagocytic mechanism are as follows :

i) hypomotility of neutrophils
In this condition, actin in the neutrophils does not polymerize normally; as a result, the neutrophils move slowly.
ii) congenital deficiency of integrins in the leukocyte
iii) chronic granulomatous disease
In this condition, there is a failure to generate O_2^- in both the neutrophils and monocytes; thus, there is inability to kill many phagocytosed bacteria.
iv) Severe congenital glucose 6-phosphate dehydrogenase deficiency
In this condition, there is failure to generate NADPH; as mentioned above, NADPH is required for producing O_2^-; consequently, the patient has multiple infections because of failure to generate O_2^-
v) Congenital myeloperoxidase deficiency,

In this condition, hypohalite ions are not formed; thus, there is decrease in ability to attack microbes.

Lymphocytes

Site of production of lymphocytes after birth

i) Some lymphocytes are formed in the bone marrow.
ii) However, most are formed in the lymph nodes, thymus, and spleen. The precursor cells are originally from the bone marrow; these precursor cells then get processed either in the thymus or bursal equivalent. These processed precursor cells move to the lymph nodes, thymus and spleen.

Release into the circulation

From their site of production, the lymphocytes enter the bloodstream mostly via the lymphatics. At any given time, only about ***2%*** of the body lymphocytes are in the ***peripheral blood***. ***Most*** of the rest are in the ***lymphoid organs***. Approximately, 3.5 x 10^{10} lymphocytes per day enter the circulation via the thoracic duct alone; however, this count includes cells that reenter the 1ymphatics and thus traverse the thoracic duct more than once.

Function

Lymphocytes play a very important role in immunity.

MCQs

Q. Which of the following is/are phagocytic

a. Neutrophil
b. Eosinophil
c. Basophil
d. All

'd'

Q. Maximum motility is shown by

a. Monocyte
b. Neutrophil
c. Basophil
d. Myeloblast

'b'

Motility is most marked in the neutrophils and in the later myelocytes.
It is present in the eosinophils, basophils and monocytes.
It is absent in myeloblast and lymphoblasts.
It is of a different character in lymphocytes.