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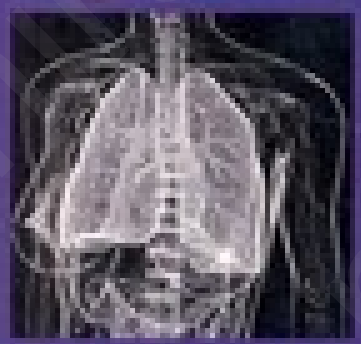
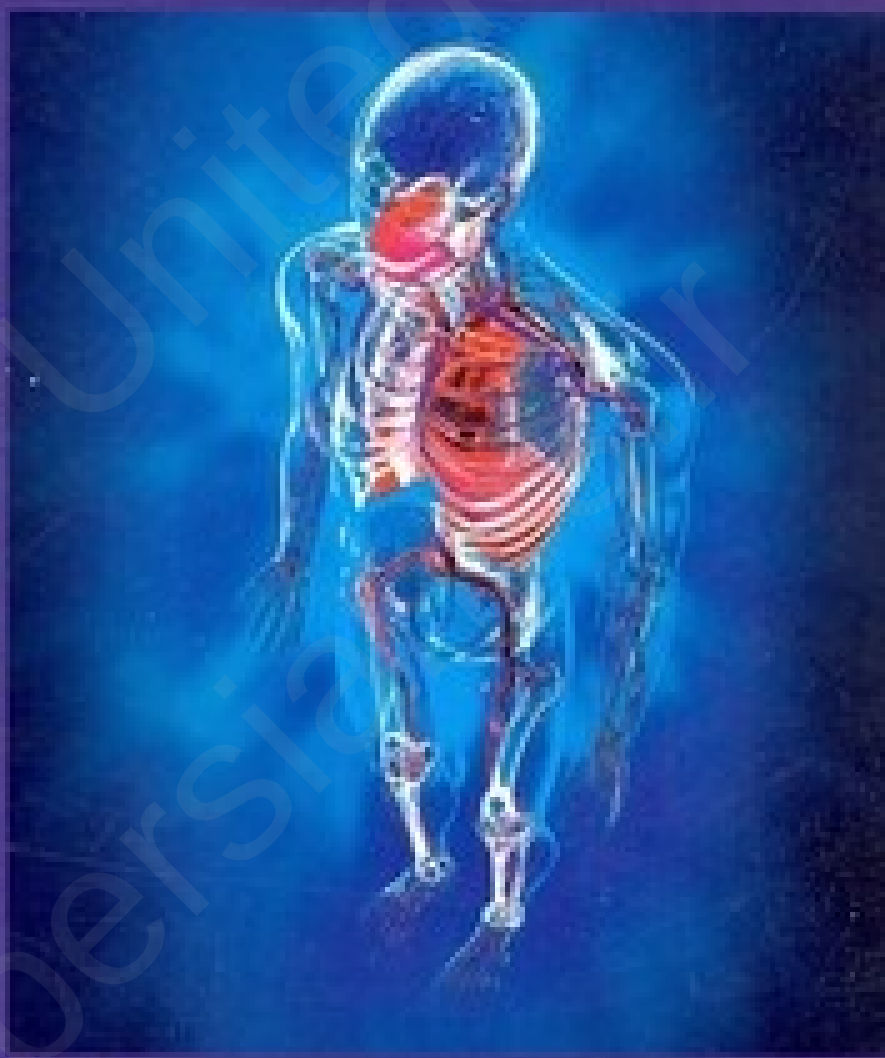
THE RELIABLE ICON IN

# PHYSIOLOGY

*Preparatory Manual for Undergraduates*





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SANOOP KS
MRIDUL GS
NISHANTH PS

*Foreword*
**Swarnalatha PK**



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# PHYSICON

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# PHYSIOLOGY

(*Preparatory Manual for Undergraduates*)

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# Dedicated to

***Our Parents***

*Whose blessings and love have always been our precious resource*

***Our beloved teacher, Dr Swarnalatha PK***

*Who laid the foundation for our interest in the subject and kept the flame glowing against all winds*

***Almighty***

*Whose mighty grace strengthens all our weaknesses from day one to this day and for the days to come ...*

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# Foreword

It is my great pleasure to write the foreword to this book **Physicon—The Reliable Icon in Physiology (Preparatory Manual for Undergraduates)** compiled by my students Dr Sanoop KS, Dr Mridul GS, Dr Nishanth PS of 2007 MBBS batch of Kannur Medical College, Kannur, Kerala, India. Having realized the gray areas in the study of Physiology themselves, they come out with their valuable work. Physicon is a user friendly book which will help the undergraduate medical students to understand the principles and learn the subject of Physiology. It is a handy and trustworthy companion written in simple and lucid language with plenty of appropriate illustrations to enable a better understanding. The book contains every detail needed for the MBBS examination and can be read within the time frame available to the students. But students should read their standard textbooks whenever they get time, as their aim should not only be a pass in Physiology but also a thorough knowledge in subject which is the basis of General Medicine. I hope, this book would inspire students to make a mark for themselves and the college in their first MBBS university examinations. My sincere and heartfelt wishes for the success of the book. I wish all the best of luck in achieving greater heights.

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# Preface

*PHYSICON—The Reliable Icon in Physiology (Preparatory Manual for Undergraduates)*, designed to provide a concise knowledge of the subject, is finally at your reach. The purpose of this book is to serve as a companion during the first MBBS Physiology examination preparation. A student must have good command over the subject, as Physiology forms the basis of General Medicine, so the subject has to be learnt as it is from its roots. Many standard books for Physiology are available; both by Indian as well as Foreign authors. In these books, certain chapters are dealt clearly with appropriate illustrations while leaving the rest. So, students need to refer more than one textbook to master the subject, this is difficult particularly during the examination periods. This inspired us to bring forth a single comprehensive and examination-oriented companion in Physiology, which could provide all the information, an undergraduate need to know, so as to appear for an examination with confidence.

A concerted effort has been made to provide concise and comprehensive coverage of the subject with simple language, self-explanatory diagrams, flow charts and illustrations. Practicals are also covered in a systematic manner with complete viva questions. We have also included wide collections of MCQs and reasoning type questions. A question bank containing the previous university examination questions has been included taking advantage of the fact that most questions are generally repeated.

We are very much indebted to our beloved teacher, Dr Swarnalatha PK (Associate Professor, Department of Physiology, Kannur Medical College, Kannur, Kerala, India), whose guidance and inspiration helped us throughout the tedious task of making this project a reality. She has been with us in all stages from day one.

We hope our efforts would meet the expectations of the students. We are sure that the students will find the book in this present form more useful. The book is primarily intended for undergraduate MBBS students, though we believe it should prove useful to other health professionals like BDS, Ayurveda, Homeopathy, Nursing, BPT, etc. because of its simplicity. This material is in no way a substitute for any standard textbook. As this is an examination-oriented book, you should read your textbooks first, before reading this book.

Sincere attempts have been made to maintain the accuracy and correctness of the subject. But we request all the readers to send their valuable suggestions and feedback to kmcphysicon@gmail.com or log on to www.facebook.com/Physicon and it will be acknowledged. As we conclude, we would like to bow in front of Almighty's grace with which we are blessed abundantly so as to make the dream called Physicon into a reality.

Wishing you all the best

**Sanoop KS**
**Mridul GS**
**Nishanth PS**

# Acknowledgments

The gratitude we feel for all those mentioned below is too great and is quite impossible to express our feelings in words. We urge the reader to take a few minutes to read this section before moving on to the rest of the book.

We thank Dr PP Venugopalan (Medical Director and Dean, Kannur Medical College, Kannur, Kerala, India), Dr Shivasubrahmanyam (Associate Professor, Department of Biochemistry, Kannur Medical College, Kannur, Kerala, India) and our families for their constructive criticism, advice and their moral support.

We are also grateful to the MBBS 2007 batch of Kannur Medical College, Kannur, Kerala, India for their indispensible help, encouragement and support without which 'Physicon' would have never reached its present state. We owe our special thanks to our Juniors—2008, 2009 and 2010 MBBS of Kannur Medical College for their continuous support and valuable suggestions.

We express our sincere gratitude to Shri Jitendar P Vij (Chairman and Managing Director), Mr Tarun Duneja (Director-Publishing), Mr KK Raman (Production Manager), Mr Sunil Kumar Dogra (Production Executive) and Mr Neelambar Pant (Production Coordinator) of M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India for publishing the book and materialize our dreams.

We express our gratitude to Mr Jose (Branch Manager, Jaypee Brothers Medical Publishers, Kochi branch), Mohit Ghai, Akhilesh Kumar Dubey, Binay Kumar, Ram Kumar and all other staff members of Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India for their painstaking efforts in bringing out this book.

Last but not least, we thank Amit Darwin (2006 MBBS, Kannur Medical College), Rejith Sreenivasan (2006 MBBS, Kannur Medical College), Shijin PK (2007 MBBS, Kannur Medical College), Arun Ramesh(2007 MBBS, Kannur Medical College), Anjali Vijayan (2007 MBBS, Kannur Medical College), Amritha Rajendran(2007 MBBS, Kannur Medical College), Shahnaz (2007 MBBS, Kannur Medical College), Hema (2007 MBBS, Kannur Medical College), Muneer A (2008 MBBS, Kannur Medical College), Saneesh PS (2009 MBBS, Kannur Medical College), Sanu S (2009 MBBS, Kannur Medical College), Deepthi S Johnson (2009 MBBS, Kannur Medical College), Sumesh (2010 MBBS, Kannur Medical College), Sonu (2010 MBBS, Kannur Medical College), Shibily (2010 MBBS, Kannur Medical College), Khadeeja Bisrath (2010 MBBS, Kannur Medical College), Sibi (Midas offset, Kannur), Sumit (Midas offset, Kannur), and Jithu (Midas offset, Kannur).

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# Section 1

## THEORY

Chapter

# 1 General Physiology

## INTRODUCTION

Human physiology is concerned with the way various systems function and the way each contributes to the functions of the body as a whole.

## TRANSPORT ACROSS CELL MEMBRANE

By two major processes—active and passive process.

### Passive Process

Here substance moves across the membrane without any energy expenditure. It includes diffusion and osmosis.

#### *Diffusion*

It is a passive process by which molecules move from areas of high concentration to areas of low concentration. It is of two types—simple diffusion and facilitated diffusion.

***Simple Diffusion***

It occurs because the heat content of the solution keeps the solvent and the solute particles of the solution in constant motion.

*Factors affecting diffusion*

1. *Distance:* The greater the distance, the longer the time required.
2. *Size of gradient:* The larger the concentration gradient, faster the diffusion.
3. *Temperature:* The higher the temperature, faster the diffusion rate.
4. *Molecular size:* The permeability of cell membrane to a substance falls rapidly with increase in molecular weight in the range between 10,000 and 60,000. This is why glucose diffuses faster than large proteins.
5. *Lipid solubility:* Lipid soluble molecule diffuses rapidly.
6. *Surface area:* The larger the surface area, faster the diffusion.

   The rate at which a material diffuses through the membrane is given by Fick's law of diffusion.

Net rate of diffusion =

$$\frac{\text{Diffusion coefficient} \times \text{area of membrane} \times (C_{in} - C_{out})}{\text{Thickness of membrane (or diffusion distance)}}$$

Where $C_{in}$ and $C_{out}$ = Concentration of material inside and outside of the membrane.

***Facilitated Diffusion***

It is a carrier- mediated process that enables molecules that are too large to flow through membrane channels by simple diffusion. The carrier molecule undergoes repetitive spontaneous configurational changes during which, the binding site for the substance is alternately exposed to the ICF and ECF (Fig. 1.1). For example:

a. Glucose transport by the glucose transporter (GLUT) across intestinal epithelium.
b. Transport of glucose into RBC, muscle and adipose tissue in presence of insulin.

#### *Osmosis*

It refers to diffusion of water or any other solvent molecules through semipermeable membrane.

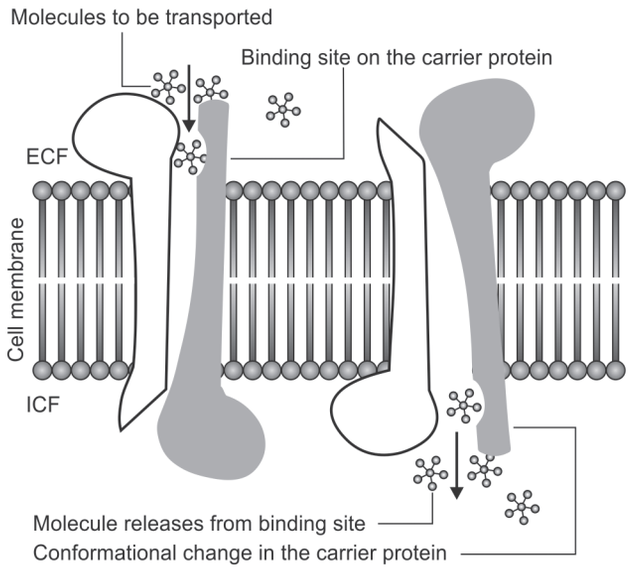



**Fig. 1.1:** Facilitated diffusion

## Active Transport Process

Substances are transported against their chemical and electrical gradient. This form of transport require energy. It includes:

a. Primary active transport
b. Secondary active transport
c. Vesicular transport

### *Primary Active Transport*

They directly use energy from the hydrolysis of ATP. It consists of:

i. $Na^+ – K^+$ pump
ii. $Ca^{2+}$ pump
iii. Potassium hydrogen pump

i. ***$Na^+$- $K^+$ pump***

It is an electrogenic pump. Here $3Na^+$ ions moves out and two $K^+$ ions moves in. It uses ATPase as the carrier molecule. ATPase is composed of 6 subunits, 3 α-and 3 β-subunits. Sodium and potassium transport occurs through α subunits. α subunit has ATPase enzymatic activity. Binding sites are present on its intracellular and extracellular faces.

*Mechanism of action (Fig. 1.2):* Binding of $3Na^+$ ions and ATP to a carrier protein inside the cell transfers high energy phosphate group from ATP to aspartic acid residue of α-subunit of ATPase (phosphorylation). This causes change in configuration of protein resulting in $3Na^+$ ions to move out of the cell.

When $2K^+$ ions bind to carrier protein on the outside of the cell, the aspartic acid - phosphate bond is hydrolyzed (dephosphorylation).This causes second change in configuration of protein resulting in $2K^+$ ions to move into the cell.

*Clinical significance:* Digitalis, a drug used for the treatment of heart failure, increases myocardial contractility by binding to α-subunit and interfering with the dephosphorylation step of transport process. This action is prominent in failing heart.

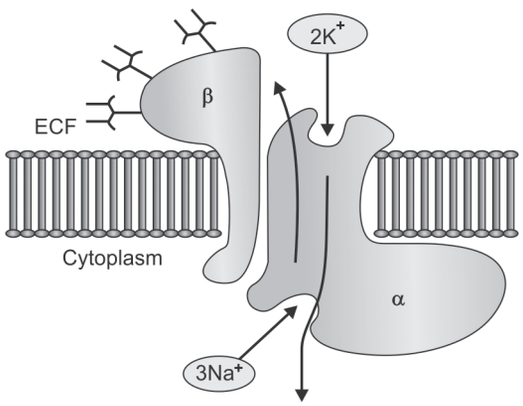



**Fig. 1.2:** Mechanism of operation of $Na^+ – K^+$ pump

ii. ***$Ca^{2+}$ pump***

It is present in sarcoplasmic reticulum of muscle to maintain intracellular $Ca^{2+}$ concentration. It is also present in cell membrane and cell organelle membrane. In the cell membrane, the direction of $Ca^{2+}$ is from cytoplasm to ECF. In the cell organelle membranes, it is from cytoplasm to the organelle lumen.

iii. ***Potassium-hydrogen pump***

It is present in cells of gastric mucosa and renal tubules where it causes secretion of $H^+$.

## Some Channel Blockers

Na channels—TTX (tetrodotoxin), STX (saxitoxin)
K channels—TEA(tetraethylammonium)
Ca channels—verapamil, nifedipine
$Na^+ – K^+$ ATPase—ouabain, digitoxin.

### *Secondary Active Transport*

Here the active transport of $Na^+$ is coupled with the transport of other substances.

***Mechanism***

When both $Na^+$ and the substance are bound to the carrier molecule , the carrier undergoes configurational change during which both these molecule are transported across membrane (Fig. 1.3). For example:

1. Co-transport of glucose and amino acids along with $Na^+$ ions from the proximal renal tubules.
2. Sodium counter transport of $Ca^{2+}$ and $H^+$ (transport in a direction opposite to the primary ion ($Na^+$).

### *Vesicular Transport*

By endocytosis and exocytosis (Fig. 1.4)

i. *Endocytosis:* These are of two types:

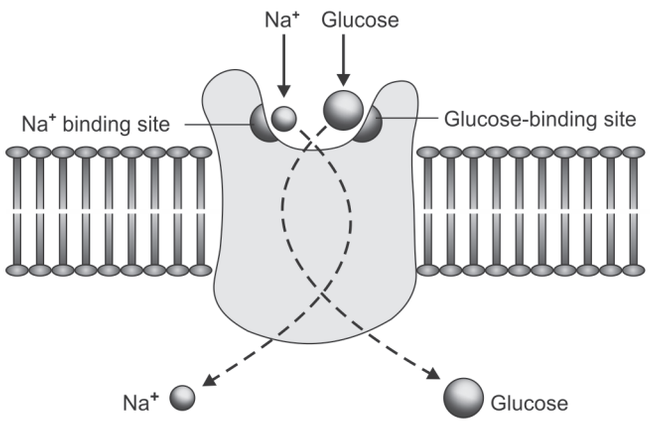



**Fig. 1.3:** Secondary active transport of glucose

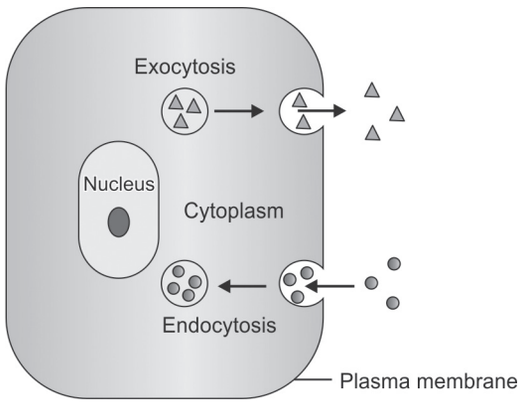



**Fig. 1.4:** Vesicular transport process

a. *Phagocytosis:* Process by which extracellular substances (bacteria, dead tissue, foreign particles) are engulfed by the cells. The substance makes contact with the cell membrane, which then invaginates. The endocytic vesicle pinches off from the cell membrane and fuses with another intracellular vesicle. For example, lysosome, from which the ingested substance is released into the ICF.
b. *Receptor:* Mediated endocytosis: The material to be transported 1st bind to a receptor and then the receptor-substance complex is ingested by endocytosis.

ii. *Exocytosis:* Substance secreted by the cell are trapped within the vesicles or granules which fuse with the membrane and release their content into ECF.

### *Carrier Type Process*

Carrier is a transport protein that binds ions and other molecules and then change their configuration, thus moving the bound molecule from one side of cell membrane to other (Fig. 1.5).

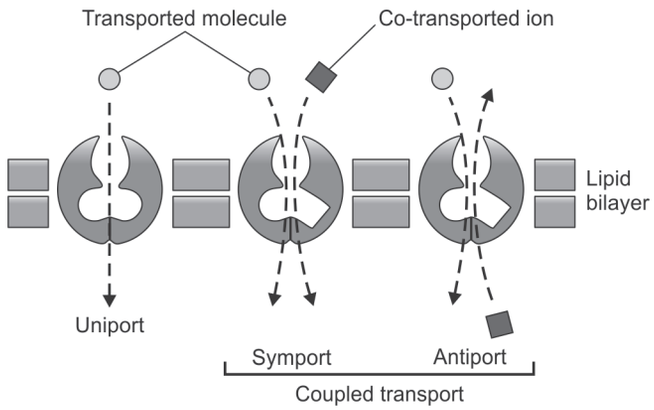



**Fig. 1.5:** Carrier type processes

#### *Types*

1. *Uniporters*: Transport a single particle in one direction. For example, facilitated diffusion of glucose.
2. *Symporters*: Transport two particles together in same direction. For example, secondary active transport of glucose.
3. *Antiporters*: Transport molecules in opposite direction. For example, $Na^+$- $K^+$ pump, $Na^+$- $Ca^{2+}$ exchangers, $Na^+$-$H^+$ exchangers.

## BODY FLUID COMPARTMENTS (FIG. 1.6)

### Extracellular Fluid

This is the fluid contained in the spaces outside the cell. Extracellular fluid (ECF) compartment includes plasma, interstitial fluid and transcellular fluid.

#### *Plasma*

It is the fluid portion of the blood. It represents 25% of the ECF. Its volume can be calculated from blood volume and PCV.

Plasma volume = blood volume × (100 – hematocrit/100)

where, blood volume = 80 ml/kg of body weight.

#### *Interstitial Fluid*

It is that part of ECF that is outside the vascular system. It surrounds all cells except blood cells and includes lymph.

#### *Transcellular Fluid*

It represents fluid in the lumen of structures lined by epithelium. It includes digestive secretions, sweat, CSF, pleural,

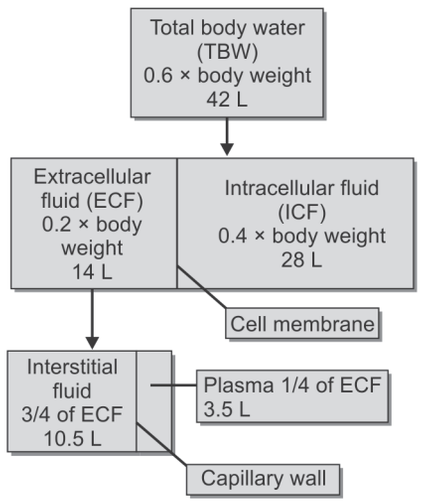



**Fig. 1.6:** Distribution of total body water (normal 70 kg man)

peritoneal, synovial, intraocular, pericardial fluids, bile and luminal fluids of the gut, thyroid, cochlea.

### Intracellular Fluid

This is the fluid containing within the body cells. Its volume varies.

### Measurement of Body Fluids

The volume of water in each fluid compartment can be measured by the indicator dilution principle. This is based on:

i. The amount of a substance injected intravenously (A)
ii. The volume in which that substance is distributed (V)
iii. Final concentration attained (C)
C = A/V, i.e. V=A/C.

#### *Characteristics of Indicator*

- Should be easy to measure
- Nontoxic
- Must mix evenly
- Must remain in compartment being measured
- Must not alter water distribution
- Must be unchanged by the body.

#### *Extracellular Fluid Measurement*

The ECF volume is difficult to measure as the limits of this space are ill defined and few substances mix rapidly in all parts of the space while the remaining are exclusively extracellular.

***Methods***

- Most accurate method to measure ECFV is by using inulin.
- As $Cl^-$ is largely extracellular, radioisotope of Cl have been used for determining ECFV.
- Mannitol and sucrose have been also used.

***Plasma volume***

It is measured by two dilution methods.

i. The first method employs substances that neither leave the vascular system nor penetrate the RBC. It includes:
   - Evan's blue dye
   - Radioiodinated human serum albumin
   - Radioiodinated gamma-globulin and fibrinogen.
ii. Second method is based on the fact that the radio isotopes of the phosphorous ($P^{32}$), iron ($Fe^{56,57}$) and chromium($Cr^{51}$) penetrate and bind to RBC. Therefore the red cell volume, i.e. volume occupied by all the circulating RBC in the body can be measured by injecting tagged RBCs intravenously and after mixing has occurred, measuring the fraction of the RBCs that is tagged. Commonly used tag is $Cr^{51}$ that is attached to the cells by incubating them in a suitable 'Cr' solution. Then,

$$\text{Plasme volume} = \text{Blood volume} \times \frac{100 - \text{PCV}}{100}$$

(practically PCV = volume)

***Interstitial fluid volume***

It cannot be measured directly because as it is difficult to sample and no substance is distributed exclusively in this compartment. Interstitial fluid volume is determined as the difference between ECFV and plasma volume.

#### *Intracellular Fluid Volume Measurement*

Intracellular fluid volume (ICFV) cannot be measured directly by dilution, because no substance is confined exclusively to this compartment after intravenous administration. It is determined indirectly as:

$$\text{ICFV} = \text{TBW} - \text{ECFV}$$

Total body water can be measured by **indicator dilution principle.** Deuterium oxide (heavy water) has properties that are slightly different from water, but in equilibration experiments for measuring TBW, it gives accurate results. Tritium oxide and aminopyrine have also been used to measure TBW.

## INTERCELLULAR CONNECTIONS (FIG. 1.7)

Two types of junctions form between the cells that makes up tissues.

- Junction that fasten the cells to one another and to surrounding tissues
- Junctions that permit transfer of ions and other molecule from one cell to another.

### Tight Junction (Zonula Occludens)

It is the region where the cell membranes of the adjacent cells fuse together firmly. It is present in the apical margins of

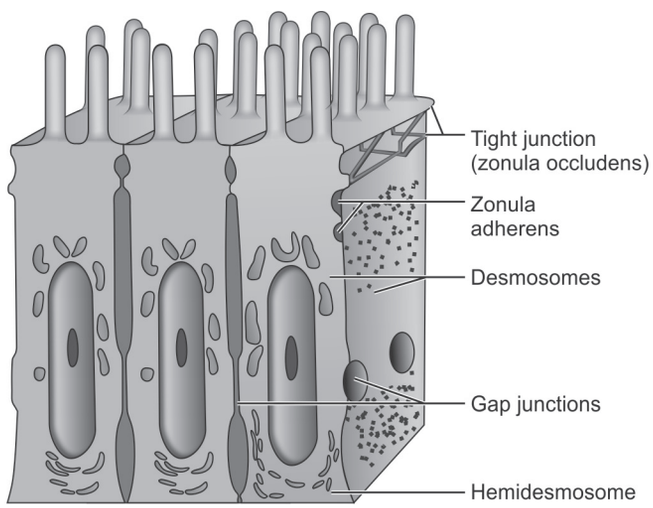



**Fig. 1.7:** Intercellular connections

epithelial and endothelial cells in the intestinal mucosa, wall of renal tubule, capillary wall and choroid plexuses. It is made up of two ridges one half of ridge is from one cell and the other half from the other cell. It provide strength and stability to the tissues, prevents lateral movements of proteins and lipids in the cell membrane, in brain capillaries it forms blood brain barrier.

### Zona Adherens

It is a continuous structure on the basal side of zona occludens, and it is a major site for the attachment of intracellular microfilaments.

### Desmosomes

They are patches characterized by apposed thickenings of the membranes of two adjacent cells. This holds adjacent cells firmly together in areas that are subjected to stretching, such as skin.

### Hemidesmosomes

It looks like half - desmosomes that attach cells to the underlying basal lamina and are connected intracellularly to intermediate filaments.

### Gap Junctions

It is present in heart, basal part of epithelial cells of intestinal mucosa. Here, the cytoplasm of the two cells is connected by the channels formed by the membranes of both cells. Each channel consist of two halves. Each half belongs to one of the adjacent cells. It helps in the exchange of chemical messengers between the cells and in rapid propagation of AP (action potential) from one cell to another.

## ACTION POTENTIAL

Action potential can be defined as sequence of changes in the membrane potential of an excitable cell due to opening and closure of different ion channels after the application of a threshold stimulus.

### Phases

#### *Resting Membrane Potential Stage*

Here inside of nerve is negative and the outside of nerve is positive (Fig. 1.8). RMP = –70 mV. Membrane is maintained in polarized state by:

- Due to distribution of ions across the cell membrane. Some $K^+$ ions diffuses out of the cell along its concentration gradient while non-diffusable an ions (e.g. proteins) stay in the cell.

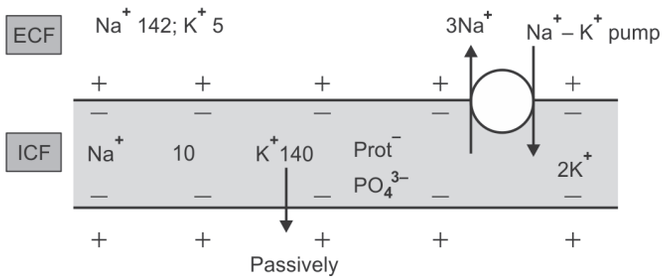



**Fig. 1.8:** Resting membrane potential

- $Na^+$ influx does not compensate for $K^+$ efflux, because membrane at rest is less permeable to $Na^+$ than $K^+$.
- $Na^+$- $K^+$ pump cause continuous pumping of $3Na^+$ to the outside for each $2K^+$ ion pumped inside the membrane. This creates an additional degree of negativity.

*Stimulus artifact:* When stimulus is applied there is brief irregular deflection of base line due to a current leakage from stimulating electrode to the recording electrode.

*Latent period:* It corresponds to the time it takes to travel along the axon from the site of stimulation to the recording electrode (Fig. 1.9).

#### *Depolarization*

When the membrane potential reaches a voltage between –70 and –50 mV, there occurs sudden conformational change in the activation gate of sodium channels, flipping it into open state (voltage gated sodium channels has 2 separate gates—activation and inactivation gate) called as activated state and sodium ions moves in Figures 1.10A and B. The tracing rises rapidly till +35m V. Now inside of the nerve becomes positive and the outside of nerve is negative.

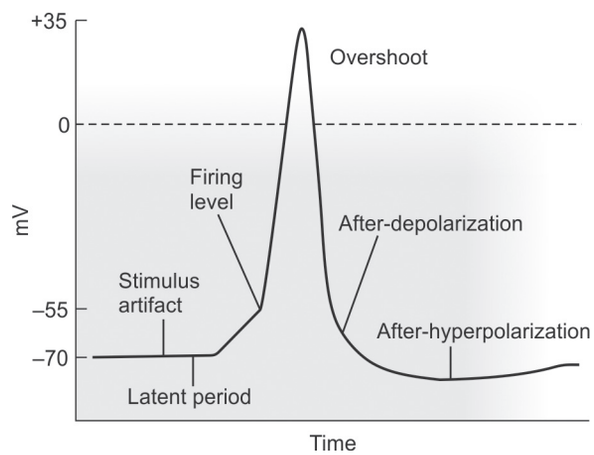
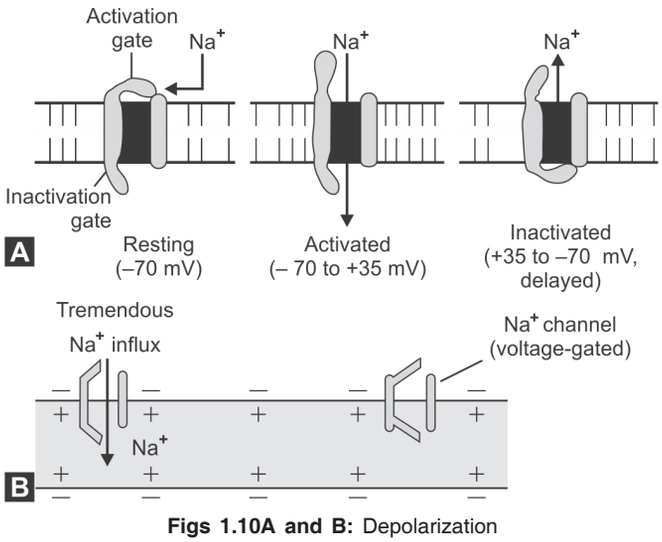



**Fig. 1.9:** Action potential in a neuron




**Figs 1.10A and B:** Depolarization

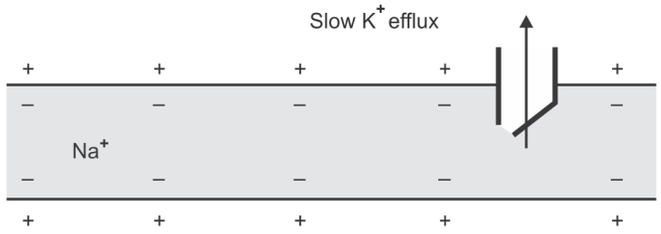



**Fig. 1.12:** After depolarization

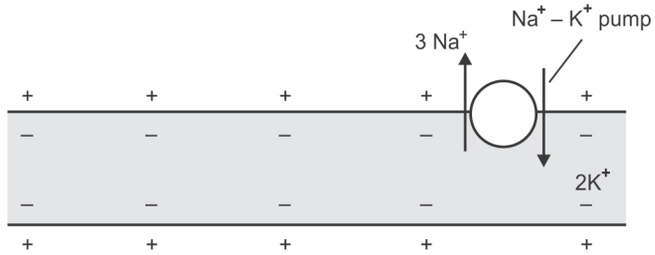



**Fig. 1.13:** After hyperpolarization

### *Repolarization*

After sodium channel has remained open for 10,000 of a second, it suddenly closes. At this point the membrane potential begins to recover back to RMP. Repolarization starts with $K^+$ efflux due to opening up of voltage gated $K^+$ channels (Fig. 1.11). A very important characteristic of sodium channel inactivation process is that the inactivated gate will not reopen until the membrane potential returns to RMP.

### *After Depolarization*

At the termination of spike potential $K^+$ conduction is slowed down and thus a few milliseconds are delayed in restoring the membrane potential. This last phase of slow $K^+$ efflux is called after depolarization (Fig. 1.12).

### *After Hyperpolarization*

Resting membrane potentials is achieved by the active $Na^+ – K^+$ pump mechanism which transport $3Na^+$ out and $2K^+$ in (Fig. 1.13).

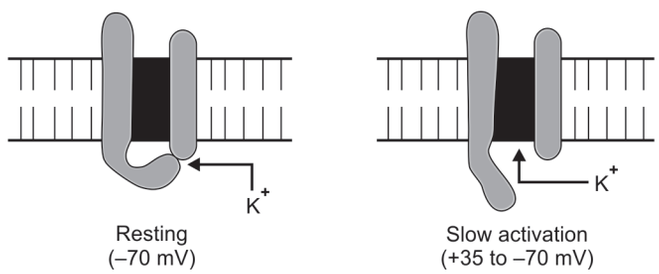



**Fig. 1.11:** Repolarization

## Properties of Action Potential

### *Threshold Stimulus*

It is the minimum intensity of stimulating current that after acting for a given duration will just produce an action potential.

***Note:*** The relationship between the strength and duration of a stimulus has been studied by varying the duration of stimulus and finding out threshold strength for each duration. Following information can be gathered from strength-duration curve.

***Rheobase and Chronaxie (Fig. 1.14)***

The weakest current strength which can excite a tissue, if allowed to flow through it for an adequate time is called rheobase. The time for which it is applied is called utilization time. The length of time for which a current of twice 'rheobase' intensity must be applied to produce a response is called chronaxie.

### *All or None Response*

The action potential is an all or none response to stimuli, i.e. if the stimulus is subthreshold (not adequate), no action potential is produced. Once threshold is reached, a full-fledged action potential is produced. Further increase in the intensity of a stimulus produces no increment in the height of the action potential provided the other experimental condition remains the same.

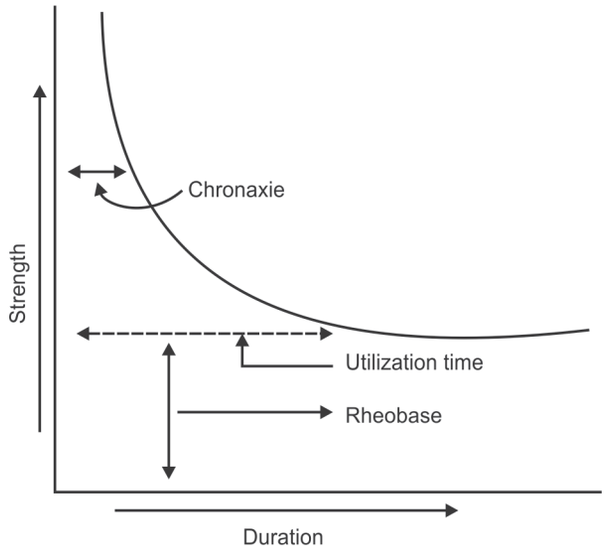



**Fig. 1.14:** Strength-duration curve

### *Accommodation*

If an excitable cell is applied with a constant strength of current, the site of membrane under stimulation fails to produce AP, i.e. the membrane adapts to the applied stimulus. This is due to slower opening and delayed closing of the voltage gated $K^+$ channels.

### *Conductivity*

The action potential developed at one location on the excitable cell acts as a stimulus for the production of an AP in the adjacent region of the membrane. The excitation impulse is conducted along the cell membrane as a wave of depolarization.

### *Refractory Period*

If two successive stimuli of more than threshold intensity are applied to an excitable cell, it is found that for sometime after the first stimulus, the cell becomes refractory. There are two types of refractory period (Fig. 1.15).

a. *Absolute refractory period:* Begins from the time the firing level is reached till the repolarizatoin is approx 1/3rd complete. During this period no strong stimulus can initiate the fresh impulse.
b. *Relative refractory period:* Begins at the end of ARP to the start of the after depolarization. During this stimuli stronger than normal stimulus can cause excitation.

## Saltatory Conduction

Depolarization in myelinated axons jumps from one node of Ranvier to the next. This jumping of depolarization from node to node is called saltatory conduction. It is a rapid process, and myelinated axons conduct up to 50 times faster than the fastest unmyelinated fibers (Fig. 1.16).

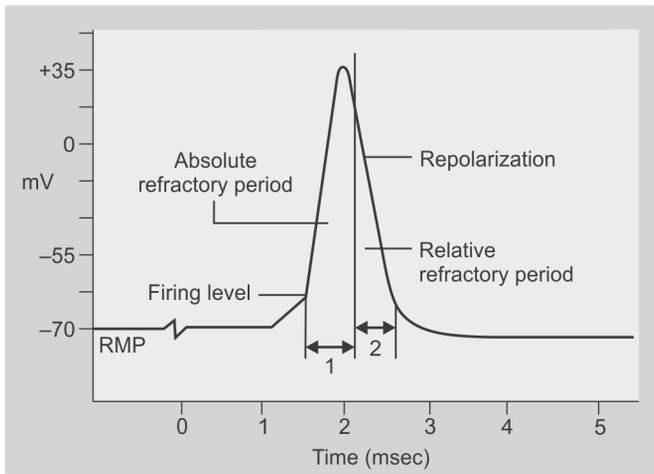



**Fig. 1.15:** Refractory periods

## Monophasic Action Potential

In this one microelectrode is placed inside the nerve fiber and the other electrode on the outer surface. These electrodes are then connected to the cathode ray oscilloscope (CRO). Monophasic record has following components:

- Depolarization
- Repolarization

## Biphasic Action Potential

Here both the electrode are placed on the outer surface of nerve fibers, and they are connected to a CRO. When nerve is stimulated a record of alternate deflection one positive above the baseline and one negative below the baseline is depicted.

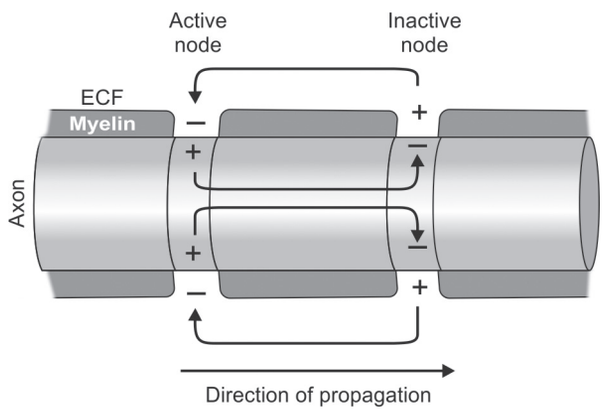



**Fig. 1.16:** Mechanism of saltatory conduction

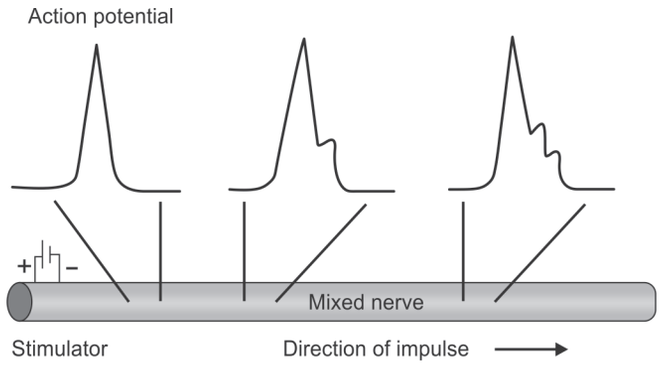



**Fig. 1.17:** Compound action potential: Record obtained with recording electrodes at various distances from the stimulating electrodes along a mixed nerve

## Compound Action Potential

Compound action potential is the monophasic recording of action potential from a mixed nerve which contains different types of nerve fibers with varying diameter. Therefore, the compound action potential represents an algebraic summation of the all or none action potential of many axons (Fig. 1.17).

### *Causes of Compound Action Potential*

A mixed nerve is made up of families of fibers with varying speed of conduction. Therefore,

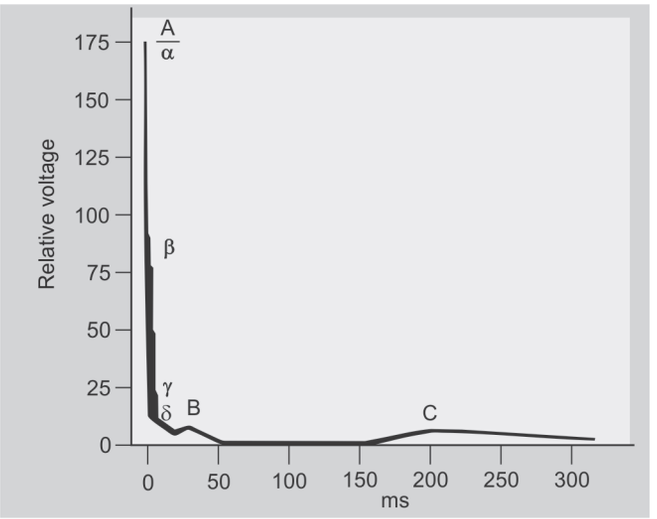



**Fig. 1.18:** Reconstruction of a compound action potential to show relative sizes and time relationships of the components

1. When all the fibers are stimulated, the activity in fast conducting fibers arrives at the recording electrodes sooner than the activity in slower fibers.
2. The farther away from the stimulating electrodes the action potential is recorded, the greater is the separation between the fast and slow fiber peaks (Fig. 1.18).

In general, group 'A' fibers make maximum contribution to compound action potential and group 'C' to the least.

Chapter

# 2 Circulating Body Fluids

## BLOOD

The circulating system is the transport system that supplies $O_2$ and substances absorbed from the tissues, returns $CO_2$ to the lungs and products of metabolism to the kidney, functions in the regulation of body temperature, distributes hormones and other agents that regulate cell function. The blood is the carrier of these substances.

The cellular elements of the blood represents 45% of the total blood volume. It includes white blood cells, red blood cells, platelets and are suspended in the plasma. Plasma is a clear, straw colored fluid portion of the blood and represents 55% of the total blood volume. It contains 91–92% water, 8–9% solids. The solids comprise both organic [8%; plasma proteins, carbohydrates, enzymes, fats, hormones, nonprotein nitrogenous (NPN) substances] and inorganic (1%; sodium, calcium, potassium, magnesium, bicarbonate, chloride, phosphate, copper, iron).

The normal total circulating volume is 5600 ml in a 70 kg man (about 8% of body weight). The pH is 7.35–7.45 (average 7.4) and the specific gravity is 1055–1062. Blood is five times more viscous than water. Salinity of blood is 0.9 N.

### Functions of Blood

1. *Respiratory:* Helps in the transport of $O_2$ and $CO_2$
2. *Nutritive:* Distribute various nutrients to all parts of the body
3. *Excretory:* Transports waste materials to the organs of excretion
4. *Defense mechanism:* Due to the presence of antibody.
5. *Storage function:* Acts as storehouse for different materials like nutrients, water, electrolytes, etc.
6. Regulation of body temperature (due to high specific heat of blood).
7. *Regulation of acid-base balance:* Plasma proteins and Hb acts as buffers.
8. Plays a major role in homeostasis.

## PLASMA PROTEINS

The plasma proteins include albumin, globulin, fibrinogen, prothrombin. The total amount of plasma proteins in the blood is 6.4–8.3 gm %. The further details about each of them are given in Table 2.1. Normal A/G (albumin–globulin) ratio is 1.7:1. It is reversed in liver disorders. Plasmapheresis/ Whipple's experiment is an experimental procedure done in animals to demonstrate the importance of plasma proteins.

### Functions of Plasma Proteins

1. *Coagulation of blood:* Due to the presence of fibrinogen, prothrombin and clotting factors.
2. *Defense mechanism of body:* Gamma-globulins produce antibodies.
3. *Maintain colloidal osmotic pressure (COP):* Eighty-percent of COP is due to albumin (COP is inversely proportional to molecular size and directly related to concentration of molecule).

**Table 2.1: Types of plasma proteins and functions**

| *Type* | *Molecular weight* | *Normal plasma level* | *Site of production* | *Function* |
|---|---|---|---|---|
| Albumin | 69000 | 3.5-5 gm% | Liver | Binding and carrier protein, osmotic regulation |
| Globulin | 90000–156000 | 2-3 gm% | Recticuloendothelial cells, plasma cells | Mediates immunity, transport proteins like transferin, ceruloplasmin, hemopexin are different forms of globulin |
| Fibrinogen | 350000 | 0.2-0.4 gm% | Liver | Important for clotting of blood, responsible for major part of viscosity |
| Prothrombin | 68000 | 0.1 gm% | Liver | Important for clotting of blood |

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4. *Transport:* Albumin and globulin transports various hormones, enzymes, bilirubin and metals like Cu, Fe, etc.
5. *Acid-base regulation:* Due to buffering action.
6. *Provides stability to blood:* This is due to the presence of globulin and fibrinogen. If blood loose viscosity RBC will pile upon each other and leads to *Rouleaux formation.*
7. *Maintains systemic arterial BP constant:* Viscosity of the blood is mostly due to fibrinogen.Arterial BP depends on viscosity of the blood.
8. Acts as protein store.

### *Hyperproteinemia*

Increase in level of plasma proteins and is seen in conditions which causes hemoconcentration (diabetes insipidus).

### *Hypoproteinemia*

Decrease in level of plasma proteins. It is seen in malnutrition, burns, malabsorbtion, hemorrhages. This causes decrease in COP; therefore increase in filtration occurs at arterial end and decrease in absorption at venous end, resulting in edema.

### *In Liver Disorders, A/G Ratio Reverses*

When body tissues are damaged, though plasma albumin falls, plasma immunoglobulin increases as a result of plasma cell hyperplasia causing A/G ratio reversal.

### *Multiple Myeloma*

Increase in the level of globulin due to malignant growth of plasma cells.

## HEMOGLOBIN

Heme portion of Hb is synthesized from glycine and succinyl CoA. Heme is synthesized by cells of erythroid series in red bone marrow. Hb starts appearing in developing RBC at intermediate normoblastic stage.

### Structure of Hb

Hemoglobin is a globular molecule made up of four subunits. Each subunit contains a heme moiety conjugated to a polypeptide (globin). Heme is an iron containing porphyrin derivative. There are two pairs of polypeptides in each Hb molecule. Hb A consists of two types of polypeptides; α and β. One Hb molecule can combine with four molecules of $O_2$.

### *Normal Values*

Males: 14 –18 gm% (avg -15.5 gm%)
Females: 12–15.5 gm% (avg -14 gm%)

### Types of Hb

#### *Normal Varieties*

1. Adult Hb are of two types:
   - Hemoglobin A ($\alpha_2\beta_2$)
   - Hemoglobin A2 ($\alpha_2\delta_2$)
2. Fetal Hb ($\alpha_2\gamma_2$)

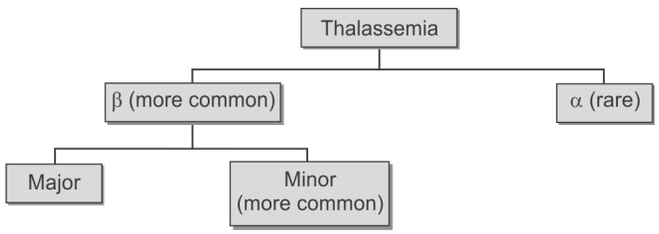
#### *Abnormal Varieties*

3. *Hemoglobinopathies;* here abnormal polypeptides are produced.
   - HbS: In the β chain, glutamine at the 6th position is replaced by valine. When HbS is reduced, it precipitates into crystals within RBCs leading to sickling of RBCs. Sickle shaped RBCs are more fragile resulting in sickle cell anemia.
   - HbC
   - HbE
   - HbI, etc.
4. *Thalassemias (Flow chart 2.1):* Both α and β chains are present and are normal in structure, but produced in decreased amounts or absent.

*Major β thalassemia (Cooley's anemia or Mediterranean anemia):*
- Less common
- Total absence of chain synthesis
- Homozygous transmission
- Victim usually dies.

*Minor β thalassemia*
- More common
- Partial synthesis of β chain
- Heterozygous transmission

**Flow chart 2.1:** Types of thalassemia




### *Heme-Heme Interaction*

In the initial phase of oxygenation the combination of heme and $O_2$ is a bit slow. But once a little of $O_2$ has combined with heme further interactions are facilitated. This is called heme-heme interaction and this explains the sigmoid shape of $O_2$ dissociation curve.

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## Catabolism of Hb (Flow chart 2.2)

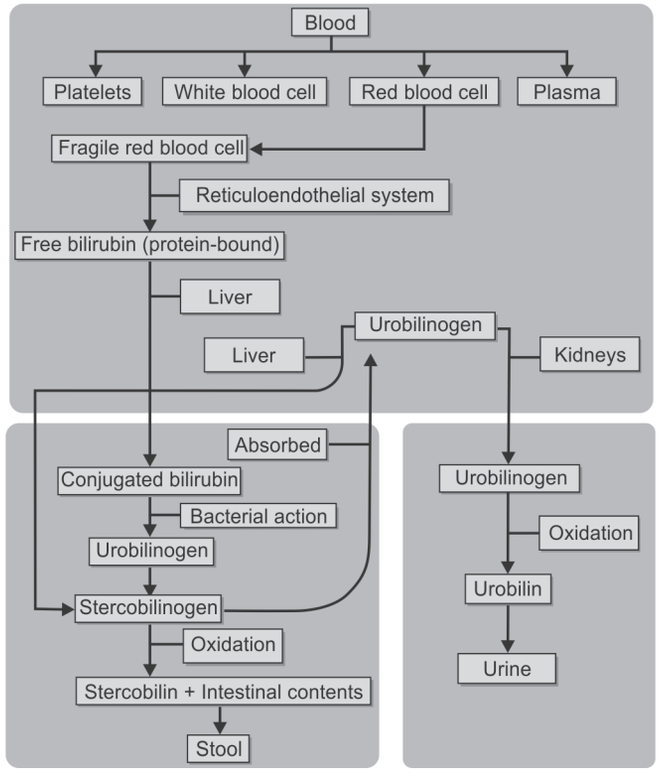
When the RBCs become old their walls become weak and their shape changes and finally the RBC are broken down. RBCs are destroyed mainly in the spleen by the RE cells. Hb is then released from RBC, which splits into heme and globin.

The end products of heme catabolism are bile pigments. Bilirubin has no function in the body so excreted through bile. Globin is broken into amino acids within the RE (reticuloendothelial) cells, which will be later utilized for synthesis of body proteins. Fe is then released into plasma and is transported by transferrin to the storage sites. The porphyrin ring is broken down in RE cells of liver, spleen and bone marrow where it gets converted into biliverdin (green pigment).

Biliverdin gets reduced to form bilirubin (red orange), which is released into the plasma. This unconjugated bilirubin soluble in lipid solvents is carried by plasma in combination with albumin to liver (so not excreted into urine by kidney). In the liver, bilirubin undergoes conjugation with glucuronic acid and forms bilirubin mono and diglucuronide (soluble in water). Bilirubin diglucuronide is hydrolyzed and reduced by bacteria in the gut to urobilinogen (colorless).

Most of urobilinogen is oxidized by intestinal bacteria to stercobilin, which gives the feces the brown color. Some of the urobilinogen enters the portal blood. The remaining urobilinogen is transported by the blood to the kidney, where 5% of it is converted to yellow urobilin and excreted, giving the urine its color. Most of the reabsorbed urobilinogen is re-excreted by the liver back into gut.

**Flow chart 2.2:** Catabolism of hemoglobin




## ERYTHROCYTES (RBC)

| | | |
|---|---|---|
| Normal count | : | Males 5 – 6 million cells/cu mm<br>Females – 4.5 – 5.5 million cells/cu mm |
| Diameter | : | 7.2 μm (avg) |
| Thickness | : | 2 μm (avg) |
| Volume | : | 78 – 94 $\mu m^3$ |
| Hematocrit (PCV) | : | Males 47% and Females 42% |
| Lifespan | : | 120 days |
| Site of production | : | Bone marrow |
| Site of destruction | : | Tissue macrophage system. |

### *Advantages of Biconcave Shape*

- Can squeeze through capillaries very easily
- Can withstand endosmosis
- Large surface area is provided which help in quick exchange of gases.

### *Functions*

- Gas transport
- Acid-base balance
- Formation of bilirubin
- Responsible for major portion of viscosity of whole blood
- Helps in identifying blood groups as it contains antigen on its surface.

### *Red Cell Fragility*

Red blood cells shrink in solutions with an osmotic pressure > normal plasma (0.9N). In solutions with a lower osmotic pressure they swell, becoming spherical and lose their Hb (hemolysis). The tendency to hemolyze is called fragility. In hereditary spherocytosis (congenital hemolytic icterus) cells hemolyze more readily than normal cells in hypotonic NaCl solutions. Fragility is high in G6PD deficiency. Red cells can also be lysed by drugs and infections.

**Hereditary Spherocytosis**

Common cause of hereditary hemolytic anemia. The membrane of RBC is made of spectrin and is anchored to transmembrane protein band 3 by the protein ankyrin. Hereditary spherocytosis is caused by defects in band 3, spectrin and ankyrin.

## RBC Indices

The number, shape, volume and color of RBCs indicate the quality of blood. Blood indices have got a diagnostic value in determining the type of anemia. These are:



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### *Mean Corpuscular Volume (MCV)*

It is the volume of a single RBC in cubic microns.

$$MCV = \frac{\text{PCV per 100 ml blood} \times 10\ \mu m^3}{\text{RBC count in million/cu mm}}$$

Normal value : 87 $\mu m^3$

### *Mean Corpuscular Hemoglobin (MCH)*

It is the average amount of Hb in a single RBC in pictogram.

$$MCH = \frac{\text{Hb in gm\%} \times 10\ pg}{\text{RBC count in million/cu mm}}$$

Normal value : 29 pg

### *Mean Corpuscular Hemoglobin Concentration (MCHC)*

It is the Hb concentration in a single RBC or it is the amount of Hb expressed as % of the volume of a RBC.

$$MCHC = \frac{\text{Hb in gm\%} \times 100}{\text{PCV per 100 ml blood}}$$

Normal value: 34%

### *Color Index*

It denotes the ratio of Hb to RBC.

$$\text{Color index} = \frac{\text{Hb\%}}{\text{RBC\%}}$$

Normal value: 1

## Erythropoiesis

Formation of red blood cells is called erythropoiesis. In normal adult human, the site of production is bone marrow (red bone marrow). In the first-three months of intrauterine life, blood cells develop from mesoderm of yolk sac or area vasculosa (mesoblastic stage). After 3 months, up to 5 months of fetal life red blood cells are developed from liver and spleen (hepatic stage). From 5th month onwards up to birth and up to adulthood from red bone marrow (myeloid stage).

In children erythropoiesis occurs in:

- All bones with red marrow (mainly)
- Liver and spleen

In adults erythropoieses occurs in red bone marrow which includes:

- Ends of long bones (shaft is converted to yellow marrow)
- Flat bones (skull, vertebrae, ribs, sternum, pelvis).

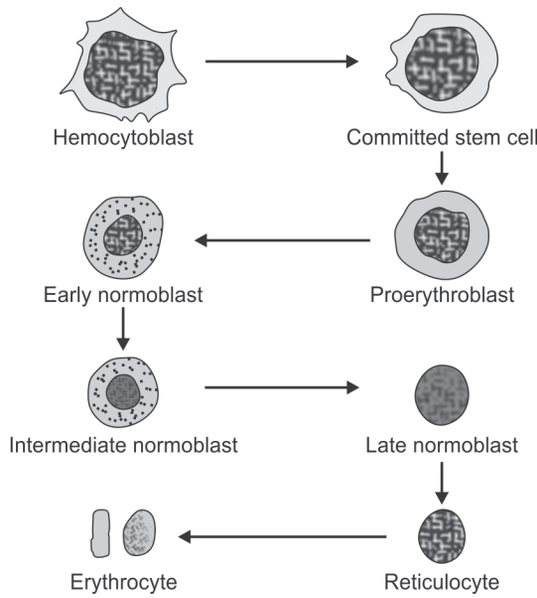


**Fig. 2.1:** Stages of erythropoiesis

### *Stages of Erythropoiesis (Fig. 2.1)*

#### *Hemocytoblast*

- It is considered as a pleuripotent stem cell (noncommitted)
- Diameter: 18–20 μm
- Nucleated with thin rim of basophilic cytoplasm
- Nucleus may contain two or more nucleoli with open chromatin.
- They proliferate extensively and give rise to committed stem cell.

#### *Committed Stem Cells*

- Develop from pleuripotent stem cells.
- Two types; myeloid and lymphoid.
- They have become committed to give rise to a particular line of cells (either erythrocytes, platelets, monocytes, etc.).
- Committed stem cells of myeloid series gives rise to all types of blood cells except lymphocytes.

#### *Progenitor Cells*

- Develop from committed stem cells
- Progenitor cells are of two types:
  - BFU-E (burst forming unit of erythrocyte series)
  - CFU-E (colony forming unit of erythrocyte series)
- BFU-E give rise to CFU-E cells.

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### Proerythroblast

- The first blast cell (immature cells) belonging to red blood series
- They are formed from CFU-E stem cells
- Large nucleus, distinct nucleoli, open chromatin
- Basophilic cytoplasm
- Shows active mitosis.

### Early Normoblast

- Size further decreases
- No nucleoli, condensed chromatin threads
- Cytoplasm is basophilic
- Shows active mitosis.

### Intermediate Normoblast

- Cell size reduces
- Chromatin thread further condenses
- Hb starts appearing
- Cytoplasm becomes polychromatic
- In the later part mitosis stops.

### Late Normoblast

- Further reduction in cell size
- Nucleus moves to periphery
- Further condensation of chromatin threads
- In the later part nucleus becomes pyknotic
- Further increase in concentration of Hb
- Cytoplasm is mostly eosinophilic (acidic).

### Reticulocyte

- Cell size reduces and almost same size of matured RBC (7-9 μm)
- No nucleus
- When stained with dyes like brilliant cresyl blue, cytoplasm shows a small reticulum (due to the presence of RNA) and hence the name
- Cytoplasm is eosinophilic.

### Erythrocyte

- Fully eosinophilic
- Non-nucleated, biconcave
- *Diameter*: 7.2 μm.

## Factors Affecting Erythropoiesis

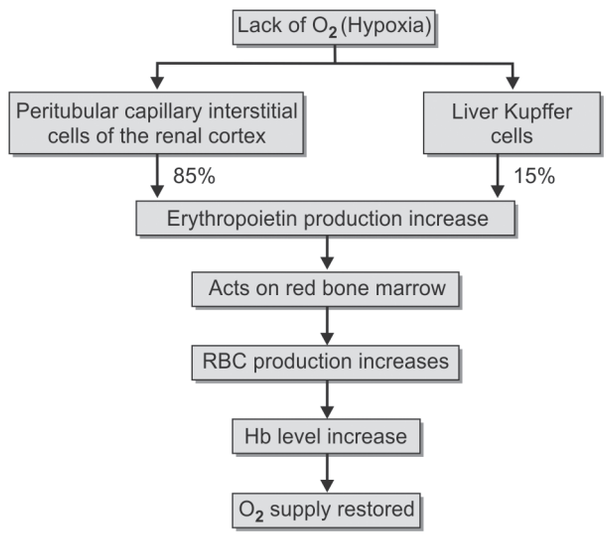
### General Factors

***Erythropoietins***

- Glycoprotein in nature, also called hemopoietin or erythrocyte stimulating factor.
- It is secreted by interstitial cells in peritubular capillaries of kidney and by hepatocytes in the liver. In adults 85% of secretion comes from kidney, 15% from liver.
- It acts from the stage committed stem cell. It causes early differentiation of erythropoietin sensitive stem cells to pro-erythroblast and subsequently to mature RBCs. It prevents apoptosis of red cells. It increases synthesis of RNA, DNA, globin, ferritin which increases heme synthesis. It increases the release of reticulocytes from bone marrow.
- Stimulants for secretion includes hypoxia (most important), androgens, cobalt salts, catecholamines, alkalosis.
- Estrogen decreases the production of erythropoietin. This is the reason for decreased red cell count in females.

***Lack of $O_2$ (Flow chart 2.3)***

**Flow chart 2.3:** Role of hypoxia on erythropoiesis




***Hormones***

Testosterone, thyroxine, corticosteroids, growth hormone favors and estrogen inhibits erythropoiesis.

***Hemopoietic growth factors***

These are interleukins and stem cell factor. Generally these factors induce the proliferation of pleuripotent stem cells.

### Maturation Factors

1. *Vitamin $B_{12}$ and folic acid:* They are called extrinsic factors and are necessary for DNA synthesis. Erythroblast need them before every mitosis and deficiency leads to failure in maturation and reduction in cell divisions.
2. *Iron:* It is necessary for Hb synthesis.
3. *Castle's intrinsic factor:* It is produced by parietal cells of the stomach. It is essential for the absorption of vitamin $B_{12}$.



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4. *Dietary factors:* Proteins help in globin formation. Fe, Mn, Cu, Co helps in heme formation. Vitamin C and Ca increases iron absorption from gut.

***Note:*** Androgens has stimulating effect on erythropoietin. Estrogen decreases hepatic synthesis of globulin. They also depress the erythropoietic response to hypoxia. That is why in females, RBC count is less as compared to males.

## Anemia

Anemia is a clinical condition characterized by decrease in $O_2$ carrying capacity of blood due to either decrease in the number of RBCs or their content of Hb or both.

### Grading

*Mild anemia:* Hb 8–12 gm%
*Moderate anemia:* Hb 5–8 gm%
*Severe anemia:* Hb < 5 gm%

### General Clinical Features of Anemia

1. Generalized weakness, tenderness and fatigability.
2. Pallor of skin and mucous membrane.
3. Respiratory symptoms like breathlessness.
4. CVS manifestations like palpitation, tachycardia and cardiac murmurs.
5. CNS features due to cerebral hypoxia like lethargy, headache, tinnitus and confusion.
6. Ocular manifestations like visual disturbances, retinal hemorrhage.
7. Gastrointestinal symptoms like anorexia, nausea, constipation.
8. *Reproductive system:* Menstrual disturbances like amenorrhea, menorrhagia in females.
9. Renal system involvement.
10. BMR increases in severe anemia.

### Classification

***Morphological/Wintrobe's classification***

Based on the size and color of RBC (i.e based on MCV and MCHC):

- Normocytic normochromic
- Normocytic hypochromic
- Macrocytic normochromic
- Macrocytic hypochromic
- Microcytic normochromic
- Microcytic hypochromic.

***Etiological/Whitby's classification (Table 2.2)***

Based on the cause of anemia:

- Hemorrhagic: Due to blood loss
- Hemolytic: Due to destruction
- Nutritional deficiency
- Aplastic due to decreased formation.

## Pernicious Anemia/Addison's Anemia

*(Pernicious means destructive or injurious)*

### Causes

This is due to lack of intrinsic factor. Consequently there will be failure in the absorption of vitamin $B_{12}$. Production of intrinsic factor is affected due to atrophy of gastric mucosa.

RBCs are macrocytic normochromic. Excessive destruction of RBCs produces mild hemolytic jaundice. Bone marrow

**Table 2.2: Etiological/Whitby's classification of anemia**

| *Types of anemia* | *Causes* | *Morphology of RBC* |
|---|---|---|
| Hemorrhagic | Acute loss of blood | Normocytic normochromic |
| | Chronic loss of blood | Normocytic hypochromic |
| Hemolytic | • Hypersplenism<br>• Infections (malaria)<br>• Drugs (quinine, aspirin)<br>• Poisons (snake venom) | Normocytic normochromic |
| | • Congenital/Acquired default in shape of RBC | Sickle cell anemia: Sickle shaped<br>Thalassemia: Microcytic hypochromic |
| Nutrition deficiency | Iron | Microcytic hypochromic |
| | Protein | Macrocytic hypochromic |
| | Vitamin $B_{12}$ | Macrocytic normochromic |
| | Folic acid | Macrocytic normochromic |
| Aplastic | • X-ray irradiation<br>• Bone marrow disorder | Normocytic normochromic |

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becomes hyperplasic due to increased hypoxic stimulation for erythropoiesis. Neurological disorders are seen in extreme conditions.

### Reticulocyte Response

Increase in number of reticulocytes after vitamin $B_{12}$ therapy. This is due to proliferation of bone marrow and numerous young RBC pass into circulation.

## Folic Acid Deficiency Anemia

Anemia is megaloblastic as seen with vitamin $B_{12}$ deficiency. But neurological disorders may not develop.

### Causes of Folic Acid Deficiency

a. Less dietary intake
b. Poor absorption, e.g. in steatorrhea and sprue (absorption defect is due to lack of digestive enzymes and in part due to folic acid deficiency).
c. Increased demand as in pregnancy.
d. Antifolate drugs, e.g. anticancer drugs (methotrexate).

## Iron Deficiency Anemia

It is the most common nutritional deficiency disorder present throughout the world. Iron deficiency anemia is the most common anemia in India. Iron deficiency anemia can be defined as any anemia which responds to adequate dosages of iron. With long standing severe anemia, thinning, flattening and eventually "spooning" (koilonychia) of finger nails sometimes appears.

### Causes

a. Decreased intake-milk fed infants.
b. Increased loss in acute or chronic hemorrhage (e.g. worm infestation, peptic ulcer, piles, increased menstrual blood loss).
c. *Increased demand:* Infancy, childhood, pregnancy and menstruation.
d. Defective utilization due to decreased absorption in diseases of stomach and duodenum.

### Blood Indices in Anemia's (Table 2.3)

**Table 2.3: Blood indices in anemia**

| *Index* | *Hypochromic microcytic iron deficiency anemia* | *Normochromic macrocytic megaloblastic anemia* | *Normochromic normocytic anemia* |
|---|---|---|---|
| MCV | ↓ | ↑ | – |
| MCH | ↓ | ↓ | – |
| MCHC | ↓ | – | – |
| Hb | ↓ | ↓ | ↓ |
| RBC | ↓ | ↓ | ↓ |
| Mean diameter | ↓ | ↑ | – |
| PCV | ↓ | ↓ | ↓ |

↓ Decrease ↑ Increase – Normal

***Effects of Anemia on Circulatory System***

The viscosity of the blood depends on the blood concentration of red blood cells. In severe anemia, the blood viscosity may fall to as low as 1.5 times that of water. This decreases the resistance to blood flow in the peripheral blood vessels, so that far greater than normal quantities of blood flows through the tissues and return to the heart. This greatly increases the cardiac output. Hypoxia resulting from diminished transport of oxygen by the blood causes the peripheral tissue blood vessels to dilate, allowing further increase in the return of blood to the heart and increasing the cardiac output to a still higher level. Thus, one of the major effects of anemia is greatly increased cardiac output and increased pumping workload on the heart.

***Note:*** Reverse anemia occurs after gastrectomy because gastric secretions play an important role in dissolving the iron, thereby permitting it to form soluble complexes with ascorbic acid and other substances that aids its reduction to $Fe^{2+}$ form. This is very important for absorption of iron in the duodenum even though only traces of iron absorption occur in stomach.

## Polycythemia

Abnormal increase in RBC count. Classified into two:

### Primary Type (Polycythemia Vera/Erythremia)

Increase in RBC count more than 7–8 million cells/$mm^3$. It may be due to neoplastic growth of stem cell.

### Secondary Type

Rise in RBC count (6–7 milllon/$mm^3$) occurs due to some disease or altered physiologic state (high altitude), which cause rise of erythropoietin concentration (due to hypoxia).

***Effects on circulatory system***

- Cardiac output is not far from normal due to the balance between the increased viscosity of blood and greatly increased blood volume.



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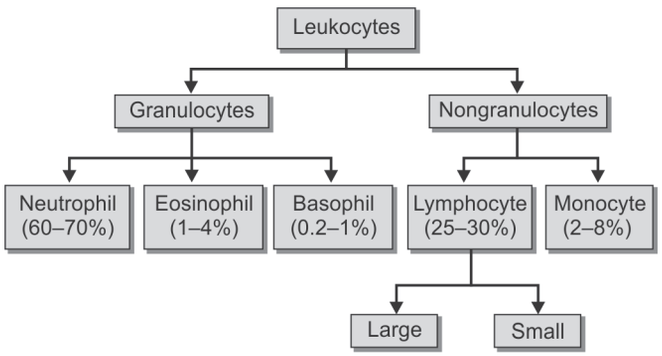
- Arterial pressure is also normal in most people with polycythemia.
- In polycythemia vera, the skin is cyanotic.

## LEUKOCYTES

The leukocytes are also called white blood corpuscles or simply the white cells of the blood. They are colorless and they defend the body against diseases by fighting against infections, malignancies, etc. Leukocytes are classified as (Flow chart 2.4).

**Flow chart 2.4:** Classification of leukocytes




### Classification

#### *Neutrophil*

*Normal count:* 5400 cells/cu mm blood (3000–6000)
*Size:* 10–14 µm diameter.
They are called first-line of defense.
Nucleus is multilobed
Cytoplasm contains fine pink granules.

##### *Functions*

1. Phagocytosis
2. They contain a fever producing substance, endogenous pyrogen.

##### *Neutrophilia*

Increase in neutrophils.

***Causes***

1. Acute infections
2. Following tissue destruction
3. Pregnancy, menstruation, lactation.

##### *Neutropenia*

Decrease in neutrophils.

***Causes***

1. Viral infection
2. Typhoid fever
3. Bone marrow depression.

#### *Eosinophil*

*Normal count:* 275 cells/cu mm (150–300).
*Size:* 10–14 µm diameter.
Nucleus is bilobed.
Cytoplasm contains coarse brick red granules.

##### *Functions*

1. During allergic conditions, eosinophils are collected at the sites and limits the intensity by degrading the effects of mediators.
2. Mild phagocytosis.

##### *Eosinophilia*

Increase in eosinophil.

***Causes***

1. Allergic conditions (bronchial asthma).
2. Parasitic infestation (hook worm).

##### *Eosinopenia*

Decrease in eosinophils.

***Causes***

1. After injection of corticosteroids.
2. Acute pyogenic infections.

#### *Basophil*

*Normal count:* 35 cells/cu mm of blood (0–100).
*Size:* 10–14 µm diameter.
S shaped nucleus.
Cytoplasm contains coarse bluish black granules which may mask the nucleus.

##### *Functions*

1. Mild phagocytosis.
2. They are responsible for inflammatory changes.
3. They liberates histamine and heparin.

##### *Basophilia*

Increase in basophils.

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***Causes***

1. Chickenpox
2. Tuberculosis
3. Influenza

### *Basopenia*

Decrease in basophils.

***Causes***

1. After administration of glucocorticoids.
2. Drug induced reactions.

## *Monocytes*

*Normal count:* 540 cells/cu mm of blood (300–600).
*Size:* 10–18 μm diameter.
They are called second-line of defense.
Kidney-shaped nucleus and placed eccentrically.

### *Functions*

1. Active phagocytosis.
2. All tissue macrophages come from monocytes.
3. They synthesize prostaglandin E and clot promoting factors.
4. They kill tumor cells.

### *Monocytosis*

Increase in monocytes.

***Causes***

1. Tuberculosis
2. Syphilis

### *Monocytopenia*

Decrease in monocytes.

***Causes***

Hypoplastic bone marrow.

## *Lymphocytes*

*Normal count:* 2750 cells/cu mm of blood (1500–4000)
*Size:* Large lymphocytes: 10–14 μm diameter
Small lymphocytes: 7–10 μm diameter
Nucleus is round, oval and central in position.

### *Functions*

Produce antibodies.

### *Lymphocytosis*

Increase in lymphocytes.

***Causes***

1. Lymphatic leukemia
2. Viral infections.
3. Tuberculosis.

### *Lymphopenia*

Decrease in lymphocytes.

***Causes***

1. Hypoplastic bone marrow
2. AIDS.

## Steps of Phagocytosis

### *Margination*

In the area of infection neutrophils get attached to the capillary endothelium.

### *Diapedesis*

Neutrophils and monocytes can squeeze through pore of blood vessels, a process called diapedesis.

### *Chemotaxis*

Bacterial products interact with plasma proteins. They produce chemotactic agents which attract neutrophil to site of infection. This is called chemotaxis. Chemotactic agents are components of complement system, leukotrienes, polypeptides from lymphocytes, basophil, mast cells.

### *Opsonization*

Opsonins are antibodies against bacteria. These antibodies cover bacteria along with component of complementary system, a process called opsonization.

### *Phagocytosis*

This coated bacteria attaches to receptors on neutrophil and they are engulfed by neutrophil by endocytosis (Fig. 2.2).

### *Degranulation*

Inside neutrophil, it becomes phagosome/phagocytic vacuole. Granules of neutrophil move towards phagocytic vacuole and discharge its contents into it and kills the bacteria. During this NADPH oxidase system is activated and there is sharp



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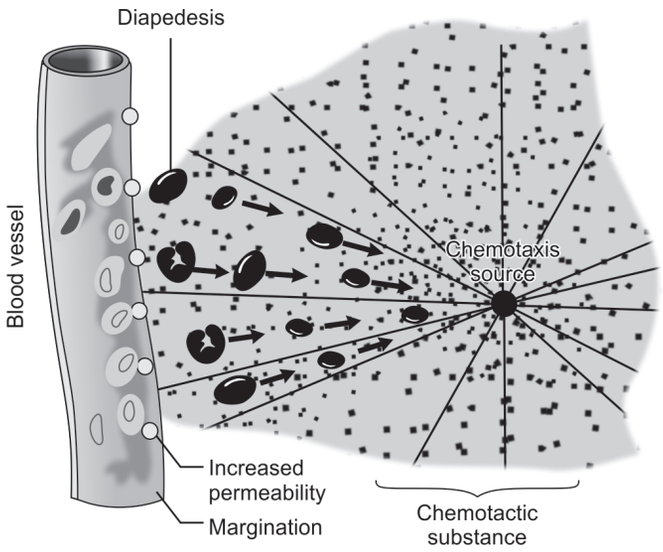



**Fig. 2.2:** Steps of phagocytosis

increase in $O_2$ uptake and metabolism, (respiratory burst) with generation of superoxide radical and $H_2O_2$. Free radical superoxide and $H_2O_2$ are both oxidants and react to form hydroxyl radical, a potent bactericidal agent.

***Notes***

1. *Agranulocytosis:* Decrease in granulocytes
2. *Myeloid leukemia:* Presence of immature WBCs in circulation.
3. *Lymphocytosis:* Increase in lymphocytes. Seen in chronic infections, viral infections, lymphoma, etc.
4. *Leukocytopenia:* Decrease in WBC count.
5. *Leukemias:* Uncontrolled production of WBC caused by cancerous mutation of myelogenous or lymphogenous cell.

## Arneth Count

It is the count of the neutrophils according to the number of lobes present in there nuclei (Table 2.4). Normal values are as follows.

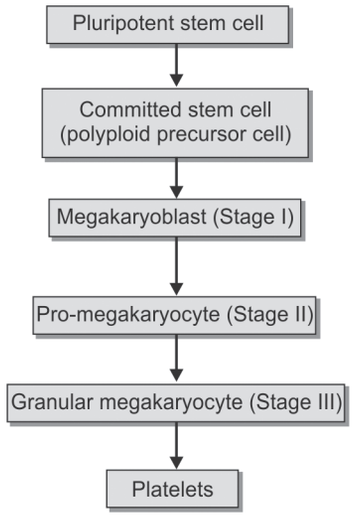
Number of lobes in the nuclei of a neutrophil inreases with the age. In circulation if there are more neutrophils with less lobes, it means more young cells are there (and vice versa). When there are more young cells, it indicates increased rate of production and more old cells means decreased rate of production. These may be due to different diseases and can be diagnosed by Arneth count.

## PLATELETS

*Normal count:* 300000 cells/cu mm (200000–500000)
*Lifespan:* 8–12 days
*Site of formation:* Bone marrow

### Stages of Formation (Flow chart 2.5)

**Flow chart 2.5:** Stages of formation




*Site of destruction:* Spleen and other reticuloendothelial cells.

***Functions***

1. Hemostasis
2. Role in blood clotting.
3. Role in clot retraction
4. Phagocytic action
5. Storage and transport function.

### Hemostasis

Spontaneous arrest or stoppage of bleeding by forming clots in the walls of damaged blood vessels while maintaining blood in a fluid state within the vascular system is called hemostasis.

**Table 2.4: Arneth count**

| *Groups* | *Group I* | *Group II* | *Group III* | *Group IV* | *Group V* |
|---|---|---|---|---|---|
| No. of lobes in nuclei | 1 lobe | 2 lobe | 3 lobe | 4 lobe | 5 lobe |
| Percentage | 5 to 10% | 25 to 30% | 45 to 47% | 16 to 18% | ≥2% |

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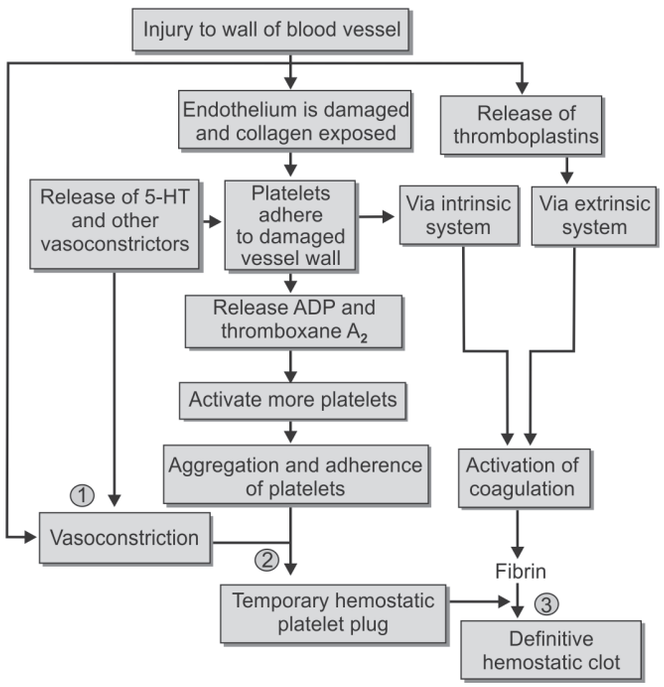
**Flow chart 2.6:** Stages of hemostasis




It occurs in three stages (Flow chart 2.6):

1. Vasoconstriction
2. Platelet plug formation
3. Coagulation of blood (conversion of platelet plug into definitive hemostatic clot).

## Mechanism of Hemostasis

### *Vasoconstriction*

Following an injury, the first event that takes place in hemostatic mechanism is vasoconstriction.

*Vasoconstriction is due to:*

- Local myogenic spasm.
- Vasoconstrictor agents released by traumatized tissues and platelets.
- Nervous reflexes.

### *Platelet Plug Formation*

When blood vessel is injured, platelets adhere to the exposed collagen and von Willebrand factor. Binding produces platelet activation which releases the contents of their granules. The released ADP acts on the ADP receptors in the platelet membranes to produce further accumulation of more platelets (platelet aggregation). Aggregation is also facilitated by platelet activating factor (secreted by neutrophils, monocytes and platelets).

Platelet aggregation causes the production of arachidonic acid derivatives like thromboxane $A_2$ and prostacyclin. Thromboxane $A_2$ further increases platelet aggregation and helps in the formation of *temporary hemostatic plug*. Thromboxane $A_2$ causes the release of norepinephrine and 5-HT (vasoconstrictor agents). Prostacyclin inhibits thromboxane $A_2$ and prevents further platelet aggregation (keeping platelet plug localized).

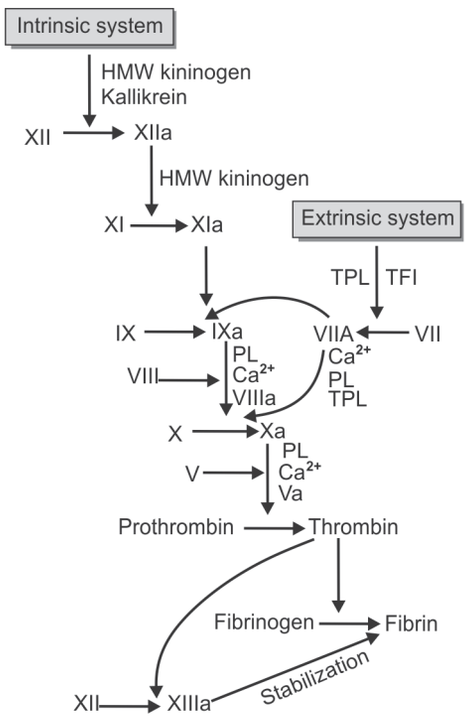
***Clinical Note***

Administration of aspirin in low dosage shifts the balance towards prostacyclin (by inhibiting thromboxane $A_2$) and inhibits platelet aggregation. Aspirin in low doses prevents MI and stroke.

### *Coagulation of Blood (Flow chart 2.7)*

It is a physiochemical change by which the liquid blood is converted into a jelly like mass called clot. Substances necessary for clotting are called clotting factors (Table 2.5).

**Flow chart 2.7:** Clotting mechanism: Intrinsic and extrinsic




## Process of Coagulation

*Clotting of blood occurs in three stages:*

1. Formation of prothrombin activator
2. Conversion of prothrombin into thrombin
3. Conversion of fibrinogen into fibrin.



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**Table 2.5: Clotting factors**

| *Factor* | *Names* |
|---|---|
| I | Fibrinogen |
| II | Prothrombin |
| III | Thromboplastin |
| IV | Calcium |
| V | Proaccelerin, labile factor, accelerator globulin |
| VII | Proconvertin, SPCA, stable factor |
| VIII | Antihemophilic factor (AHF), antihemophilic factor A, antihemophilic globulin (AHG) |
| IX | Plasma thromboplastic component (PTC), Christmas factor, antihemophilic factor B |
| X | Stuart-Prower factor |
| XI | Plasma thromboplastin antecedent (PTA), antihemophilic factor C |
| XII | Hageman factor, Glass factor |
| XIII | Fibrin-stabilizing factor, Laki-Lorand factor |

Prothrombin activator is formed by two ways:

### *Intrinsic Pathway*

Intrinsic system is triggered when blood is exposed (trauma to blood vessel) to the subendothelial collagen tissue resulting in formation of "intrinsic prothrombin activator". It occurs *in vivo* (inside body) and *in vitro* (in test tube).

The factor XII comes in contact with subendothelial collagenous tissue and is converted to factor XII a (active form of factor XII) and this reaction is catalyzed by high molecular weight kininogen and kallikrein. Active factor XII then activates factor XI and active factor XI activates factor IX. Factor VIII is activated when it is separated from von Willebrand factor. Now activated factors IX and VIII along with phospholipids, $Ca^{2+}$ activates factor X. In the presence of tissue phospholipids $Ca^{2+}$ and factor V, activated factor X catalyzes the conversion of prothrombin to thrombin.

***Note:*** Xa plus Va plus platelet phospholipid together form prothrombin activator.

### *Extrinsic Pathway*

Injury of the extravascular tissue and blood vessel causes release of substance called tissue thromboplastin (which is a complex of phospholipid and protein) from the injured tissue which activates factor VII to factor VIIa. It occurs *in vivo* only (inside body). Tissue thromboplastin and factor VII activate factors IX and X. Ultimately activated factor X catalyzes the conversion of prothrombin to thrombin in the presence of tissue phospholipids, $Ca^{2+}$ and factor Va. The last part of the pathway, i.e. from activated X onwards is common for both.

## *Conversion of Fibrinogen to Fibrin*

Now thrombin converts fibrinogen to fibrin monomer. Fibrin monomer then polymerises to form loosely arranged strands of fibrin (soft soluble clot). Later loose strands are modified into dense and tight aggregate (insoluble and elastic fibrin clot). The later reaction is catalyzed by XIIIa and $Ca^{2+}$.

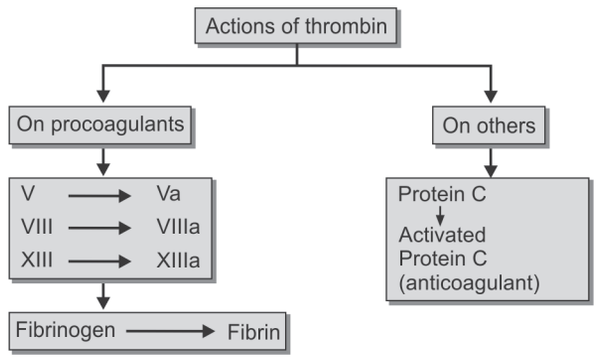
## *Clot Retraction*

After formation, the blood clot starts contracting. It contracts down to 40% of its original volume within 5–30 min. A straw colored fluid oozes out. This straw colored fluid is called serum. The compact clot is more effective hemostatic plug.

Platelet entrapped in the clot continue to release procoagulant substances. For example, fibrin stabilizing factor, which causes more and more cross linking bonds between adjacent fibrin fibers. Platelet themselves contribute directly to clot retraction by activating platelet thrombosthenin, actin and myosin.

## *Actions of Thrombin (Flow chart 2.8)*

**Flow chart 2.8:** Actions of thrombin




## *Actions of Calcium*

1. It accelerates the conversion of X to Xa and VII to VIIa.
2. The conversion of prothrombin to thrombin requires $Ca^{2+}$.
3. The conversion of soft soluble fibrin clot to firm insoluble clot is catalyzed by $Ca^{2+}$. But $Ca^{2+}$ deficiencies do not produce coagulation disorders because only traces of $Ca^{2+}$ are required for coagulation.

## *Limiting Reactions*

These reactions are:

- Prevent intravascular thrombosis
- Maintains blood in fluid state.

These reactions include:
1. Antithrombin III is a circulating protease inhibitor. It inhibits active forms of factors IX, X, XI, XII.
2. The platelet aggregating effect of thromboxane $A_2$ is balanced by antiaggregating effect of prostacyclin, which causes clots to form at the site when a blood vessel is injured but keeps the vessel lumen free of clot.
3. Heparin (a naturally occurring anticoagulant) facilitates the action of antithrombin III.
4. Removal of activated clotting factors by the liver.
5. Smoothness of endothelium prevents platelet adhesion and extension of clot into blood vessel.
6. Negatively charged particles present over endothelial lining, repel the clotting factors.
7. Continuous movement of blood does not allow clot formation.
8. Simultaneous activation of fibrinolytic system along with clotting mechanism.

## Fibrinolytic System

This system keeps lumen of blood vessels patent by dissolving clot. Plasmin (fibrinolysin) is the active component of fibrinolytic system. The endothelium of blood vessels (except those in cerebral microcirculation) produce thrombomodulin (a thrombin - binding protein). Thrombin binds to thrombomodulin and forms a complex. Thrombomodulin - Thrombin complex activates protein C.

Activated protein C along with its cofactor protein S, in activates factors V, VIII and inactivates an inhibitor of tissue plasminogen activator. Plasmin is formed from plasminogen by the action of thrombin and tissue plasminogen activator (Flow chart 2.9). Thus formation of plasmin is enhanced. Plasmin lyses fibrin and fibrinogen, with the production of fibrinogen degradation products that inhibit thrombin.

## Anticoagulants

### *Heparin*

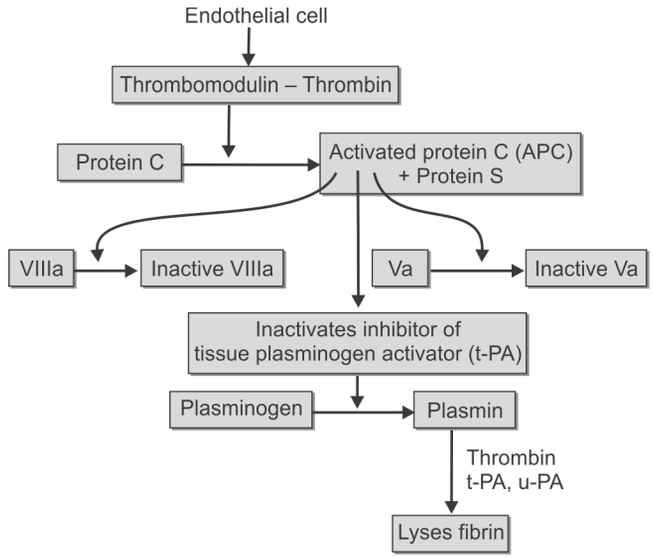
It is a mucopolysaccharide, natural anticoagulant, secreted by granules of mast cells and basophils. It facilitates the action of antithrombin III and thereby inhibits active forms of factors IX, X, XI, XII.

### *Vitamin K Antagonists*

a. Dicumarol
b. Warfarin
c. Phenindione.

Vitamin K is essential for liver formation of clotting factors like II, VII, IX, X. All these factors are synthesized by the liver as inactive zymogens.

**Flow chart 2.9:** Steps involved in the formation of plasmin (fibrinolysin)




### *Oxalate Compounds*

They prevent coagulation by forming calcium oxalate. Thus $Ca^{2+}$ is removed from blood. A mixture of ammonium oxalate and potassium oxalate in the ratio of 3:2 is used. Potassium oxalate alone causes shrinkage of RBCs. Ammonium oxalate alone causes swelling of RBCs. But together these substances do not alter cellular activity.

### *Citrates*

Citrates combine with $Ca^{2+}$ in blood to form calcium citrate. Reduction in $Ca^{2+}$ level prevents coagulation.
Na, K and $NH_3$ citrates are used.

### *EDTA*

They prevent blood clotting by removing $Ca^{2+}$ from blood. Blood can be kept in fluid state by:
- Keeping at low temperature
- Keeping in siliconized vessels
- Diluting blood with saline.

## Abnormalities of Hemostasis

### *Thrombosis*

Formation of clots inside blood vessels is called thrombosis.

### *von Willebrand Disease (vWD)*

Deficiency of vWF causes a bleeding disorder called vWD. This protein is responsible for platelet adherence to endothelium of

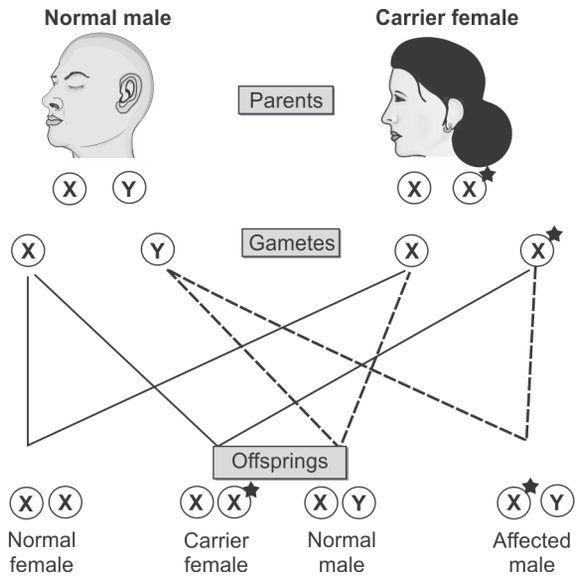



**Fig. 2.3:** Transmission of hemophilia

blood vessels during hemostasis. von Willebrand factor complexes with factor VIII and in circulation the complex as a whole circulates. Thus, it is responsible for survival and maintenance of factor VIII in plasma. In vWD, platelet adhesion is reduced and thus hemostasis is affected.

### *Hemophilia*

It is a bleeding disorder due to deficiency of some clotting factors that occurs exclusively in males. It is an inherited sex linked anomaly due to an abnormal gene on X-chromosome (Fig. 2.3). Here clotting time is prolonged (normal: 3–8 min) but bleeding time is normal (normal: 2–5 min).

***Treatment***

a. Fresh blood transfusion (factor VIII is lost on storage).
b. Injecting factor VIII and IX.
c. Injecting thrombin or thromboplastin. It is of two types:
   - Hemophilia A (classical hemophilia)
     Factor VIII is absent. It is relatively common.
   - Hemophilia B (Christmas disease)
     Factor IX is deficient.

### *Purpura*

It is a condition characterized by spontaneous hemorrhages beneath the skin, mucous membrane and in the internal organs. Bleeding time is prolonged (normal: 2–5 min). Clotting time is normal (normal: 3–8 min).

It may be due to:
- Decreased platelet count (thrombocytopenic purpura)
- Drug induced (quinine, ergot, iodine, etc.).
- Defective capillary contractility.

***Forms***

a. Thrombocytopenic purpura (decreased platelet count)
b. Athrombocytopenic purpura (normal platelet count)
c. Thromboasthenic purpura (abnormal circulating platelet but platelet count is normal).

***Treatment***

a. Injecting corticosteroids or ACTH
b. Splenectomy.

## BLOOD GROUPS

### ABO Blood Group Systems (Table 2.6)

**Table 2.6: ABO blood groups**

| *Blood group* | *Erythrocyte contains (agglutinogen)* | *Plasma contains (agglutinin)* |
|---|---|---|
| A | A | anti-B (β) |
| B | B | anti-A (α) |
| AB | A and B | Nil (o) |
| O | Nil | anti-A and anti-B (α and β) |

### Landsteiner's Law

- If a particular agglutinogen (antigen) is present in the RBCs, the corresponding agglutinin (antibody) must be absent in the plasma.
- If a particular agglutinogen is absent in the RBCs, the corresponding agglutinin must be present in the plasma.
- The second part of the law is not applicable to Rh, M and N blood groups.

### Compatibility between Different Groups (Table 2.7)

**Table 2.7: Blood groups compatibility**

| Donor's group | *Recipient's group* | | | |
|---|---|---|---|---|
| | A (Aβ) | B (Bα) | AB (AB nil) | O (nil αβ) |
| O | ✓ | ✓ | ✓ | ✓ |
| A | ✓ | × | ✓ | × |
| B | × | ✓ | ✓ | × |
| AB | × | × | ✓ | × |

✓ = no mismatching; × = mismatching

### Cross Matching

In clinics, cross matching is always done before blood transfusion. There are two types of cross matching—major (Direct) and minor (Indirect).

***Direct cross matching***

Here donors RBCs are mixed with recipients plasma and checked for agglutination. The donor's plasma get diluted with recipients plasma so that agglutination of recipients RBCs occur rarely.

***Indirect cross matching***

Here the donor's plasma is reacted with recipients RBC and checked for agglutination. If agglutination occurs during either of the both tests, the blood from that person is not used for transfusion.

***Note***

1. H antigen is normally present in all individuals of all blood types.

***Bombay blood group:*** Individuals with Bombay phenotype (hh) do not express H. Since there is no H antigen, there is no antigen A or antigen B on red cells. However, the plasma contains anti-A, anti-B and anti-H antibodies. As a result such a person can receive blood only from a person having Bombay blood type.

2. ABO incompatibility: The antibodies of ABO blood group are of the IgM variety. They cannot cross the placenta. So there are no complications due to ABO incompatibility.

## The Rh System

Rh factor is an antigen present in RBC. This system primarily comprises of C, D and E antigens. D is the most antigenic compound and the term Rh+ve generally means that the individual has agglutinogen D. The antibody in this system is called anti-D and it is produced only when a Rh –ve individual receives the D antigen. The antibodies are of IgG variety. Rh factor is an inherited dominant factor.

### Hemolytic Disease of Newborn

When an Rh–ve mother carries an Rh+ve fetus, small amount of blood leak into the maternal circulation at the time of delivery. During postpartum period, the mother develops Rh antibody in her blood. When the mother conceives for the second time and if the fetus happens to be Rh+ve again, the Rh antibody from mother's blood crosses the placental barrier and enters fetal blood (only Rh antigen cannot cross the placental barrier whereas the Rh antibody can cross it). The Rh antibodies which enter the fetus cause agglutination of fetal RBCs resulting in hemolysis. The changes in the fetus are termed as hemolytic diseases. The various forms of hemolytic disease of newborn (HDN) are:

#### Erythroblastosis Fetalis

The disease is also called icterus gravis neonatorum. The infant is jaundiced due to excessive destruction of RBC. Due to severe hemolysis, anemia develops and fetal body tries to compensate and as a result large number of premature red cells (erythroblasts) appear in peripheral circulation of fetus.

#### Hydrops Fetalis

If hemolysis is more severe, death of the fetus occurs in the uterus or may develop severe jaundice, anemia and edema.

#### Kernicterus

It is a condition which develops when bilirubin deposition occurs in basal ganglia of brain (as BBB is not developed in fetus and newborn infants) producing abnormalities in the functions of basal ganglia.

#### Treatment of HDN

1. Phototherapy: Neonatal jaundice can be treated by phototherapy (bilirubin is photoisomerized to lumirubin which can be excreted in bile).
2. Drugs like phenobarbitone.
3. Exchange blood transfusion soon after birth, i.e. to replace the neonates blood with Rh –ve blood.

#### Prevention of HDN

Administration of anti-Rh antibodies (anti-D antibody) soon after child birth, if Rh –ve mother gives birth to Rh +ve child. It is also administered to expectant mother starting at 28–30 week of gestation.

## Blood Transfusion

#### Indications

Blood loss, blood disorders, blood diseases, poisoning, acute infections, shock, etc.

#### Complications of Blood Transfusion

***Due to mismatched transfusion***

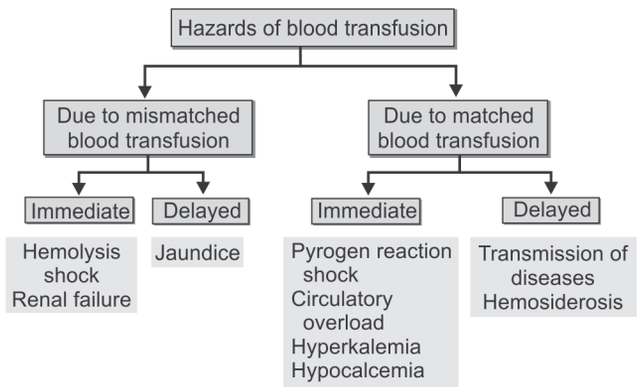
The antibodies in the recipient's serum attach to the antigens of donor's RBC. This antigen-antibody reaction leads to agglutination (forming clumps). The RBCs are first agglutinated and then undergo hemolysis. The clumps of cells may block smaller blood vessels in the coronary/pulmonary/renal circulation. This may result in shock. The hemolyzed RBCs causes increased release of Hb which gets metabolized to

bilirubin and may lead to jaundice. If the amount of Hb in the renal tubules is sufficiently high, kidney failure can develop.

***Which are not due to mismatched transfusion (Flow chart 2.10)***

a. Excess volume of transfusion can cause hypervolemia. As stored blood cells lose $K^+$ to the external plasma, hyperkalemia results.
b. Blood is stored using citrates and transfused blood contains enough citrates. With massive transfusion of citrated blood, citrate removes the $Ca^{2+}$ ions of recipient's blood. This results in hypocalcemia.
c. Hemosiderosis (due to excess Fe).
d. Pyrogenic reactions like fever.
e. Allergic reactions and shock.
f. Transmission of diseases like AIDS, malaria, syphilis, etc.

**Flow chart 2.10:** Hazards of blood transfusion




## Blood Storage

For better long-term preservation of blood and for transfusion purposes, citrate is used in combination with dextrose in the following forms.

### *Acid-Citrate-Dextrose (ACD) Solution*

*Trisodium citrate, citric acid and dextrose:* pH is 5.4, add 10 volumes of blood to 1.5 volumes of solution. In this form blood can be stored up to 21 days.

### *Citrate-Phosphate-Dextrose-Adenine (CPD-A) Solution*

*Trisodium citrate, citric acid, dextrose and adenine:* pH is 5.6–5.8, add 7 volumes of blood to 1 volume of solution. In this form blood can be stored up to 35 days.

*Dextrose acts by*

i. Liberating lactic acid which by decreasing the pH helps in survival of RBCs both *in vitro* and *in vivo*.
ii. Providing a substrate for the metabolism which is required even at 4°C and thus helps in the survival of cell.

### *Changes in the Stored Blood (Preservation Injuries)*

Blood stored in the blood bank suffers some changes.

1. Decrease in 2, 3 DPG, so increased affinity of Hb to $O_2$.
2. Increase in $K^+$ concentration in plasma so chance of hyperkalemia.
3. Increase in concentration of $Na^+$ in RBC.
4. Decreased viability of RBCs, so they cannot work for longer time due to decreased ATP in them.
5. Decrease in platelet count.
6. Increased fragility.

## IMMUNITY

Resistance of body against pathogenic agents is known as immunity.

Immunity is of two types:

### Innate Immunity (Nonspecific)

It is the inborn capacity of the body to resist the entry of microorganisms into the body. It represents the first-line of defense against any pathogen.

For example:

- Phagocytosis of bacteria and other invaders by WBC and tissue macrophage system
- Destruction of swallowed organisms by acids secreted from stomach and digestive enzymes
- Destruction of foreign cells and tumor cells by natural killer cells.

### Acquired Immunity (Specific)

It is the resistance developed in the body against any specific foreign body like bacteria, viruses, toxins, vaccines, etc. The key to acquired immunity is the ability of lymphocytes to produce antibodies that are specific to foreign bodies (antigen). Acquired immunity is of two types—active and passive.

#### *Active Immunity*

Acquired immunity developed by the individual as a result of antigenic stimulation like previous infections, vaccines, etc. This involves the active functioning of the person's immune system leading to the synthesis of antibodies or production of immunologically active cells.

Active immunity can be induced naturally or artificially.

- Natural active immunity—results from either subclinical or clinical infection
- Artificial active immunity—by giving vaccines.

### *Passive Immunity*

Acquired immunity developed by an individual through the transfer of blood, serum, antibody from an immune individual; in ready made form. Here, the recipients immune system plays no role. It gives immediate response and is transient. It can be natural or artificial.

- *Natural passive immunity:* Antibody transmitted from mother to fetus either through placenta or through breast milk.
- *Artificial passive immunity:* Resistance passively transmitted to recipient by administration of Ab. It is given in the form of serum; e.g. anti-tetanus serum (ATS).

*Acquired immunity has two components:* Humoral and cell mediated.

## Lymphocytes

They are responsible for specific immune response. In fetus, lymphocytes develop from bone marrow.

The lymphocyte designed to develop the cellular immunity migrates into thymus gland and are transformed into T lymphocytes. The lymphocyte designed to develop the humoral immunity are processed in liver (during fetal life) and bone marrow (after birth) and are transformed into B lymphocytes. There is a third variety of lymphocytes called natural killer cells (NK Cells).

### *Types of T Lymphocytes*

a. Helper T cells or inducer T cells (T4 cells/CD4)
b. Cytotoxic T cells or killer cells (T8 cells/CD8)
c. Suppressor T cells (T8 cells/CD8)
d. Memory T cells.

### *Types of B Lymphocytes*

a. Plasma cells
b. Memory cells.

## Humoral Immunity

It is mediated by circulating Ig antibodies in the γ-globulin fraction of the plasma proteins. Ig antibodies are produced by B lymphocytes. B lymphocytes are stimulated directly by foreign organisms or through an antigen presenting cell. Some of B lymphocytes are converted to plasma cells, producing immunoglobulin. Each plasma cell continues to produce specific Ab for several days or weeks, till it dies. Some of the B lymphocytes are converted to blast-like cells and they remain as memory B cells. On exposure to same antigen subsequently, initiate a rapid response due to the presence of memory B cells. Humoral immunity is major defense against bacterial infections.

### *Immunoglobulin*

Immunoglobulin are produced by the plasma cells. It is composed of four polypeptide chains, linked by disulfide bonds. There are two heavy chains (H) and two light chains (L). Each light chain lies parallel to the terminal portion of heavy chain. There are two areas; Fab for antigen binding and Fc for complement binding (Fig. 2.4). Terminal portions of both heavy and light chains are called variable segment. Specificity of each Ab is due to specific amino acid pattern of variable segment. Thetr are of five basic types or classes:

### *IgG*

It is the most abundant antibody present in our body. It can pass through the placental barrier and it provides natural passive immunity. They serve as opsonins and promotes phagocytosis of the bacteria. It is the antibody seen in secondary immune response.

### *IgA*

It is formed by mucosal and submucosal aggregates of lymphoid tissue. From here it is transported to epithelial cells. This provides effective defense mechanism in mucosa of alimentary canal and lungs and genitourinary tracts.

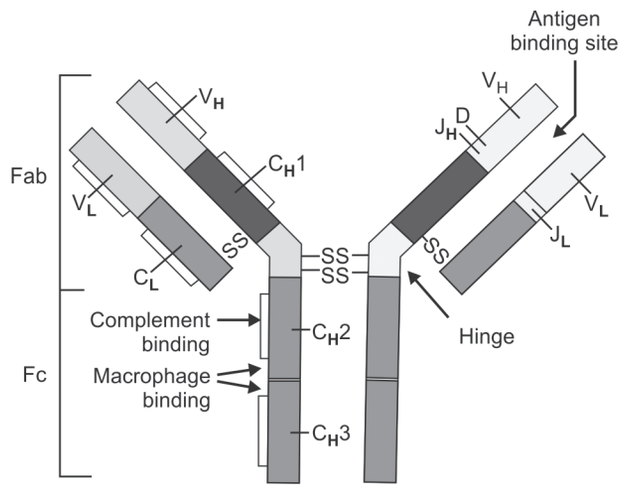



**Fig. 2.4:** Structure of an immunoglobin molecule

### IgM

Earliest Ig to be synthesized. It activates complement system. They are predominantly produced in primary immune response. Antibodies of ABO blood group system belongs to this class.

### IgE

They mediate allergy, hypersensitivity and anaphylaxis. Chiefly produced in the lining cells of respiratory and intestinal tract. They releases histamine from basophils and mast cells.

### IgD

Present on the surface of B lymphocytes and therefore involved in antigen recognition.

### Mechanism of Antibody Action

An antibody exerts its action by two mechanisms:
1. Direct action
2. Indirect action (through activation of complement system).

### Direct Action

There are multiple antigen sites on invading organisms. So antibodies can inactivate the invading agent in one of the following mechanisms:
1. *Agglutination:* Antibodies bind with antigen and forms a clump.
2. *Precipitation:* Molecular complex of antigens and antibodies becomes so large that is rendered insoluble and it precipitates.
3. *Neutralization:* Antibodies cover toxic sites of antigenic agents and make it nontoxic.
4. *Lysis:* Antibodies attack cell membrane of foreign organisms and cause destruction of organism or lysis.
5. Ab enhances opsonization and phagocytosis.

### Indirect Action

It is through activation of complement system. It is a system of about 20 proteins. Normally these are present in blood and tissue spaces and are inactive. They are activated by antigen-antibody reaction. When an antibody binds with an antigen, binding site on antibody for complement becomes activated and that will bind with complements. That will activate the complement system and activated complements produce certain effects. The effects are:

***Opsonization and phagocytosis:*** Activated complement C3b strongly activate phagocytosis by neutrophils and macrophages. These neutrophils and macrophages phagocytose foreign antigen or foreign bacteria.

***Lysis:*** One of the most important products of complement cascade is the lytic complex, which is a combination of multiple complement factors C5, C6, C7, C8, C9. Its directly cause lysis of foreign organism.

***Agglutination:*** The complement products changes the surface of invading organism and causes them to adhere one another or agglutination.

***Neutralization:*** The activated complements attack the structure of some viruses and make them nonvirulent or nontoxic. It leads to inflammatory changes, i.e. increased local blood flow, capillary leakage of proteins to interstitial space, coagulation of this proteins. These inflammatory changes immobilize the organism and prevent movement of organism from area of invasion to other part of the body.

## Cellular Immunity

It is produced by T lymphocytes that can directly attack intracellular pathogenic microorganisms like virus, fungus, bacteria, etc. They can activate macrophages which phagocytose pathogenic microorganisms. T lymphocytes require an antigen presenting cell for its action. The antigen presenting cells are, macrophages, B lymphocytes, dendrite cells in spleen and Langerhans cell of skin. MHC2 is present on membranes of antigen presenting cell (Major Histocompatibility Complex: Gene that produces proteins MHC1 and MHC2. MHC1 is present on membranes of all nucleated cells and platelets).

T lymphocytes are activated through antigen presenting cell. Antigen presenting cell (APC) phagocytoses the foreign organism, digests it and separates portion responsible for antigenicity. This gets attached to the MHC2 proteins which protrude from the surface of APC. This MHC2 antigen complex is recognized by an appropriate T lymphocyte and T lymphocyte gets attached to this complex. This will activate the T lymphocyte (CD4 or helper T cells). The activated T cells proliferate and a clone of activated T cells is produced, some remain as memory T cells. The following effects are produced by activated T cells.
1. Interleukins are produced and these activate further proliferation of T cells.
2. Interleukins produced by activated T cells activate B lymphocyte.
3. Activated T lymphocytes activate CD8 or cytotoxic T cells. Cytotoxic T cells cause cell lysis directly.
4. Activated T cells lead to inflammation and delayed allergic reactions.

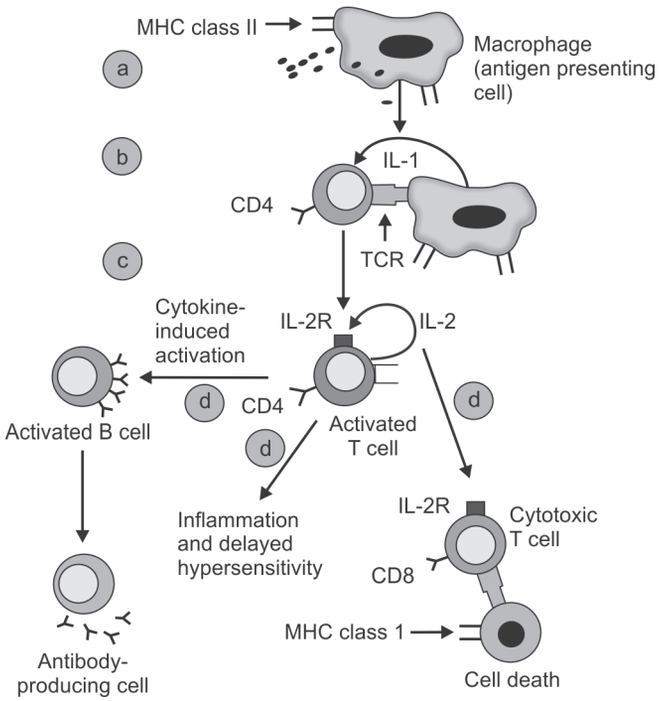



**Fig. 2.5:** Acquired immunity

During the second exposure, the memory cells are stimulated and produce more quantity of antibodies at a faster rate, than the first exposure.

### *Summary of Acquired Immunity*

a. When an antigen enters the body, it is ingested by macrophages and is partially digested. Antigen peptide fragments then combine with MHC-2 and move to cell surface.
b. This processed antigen with macrophage then binds with CD4 cell. CD4 cell is activated and it secretes interleukin 2 (IL-2).
c. IL-2 cause the cell to multiply, forming a clone.
d. The CD4 cells then activate B lymphocytes causing them to proliferate and transform into memory B cells and plasma cells or it may activate cytotoxic CD8 cell. The plasma cells secrete large quantities of antibodies (immunoglobulins) into general circulation (Fig. 2.5).

The CD8 cell can also be activated by forming a synapse with an MHC 1 antigen presenting cell.

## Reticuloendothelial System

They are special groups of cells scattered in different parts of the body which play an important role in the defense mechanism. The combination of monocytes, mobile macrophages, fixed macrophages and a few specialized endothelial cells in the bone marrow, spleen and lymph nodes is called reticuloendothelial system. It is also known as monocyte macrophage system (almost all these cells originate from monocytic stem cells). The macrophages can phagocytose abnormal body tissue, microbes and foreign particle. Tissue macrophages are of two types—Fixed and Wandering.

### *Site of Occurrence*

#### *Spleen and Bone Marrow*

In both these tissues, macrophages have become entrapped by the reticular meshwork of the two organs. When foreign particles come in contact with these macrophages, they are phagocytosed. They are present in both red and white pulp of spleen. Macrophages of the spleen and bone marrow are called reticulum cells. Reticulum cells of spleen can phagocytose RBC, platelets, parasite and bacteria. From the Hb of the RBC, these macrophages produce bilirubin.

#### *Lungs*

Macrophages found in the alveoli phagocytose the dust/carbon particles.

#### *Liver*

Sinusoids of the liver are lined by macrophages called Kupffer cells. It removes bacteria of portal venous blood. Portal vein contains bacteria coming from the intestine. The presence of Kupffer cells ensure effective filtration so that hepatic venous blood is free from bacteria.

#### *Lymph Nodes*

If particles are not destroyed locally in the tissues they enter the lymph and flow to the lymph nodes. The foreign particles are entrapped in these nodes in a meshwork of sinuses lined by tissue macrophages. These macrophages phagocytose the particles entering the sinuses.

## Warm and Cold Antibodies

Agglutinogens of ABO system and RH system can react with their corresponding antibodies at normal or near body temperature that is in warm environment. Therefore, this agglutinins are called warm antibodies.

But antibodies of some other blood group systems can react with their corresponding agglutinogens only at a temperature between 5°C to 20°C. They are called cold antibodies.

## LYMPHATIC SYSTEM

- Lymphatic system exists in all the organs with the exception of CNS and cornea.
- Lymph is a tissue fluid that enters the lymphatic vessels and then drains into the venous blood via the thoracic and right lymphatic duct.
- Lymph contains clotting factors and it clots on standing *in vitro*.
- It is transparent, yellowish in color, faintly alkaline and its colloidal osmotic pressure is less than that of plasma.

### *Formation*

Formation is based on transcapillary exchange (Fig. 2.6). Lymph is derived from interstitial fluid that flows into the lymphatics. It enters terminal lymphatics (same composition as interstitial fluid). The protein concentration of the lymph is near 2 gm/dl which is the average protein concentration of interstitial fluid. Even large particles such as bacteria can push their way between the endothelial cells of lymphatic capillaries (thereby enter lymph).

***Starling forces:*** The rate of filtration at any point along a capillary depends on a balance of forces called "Starling forces":

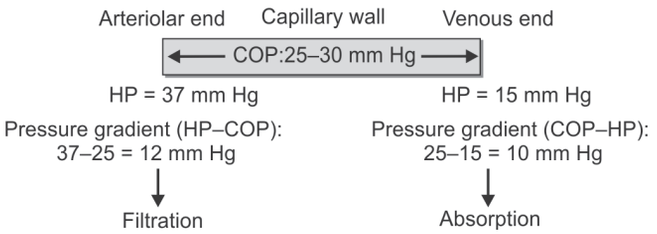



**Fig. 2.6:** Pressure gradient across capillary wall

$$\text{Fluid movement} = k\,[(P_c - P_i) - (\pi_c - \pi_i)]$$

where,

$k$ = Capillary filtration coefficient
$P_c$ = Capillary hydrostatic pressure
$P_i$ = Interstitial hydrostatic pressure
$\pi_c$ = Capillary colloid osmotic pressure
$\pi_i$ = Interstitial colloid osmotic pressure (negligible)
$(P_c - P_i)$ = Hydrostatic pressure gradient
$(\pi_c - \pi_i)$ = Osmotic pressure

*Rate:* Total estimated lymph flow is about 120 ml/hr or 2–3 L/day.

### *Function*

1. Returns proteins, water and electrolytes from tissue spaces to the blood and thus controls concentration of proteins in the interstitial fluid, volume of interstitial fluid and interstitial fluid pressure.
2. Absorption of nutrients especially fats from the GIT.
3. Acts as transport mechanism to remove red blood cells that have lost into the tissues as a result of hemorrhage.
4. Lymph nodes act as efficient filters. They have sinuses lined with phagocytic cells that engulf bacteria, red blood cells and other particulate matter (bacteria or toxins are carried to them through lymph).
5. *Nutritive:* It supplies nutrition and $O_2$ to those parts where blood cannot reach.

### *Applied*

Hypoproteinemia causes decrease in COP, therefore increased filtration occurs at arterial end and decrease in absorption of fluid at venous end, resulting in abnormal collection of fluid in interstitial spaces called edema.

Chapter

# 3 Respiratory System

The main function of respiratory system is to extract $O_2$ from the atmosphere, to deliver it to the tissues and to take $CO_2$ from the tissues and discharge it to the atmosphere. The entire respiration can be divided into two main divisions.

- *External respiration:* It deals with the absorption of $O_2$ and removal of $CO_2$ from the body as a whole.
- *Internal respiration:* It is the utilization of the $O_2$ and production of $CO_2$ by cells and the gaseous exchange between the cells in their fluid medium.

## GENERAL PRINCIPLES

### Weibel's Lung Model (Tracheobronchial Tree)

This was introduced by ER Weibel (1963). Between the trachea and alveolar sac, the air passage divides 23 times.

Trachea is designated as generation zero. First-two major divisions of trachea constitute the "first" generation and so on. Atria or the alveolar sac is the 23rd generation (last generation). From the functional point of view tracheobronchial tree can be divided into two major zones (Fig. 3.1).

1. *Conducting zone*: The first 16 generation bronchioles form the conducting zone of air (no alveoli present). So no exchange of gases takes place here. This area forms the anatomical dead space. The 16th generation bronchioles are called terminal bronchioles.
2. *Respiratory zone:* On and from the 17th generation, few alveoli are seen. Here exchange of gases takes place, so called respiratory bronchioles.

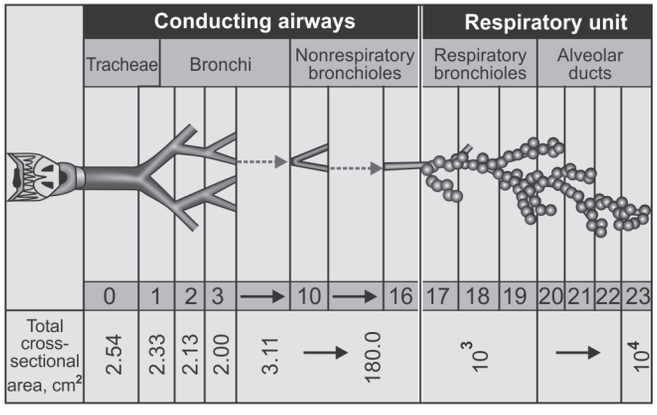



**Fig. 3.1:** Weibel's lung model

### *Advantages*

These multiple divisions increase the total cross-sectional area of airways (from 2.5 to 11800 $cm^2$) in the alveoli. As a result the velocity of airflow in small airways is greatly reduced allowing better gaseous exchange. The alveoli are surrounded by pulmonary capillaries.

### Respiratory Membrane

The air in the alveoli is separated from the blood in the pulmonary capillaries by a wall called "respiratory membrane" (Fig. 3.2). Basically, it consists of alveolar wall and the capillary wall.

The following are the six layers of the respiratory membrane:

1. A layer of surfactant lining the alveolus.
2. The alveolar epithelium.
3. Basal lamina of alveolar epithelial cells.
4. A thin interstitial space between the alveolar epithelium and the capillary membrane.

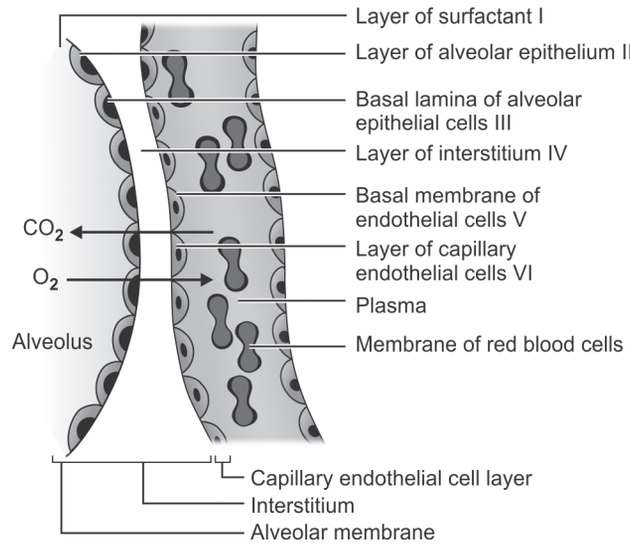



**Fig. 3.2:** Respiratory membrane

5. Basal membrane of endothelial cells.
6. A capillary endothelial membrane.

Despite these large number of layers, the overall thickness of the membrane in some areas is as little as 0.2 micrometer (average about 0.6 micrometer), except where there are cell nuclei. The total surface area of the respiratory membrane is about 70 $m^2$ in the normal adult human male, which facilitates the rapidity of respiratory exchange of $O_2$ and $CO_2$. There are about 300 million alveoli in the two lungs.

### *Factors Affecting the Rate of Gas Diffusion*

$$V_{gas} = A/T \times D \times (P_1 - P_2)$$

1. *The thickness (T) of the membrane:* Thickness increases in pulmonary edema and fibrosis of lung.
2. *The surface area (A) of the membrane:* Surface area decreases in pneumonectomy and emphysema.
3. *The diffusion coefficient (D) of the gas in the substance of the membrane:* Diffusion coefficient is directly proportional to the solubility of the gas and inversely proportional to the square root of molecular weight of gas.
4. The partial pressure difference of the gas between the two sides of the membrane ($P_1 - P_2$).

## Airway Resistance

When air flows through the airways, there is resistance to the air flow, which is referred to as airway resistance. Normal value is 1.5–2 cm $H_2O$/L/sec.

$$\text{Airway resistance} = \frac{\text{Pressure difference between atmosphere and alveolar pressure (cm } H_2O)}{\text{Airflow (L/sec)}}$$

### *Factors Affecting Airway Resistance*

1. *Total cross-sectional area:* Resistance to the airflow is inversely related to the total cross-sectional area of the respiratory passage. Therefore, the resistance to the airflow is high in the 'conducting zone' whereas it is low in the 'respiratory zone'.
2. *According to Poiseuille:* **Hagen** formula, the relation between the flow in a long narrow tube, the viscosity of fluid and the radius of the tube is :

$$F = (P_A - P_B) \times (\pi/8) \times (1/\eta) \times (r^4/L)$$

where,

F = flow, $P_A - P_B$ = pressure difference between two ends of the tube, $\eta$ = viscosity, L= length of the tube, r = radius of the tube.

Since flow $= \frac{P_A - P_B}{R}$ where, R = resistance

So, Resistance (R) $= \frac{8 \eta L}{\pi r^4}$

i.e R $\alpha 1/ r^4$

Therefore, if the radius decreases by 'half' keeping the other factors constant, the resistance increases by '16' times; but this does not occur in our body because as diameter of the airways is large, there is no difficulty in breathing.

3. *Type of flow:* Airway resistance is more in 'turbulent' flow (i.e during rapid respiration) than in 'laminar' flow or streamline flow (i.e. in quiet breathing).

## Nonrespiratory Functions of Lungs

The main function of the respiratory system in general and lungs is gas exchange. Nonrespiratory functions of the respiratory system includes:

**1. *Lung defense mechanisms***

a. The respiratory passages not only serve as gas conduits, but also humidify and cool or warm the inspired air to make it attain the body temperature by the time it reaches the alveoli.
b. Bronchial secretions contain secretory immunoglobulin (IgA) and other substances that help to resist infections and maintain mucosal integrity.
c. Pulmonary epithelium contains an interesting group of protease activated receptors (PARs), which when activated triggers the release of $PGE_2$, which in turn protect the epithelial cells.
d. Pulmonary alveolar macrophages (PAMs): These cells come originally from bone marrow. They are important component of pulmonary defense mechanisms. They are actively phagocytic and ingest inhaled bacteria and small particles. They help in processing the inhaled antigens for immunological attack. They secrete substances that attract granulocyte to the lung as well as substances that stimulate granulocyte and monocyte formation in bone marrow.
e. Prevents foreign body from reaching alveoli.
   i. *Particles ≥ 10 μm in diameter*: The hair in the nostrils strain out many particles and they settle down on mucous membrane in the nose and pharynx.
   ii. *Particles 2–10 μm diameter:* These particles when fall on the walls of the bronchi as airflow slows in smaller passages, initiates reflex bronchoconstriction and coughing, thereby the particles are moved away from lungs by ciliary escalator action.
   iii. *Particles ≤ 2 μm in diameter:* Generally reach the alveoli, where they are ingested by the macrophages.

**2. *Functions of pulmonary circulation***

a. *Reservoir for left ventricle:* If the LV output becomes transiently greater than systemic venous return, LV output

can be maintained by drawing out blood stored in the pulmonary circulation (for few strokes only).

b. *Role as a filter*: Pulmonary circulation act as a filter for many substances like fibrin clots, fat cells, detached cancer cells, agglutinated RBCs.

c. *Fluid exchange and drug absorption:* Low pulmonary hydrostatic pressure tends to pull fluid from alveoli into pulmonary capillaries, thereby keeping the alveolar surface free from liquids. This facilitates the rapid entry of drugs into systemic circulation which rapidly pass through the alveolar-capillary barrier by diffusion. For example: (i) anesthetic gases (ii) aerosols.

3. ***Metabolic and endocrine functions of the lungs***

a. Manufactures surfactant for local use, which prevents the development of surface tension between the fluid lining the alveoli and the alveolar air.

b. Substances synthesized or stored and released into the blood. For example, prostaglandins (esp. $PGE_2$ and $PGF_{2\alpha}$)

c. Contain a fibrinolytic system that lyses clots in the pulmonary vessels.

d. The lungs also activate one hormone in the pulmonary circulation.

$$\text{Angiotensin I} \xrightarrow{ACE} \text{Angiotensin II}$$

(This reaction occurs in other tissues also, but prominent in lungs)

- Angiotensin I—Inactive decapeptide
- Angiotensin II—A pressor, aldosterone stimulating octapeptide.
  Large amounts of ACE is located on endothelial cells of the pulmonary capillaries. Angiotensin converting enzyme (ACE) inactivates bradykinin.

e. It helps in the removal of serotonin and norepinephrine, thereby reducing the amounts of vasoactive substances reaching the systemic circulation. However, many other vasoactive substances like epinephrine, dopamine, oxytocin pass through the lungs without being metabolized.

***Note***

1. *Kartagener's syndrome:* It is associated with immotile cilia (due to congenital absence of axonemal dynein). This leds to recurrent lung infections. Patients with this condition are infertile due to lack of sperm motility.
2. Alveoli are lined by two types of cells:
   a. Type I (Flat cells with large cytoplasmic extensions)
   b. Type II (granular pneumocytes, that produce surfactant).

## MECHANISM OF BREATHING/VENTILATION

*Eupnea:* Rhythmic breathing at rest, consists of inspiration and expiration.

### Inspiration

It is an active process during which the contraction of the inspiratory muscles increases the intrathoracic volume. The intrapleural pressure at the base of the lungs is normally about –2.5 mm Hg (relative to atmospheric pressure) at the start of inspiration and it decreases to about –6 mm Hg. Thus lungs are pulled into a more expanded position making the pressure in the airways slightly negative and air flows into the lung.

The movement of the *diaphragm* accounts for 75% of the change in the intrathoracic volume during quiet inspiration. The other inspiratory muscles are the external intercostal muscles, which run obliquely downward and forward from rib to rib. The ribs pivot as if hinged at the back, so that when the external intercostals contract they elevate the lower ribs which pushes sternum outward causing in increased anteroposterior (AP) diameter of the chest.

#### *Inspiratory Mechanism*

During inspiration the thorax is enlarged by:

- Rib movements (movement of ribs outwards and upwards)
- Diaphragmatic movements (descent of diaphragm).

#### *Rib Movements*

*Pump handle movements:* The 2nd to the 6th ribs slope obliquely downwards and forwards from their joints with the spinal column, on inspiration the ribs move upwards pushing the sternum more anteriorly (pump handle movements; Fig. 3.3) to assume a more horizontal position by contraction of external intercostals resulting in increase in AP diameter of the chest.

*Bucket handle movement:* The lower ribs (7th to 10th) also swing outwards and upwards in inspiration causing increase in the transverse diameter of the thorax (Fig. 3.4).

#### *Accessory Muscles of Inspiration*

##### *Scalene, Sternocleidomastoid*

Active during voluntary static inspiratory efforts that help to elevate the thoracic cage during deep inspiration.

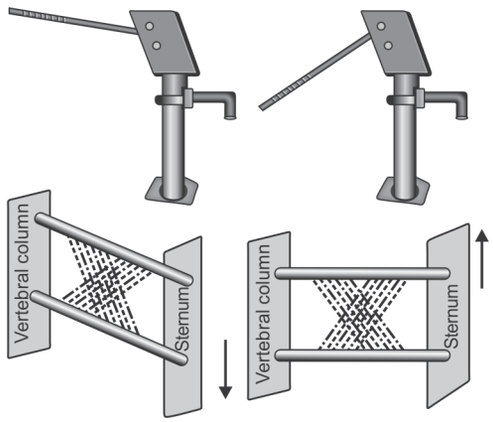



**Fig. 3.3:** Pump handle movement increases the anteroposterior diameter

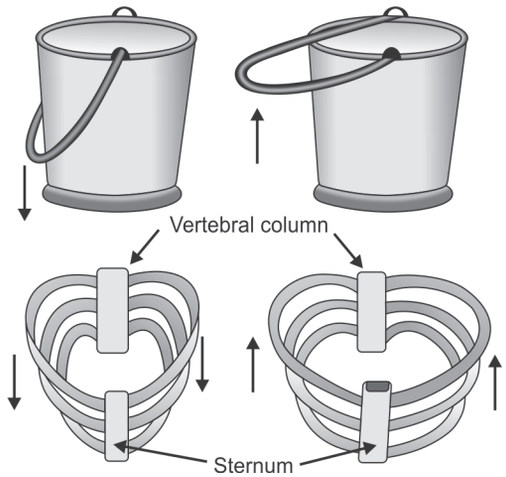



**Fig. 3.4:** Bucket handle movement increases the transverse diameter

### *Intrinsic Muscles of Larynx*

Abductor muscles of vocal cords (posterior cricoarytenoid) that contract early on inspiratory phase pulling the vocal cords apart, opening the glottis.

***Expiratory mechanism***

Quiet breathing is a passive process. But during forced expiration, e.g. exercise, bronchial asthma, the muscles of expiration contract.

*Expiratory muscles*

- Anterior abdominal muscles (abdominal recti, transversus abdominus, internal and external oblique muscles
- Internal intercostal muscle
- Accessory muscles of expiration (adductor muscles of vocal cord).

## Pressure Changes During Ventilation

### *Intrapulmonary Pressure/Intra-alveolar Pressure*

Intrapulmonary pressure is defined as the pressure in the lung parenchyma. It reduces with the expansion of the lungs and facilitates the pull of air into the lungs via the tracheobronchial tree.

In normal quiet breathing, at end-expiration and end-inspiration, as no air is going in and coming out of the lungs, the intrapleural pressure = atmospheric pressure, i.e. 760 mm Hg.

With the beginning of inspiration, as volume increases pressure decreases and intrapulmonary pressure decreases to approx 3 mm Hg below the atmospheric pressure (i.e. 757 mm Hg), but regains the pressure value at end-inspiration. As expiration follows passively, the elastic recoil of the lungs causes the intrapulmonary pressure to swing to the positive side (i.e. 763 mm Hg) (Fig. 3.5).

***Factors affecting intrapulmonary pressure***

a. *Valsalva maneuver:* Forced expiration against a closed glottis, may produce a positive intrapulmonary pressure of 100 mm Hg above atmospheric pressure.
b. *Müller's maneuver:* Forced inspiration against a closed glottis, can reduce the intrapulmonary to 80 mm Hg below the atmospheric pressure.

### *Intrapleural (Intrathoracic) Pressure*

The pressure in the "space" between the lungs and the chest wall (intrapleural space) is called intrapleural pressure. This pressure is subatmospheric and is not uniform throughout the thoracic cavity due to the effect of gravity. It is –2 mm Hg at the base and –7 mm Hg at the apex.

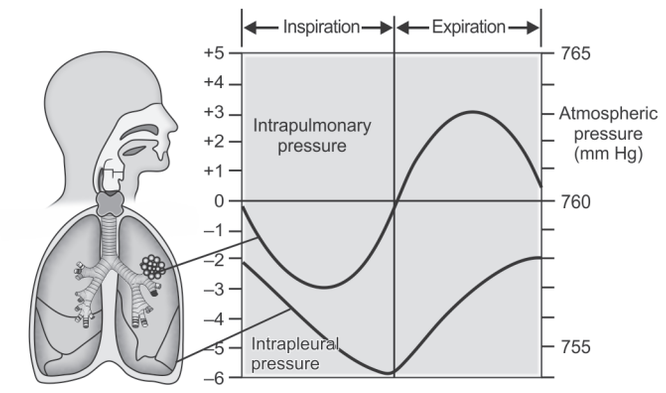



**Fig. 3.5:** Changes in the intrapulmonary and intrapleural pressure during the respiratory cycle

The negative intrapleural pressure is directly proportional to amount of thoracic expansion. Therefore during quiet inspiration, the lungs are pulled into a more expanded position causing the intrapleural pressure to decrease to about –6 mm Hg. At the end of inspiration, the muscles of inspiration relax and the intrapleural pressure becomes less negative and the lungs recoil thereby intrapulmonary pressure increases (Fig. 3.5).

***Factors affecting intrapleural pressure***

a. Deep inspiration decreases it as much as 30 mm Hg, subatmospheric (730 mm Hg).
b. *Effect of gravity:* The intrapleural pressure in standing position is more negative (–7 mm Hg) at the apices of the lungs compared to the bases (–2 mm Hg).

### *Transpulmonary Pressure*

It is the difference between the alveolar pressure and the pleural pressure. It is the pressure difference between the pressure in the alveoli and that on the outer surfaces of the lungs. It is a measure of the elastic forces in the lungs that tend to collapse the lungs at each instant of respiration, called the recoil pressure.

### *Clinical Significance*

1. Since the transmural pressure, i.e. pressure gradient between intrapulmonary and intrapleural pressure is less at the bases, therefore, the lungs are less expanded at the bases.
2. Emphysema, i.e. loss or decrease in lung elasticity which increases intrapleural pressure thereby chest expands becomes barrel-shaped.
3. Injury to thorax causes entry of air between two layers of pleura, therefore intrapleural pressure equal to atmospheric pressure. Thereby lungs collapses (pneumothorax).

## Spirometry

Pulmonary ventilation is studied by recording the volume movement of air into and out of the lungs—a process called spirometry. Spirometer consists of a drum inverted over a chamber of water, with the drum counterbalanced by a weight. In the drum there is breathing gas (air or oxygen); a tube connects the mouth with the gas chamber (Fig. 3.6). When one breathes into and out of the chamber the drum rises and falls, and an appropriate recording is made on a moving sheet of paper.

## *Lung Volumes and Capacities*

These can be divided into two major headings:
1. Static lung volumes and capacities—time factor is not involved (expressed in ml or L).
2. Dynamic lung volumes and capacities—time dependent, (expressed in ml/min or L/min).

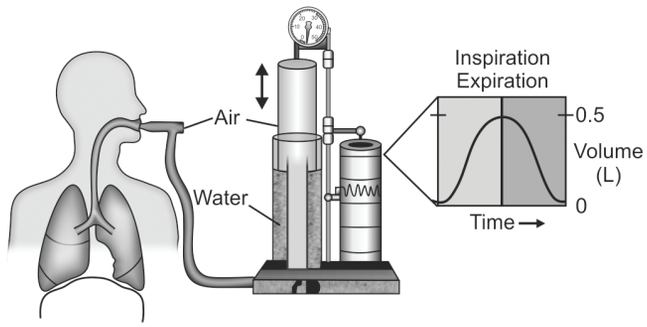



**Fig. 3.6:** Spirometry

## *Static Lung Volume and Capacities (Fig. 3.7)*

### *Volumes*

1. *Tidal volume (TV):* It is the volume of air breathed in or out of lungs, during normal quiet respiration. Normal TV is 500 ml (0.5 L in men and women). The TV increases in muscular exercise and it decreases in respiratory muscle weakness or depression of respiratory center.
2. *Inspiratory reserve volume (IRV):* The air inspired with a maximal inspiratory effort in excess of the tidal volume, i.e. the maximal volume of air that can be inspired after completing a normal tidal inspiration. Normal IRV is 3.3 L in men and 1.9 L in women.
3. *Expiratory reserve volume (ERV):* The volume of air expelled by an active expiratory effort after passive expiration, i.e. the maximal volume of air which can be expired after a normal tidal expiration. Normal ERV is 1.0 L in men and 0.7 L in women.
4. *Residual volume (RV):* The air left in the lungs after a maximal expiratory effort. Normal RV is 1.2 L in men and 1.1 L in women.

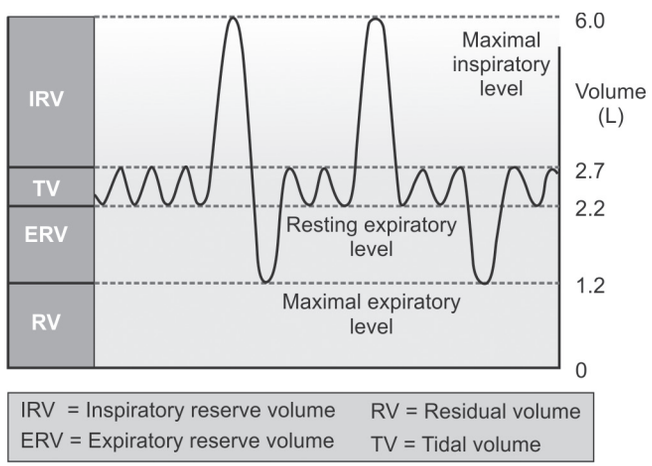



**Fig. 3.7:** Lung volumes and capacities

5. *Closing volume:* It is the lung volume above residual volume at which airways in the lower, dependent parts of the lung begin to close off because of the lesser transmural pressure in these areas.
6. *Pulmonary ventilation/Respiratory minute volume (RMV):* It is the amount of air inspired per minute. Normal RMV is 6.0 L (500 ml/breath × 12 breaths/min).

### Capacities

1. *Inspiratory capacity (IC):* It is the maximal volume of air which can be inspired after completing tidal expiration, i.e. from the end-expiratory position. IC = TV + IRV. Normal IC is 3.8 L in men and 2.4 L in women. *Range:* 2.5 L–3.7 L.
2. *Expiratory capacity (EC):* It is the maximal volume of air which can be expired after completing tidal inspiration, i.e. from the end-inspiratory position. EC = TV + ERV. Normal EC is 1.5 L in men and 1.2 in women. *Range:* 1.25 L–1.5 L.
3. *Vital capacity (VC):* The largest amount of air that can be forcefully expired after a maximal inspiratory effort, which is frequently measured clinically as an index of pulmonary function.

   *Advantages of Vital Capacity*
   - It gives useful information about the strength of the respiratory muscles; therefore maximal inspiratory and expiratory efforts can be assessed.
   - It gives useful information about other aspects of function through FEV1
     VC = TV + IRV + ERV. Normal VC is 4.8 L in men, 3.1 L in women.

   *Factors Affecting Vital Capacity*

   ***Physiological***
   a. Physical dimension, i.e. size and development of the subject. The VC more in males (2.6 L /$m^2$ BSA) than in females (2.1 L/$m^2$ BSA) because of large chest size, more muscle power, more body surface area (BSA).
   b. As age increases VC decreases due to loss of elasticity of lungs.
   c. Strength of respiratory muscles—VC increases in swimmers and divers.
   d. Pregnancy—VC decreases.
   e. Posture—in standing position VC is more than sitting or lying posture.

   ***Pathological***
   a. The VC decreases in diseases of the respiratory apparatus. For example, poliomyelitis, pulmonary fibrosis, pulmonary edema, pneumothorax, etc.
   b. Ascites, the accumulation of fluid in the abdominal cavity causes VC to decrease.
4. *Functional residual capacity (FRC):* It is the volume of air which is contained in the lungs at end-expiratory position, i.e. after completion of tidal expiration. FRC = RV + ERV. Normal FRC is 2.2 L in men and 1.8 L in women.
5. *Total lung capacity (TLC):* It is the volume of air contained in the lungs after a maximal inspiration. TLC = VC+ RV or TLC = TV + IRV + ERV + RV. Normal: TLC is 6.0 L in males and 4.2 L in women.
6. *Maximal voluntary ventilation/Maximal breathing capacity (MVV):* It is the largest volume of air that can be moved into and out of the lungs in 1 min by voluntary effort. Normal MVV 125–170 L /min.
7. *Breathing reserve (BR) or Pulmonary reserve (PR):* It is the maximum amount of air above the pulmonary ventilation, which can be breathed in or out of lungs in one minute. The BR = MVV–RMV.

## Dynamic Lung Volumes and Capacities

***Timed vital capacity (TVC) or forced vital capacity (FVC):*** Forced vital capacity is the maximal volume of air that can be breathed out as 'forcefully' and 'rapidly' as possible following a maximum inspiration. The TVC similar to VC except that there is a special stress on rapid, forcible and complete exhalation.

***Components of TVC (FVC)***

a. *$FEV_1$ (Forced expiratory volume in 1 sec):* The fraction of the vital capacity expired during the 1st second of a forced expiration or it is the volume of FVC expired in 1st sec of exhalation. Normal: 80% of FVC (Fig. 3.8).
b. *$FEV_2$ (Forced expiratory volume in 2 sec):* The volume of FVC expired in first-two seconds of exhalation. Normal: 95% of FVC.

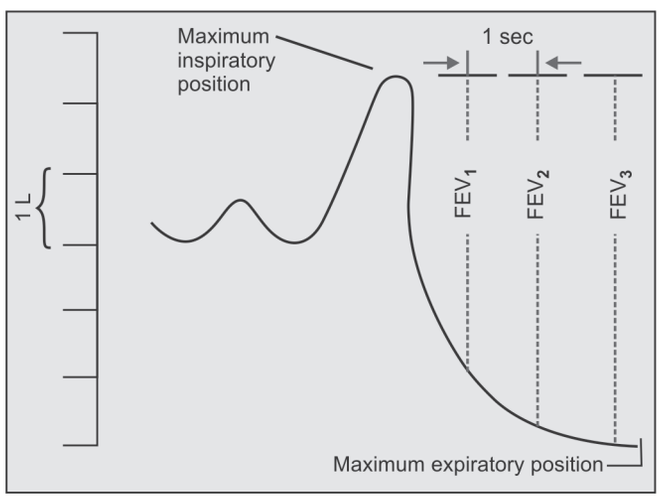



**Fig. 3.8:** Timed vital capacity

c. *$FEV_3$ (Forced expiratory volume in 3 sec):* The volume of FVC expired in first three seconds of exhalation. Normal: 98–100% of FVC.

***Clinical significance of FVC***

To distinguish between restrictive and obstructive lung disorders.

*Restrictive disorders:* Chest expansion is restricted, so VC decreases while $FEV_1$ is normal. The TLC, MVV also decreases as VC decreases. For example, kyphoscoliosis, ankylosing spondylitis (arthritis of vertebral column).

*Obstructive diseases:* Here inspiration is normal but expiration is obstructed, so VC normal while $FEV_1$ decreases. For example, bronchial asthma, emphysema (Fig. 3.9).

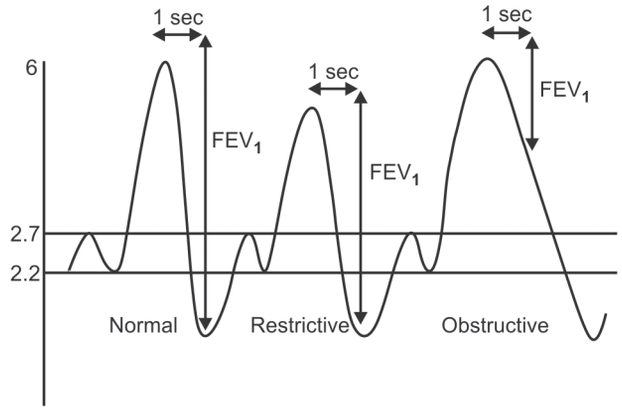



**Fig. 3.9:** $FEV_1$ in normal, restrictive and obstructive patients

***Note:*** The $FEV_1$ is much more sensitive index (i.e. most reproducible) of the severity of obstructive lung disorders, but it does not allow for the differentiation of the various causes for the obstruction.

## Surfactants

It is a lipid surface tension lowering agent lining the alveoli.

### *Composition*

It is a mixture of protein-lipid complexes made up of mainly dipalmitoylphosphatidylcholine (DPPC) lipid along with other lipids (phosphatidyl glycine, phospholipids, neutral lipids) and proteins (Table 3.1).

### *Synthesis of Surfactant*

Surfactant is produced by type II alveolar epithelial cells. Laminar bodies containing phospholipids are formed in these cell are secreted into the alveolar lumen by exocytosis in the form of tubes of lipids called tubular myelin. The lipid are later converted into phospholipids, which is the major constituent of surfactant. The surfactants are then taken by the alveolar macrophages. Some of the protein-lipid complexes are taken up by the type II alveolar cells and cycled (Fig. 3.10). Formation of the phospholipid film is greatly enhanced by the proteins in the surfactant. This material contains four unique proteins: SP-A, SP-B, SP-C and SP-D.

**Table 3.1: Composition of surfactant**

| *Component* | *% Composition* |
|---|---|
| Dipalmitoylphosphatidylcholine | 62 |
| Phosphatidylglycerol | 5 |
| Other phospholipids | 10 |
| Neutral lipids | 13 |
| Proteins | 8 |
| Carbohydrate | 2 |

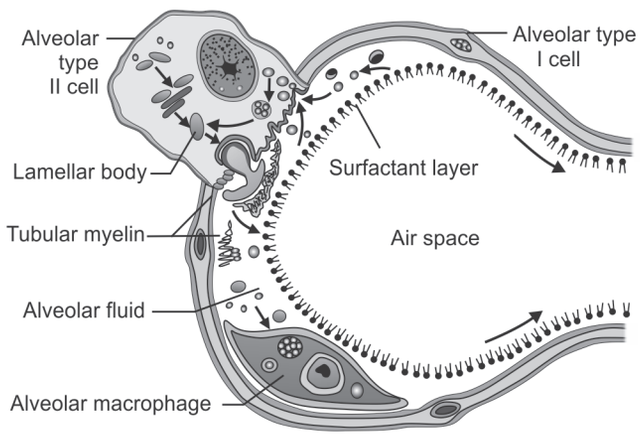



**Fig. 3.10:** Synthesis of surfactant

### *Factors Affecting Surfactant Synthesis*

1. Thyroid hormone increases the production of surfactant.
2. Glucocorticoid influence production and maturation of surfactant.
3. Insulin inhibit synthesis of surfactant.
4. Smoking reduces surfactant.

### *Functions of Surfactant*

1. *Reduction of surface tension:* According to the Law of Laplace in a spherical structure like alveoli, distenting pressure (P) equals to two times the tension, T (Surface tension on walls) divide by the radius (R).

$$P = \frac{2T}{R}$$

Surface tension is due to the intermolecular attraction between the surface molecules and thus it tries to reduce surface area and collapses the lungs. Hence this surface tension must be reduced especially during expiration. Otherwise, the lungs will collapse.

Surface tension (T) is the inward force. Therefore, with 'P' constant if the 'T' is not reduced as 'R' is reduced during expiration, surface tension may overcome the distending pressure and then lungs will collapse. But in lungs, with reduction of radius, there is reduction of surface tension by a surface tension lowering agent called surfactant.

Surface tension is inversely related to the concentration of surfactant per unit area. Surfactant molecules are spread apart as alveolar size increases during inspiration but come closer during expiration thereby adjusting surface tension during breathing. It action is more effective during expiration than during inspiration. Surface tension between the fluid and the air is 7–14 times more than between the surfactant and the air.

2. *It maintains stability of the alveoli:* Surfactant reduces surface tension so that alveoli do not collapse. In absence of surfactant air will tend to move from smaller alveoli (where pressure is more) to large aleveoli (where pressure is low) leading to collapse of small alveoli and overdistention of large alveoli (Fig. 3.11).
3. Surfactant also helps to prevent pulmonary edema by reducing surface tension.
4. Surfactant keeps the alveoli dry and thus helps in the exchange of gases.

### *Clinical Significance*

1. *Infant respiratory distress syndrome (IRDS) or Hyaline membrane disease:* Infants especially premature and infants born to diabetic mother (due to hyperinsulinemia) have deficiency of surfactant in their alveoli and there is increased surface tension. Surfactant normally appears at the 28th week of gestation and mature just before 36th week. After birth, the infant makes several strong inspiratory movements and the lung expand. Surfactant keeps them from collapsing again. So deficiency of surfactant causes both collapsing of alveoli in many areas (atelectasis) and pulmonary edema. Other factors that cause IRDS are:
   i. Low level of thyroid and glucocorticoids.
   ii. During fetal life, $Cl^-$ is secreted with fluid by the pulmonary epithelial cells. At birth, there is a shift to $Na^+$ absorption by these cells via epithelial $Na^+$ channels (ENaCs), and fluid is absorbed with the $Na^+$. Prolonged immaturity of the ENaCs contributes to the pulmonary abnormalities in IRDS.
2. *Patchy atelectasis:* Seen in patients who have undergone cardiac surgery, during which a pump oxygenator is used and the pulmonary circulation is interrupted.

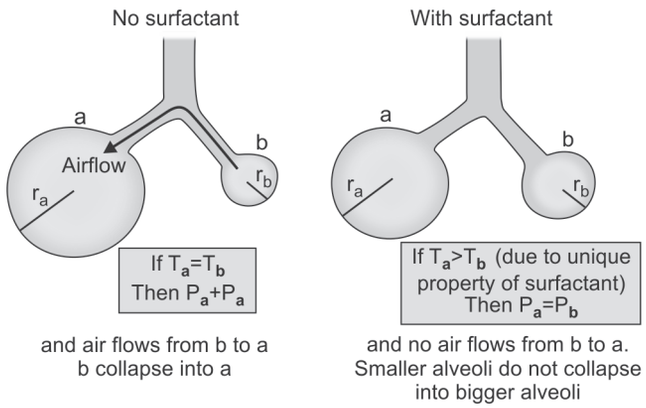



**Fig. 3.11:** Action of surfactant

## Compliance

The change in lung volume per unit change in airway pressure ($\Delta V/\Delta P$) is the 'stretchability' (compliance) of the lungs and the chest wall.

Where, V= volume of the lung, P = airway pressure, Δ= the difference. It is expressed as liter/cm $H_2O$.

### *Factors Influencing Compliance*

- Elasticity of lung
- Changes in lumen size
- Surfactants and surface tension
- Blood supply
- Interdependence
- Chest wall size, shape, deformity, infections and nerve damage

Compliance is studied under two headings:

1. Compliance of the lungs only
2. Compliance of the lungs and thoracic wall.

### *Compliance of Lung*

The extent to which the lung will expand for each unit increase in transpulmonary pressure is called lung compliance. The normal value is 0.2 L/cm $H_2O$. Compliance diagram of lungs relates lung volume changes to changes in transpulmonary pressure (Fig. 3.12). The two curves are called

1. Inspiratory compliance curve
2. Expiratory compliance curve.

Compliance is slightly greater when measured during expiration than in inspiration. The characteristics of the compliance diagram are determined by:

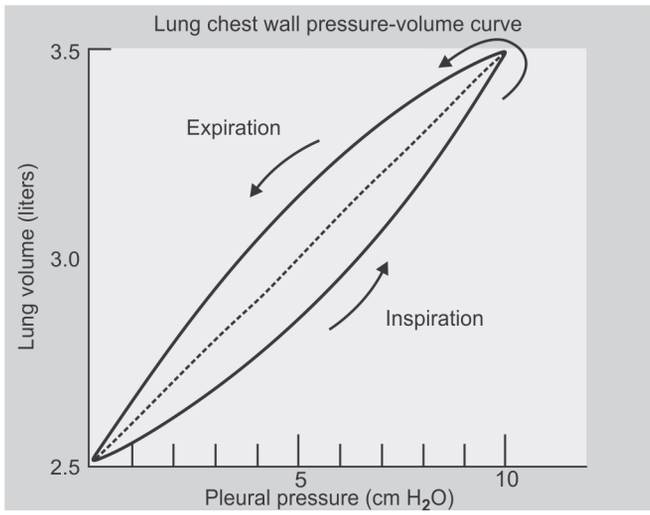



**Fig. 3.12:** Compliance of lung (Pressure/volume relationship)

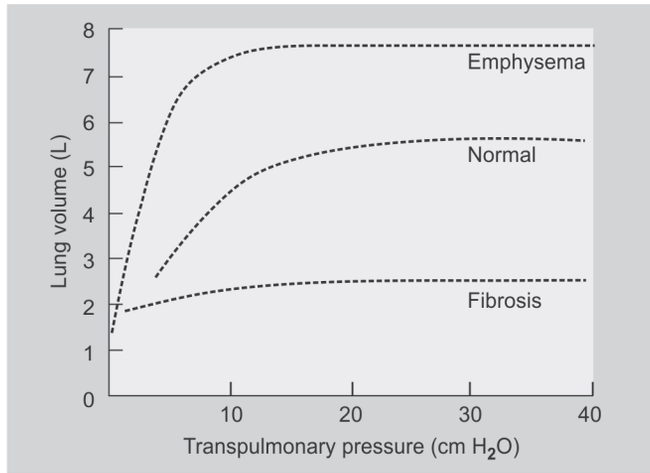



**Fig. 3.13:** Compliance in emphysema and fibrosis compared to normal

a. Elastic forces of the lung tissue itself (contributes about 1/3rd).
b. Elastic force caused by the surface tension of the fluid that lines the inside wall of the alveoli and other lung air spaces (contributes about 2/3rd).

Elastic force of the lung is determined mainly by elastin and collagen in the lung parenchyma.

### *Compliance of Lung and Thoracic Wall*

It is the compliance of the entire pulmonary system. It is measured while expanding the lungs of a totally relaxed or paralyzed person. To inflate this total pulmonary system, almost twice as much pressure is needed as to inflate the same lungs after removal from chest cage. Normal value—0.11 liter/cm $H_2O$, it signifies that when there is an increase of airway pressure by 1 cm $H_2O$, then the volume of the lungs inside the thoracic wall increases by 0.13 liter.

***Note***

- The curve is shifted downward and to the right (compliance is decreased) by pulmonary congestion and interstitial pulmonary fibrosis (stiffening, scarring of lungs) (Fig. 3.13).
- The curve is shifted upward and to the left (compliance is increased) as in emphysema.

***Specific compliance***

Compliance with reference to the lung volume at which it is measured (i.e. the FRC) is called specific compliance.

$$\text{Specific compliance} = \frac{\text{Compliance}}{\text{FRC}}$$

Specific compliance is used to compare the compliances of lungs of different sizes. In individuals with having one lung only, the lung compliance is approximately half of the normal compliance. Similarly in children because of smaller lung volume, compliance will be below normal inspite of normal distensibility. This confusion is removed with specific compliance since 'FRC' is proportionately reduced and specific compliance remains essentially constant.

## Dead Space and its Significance

It is the amount of air in the 'respiratory passage' which does not take part in exchange of gases.
It is of two types:
1. Anatomical dead space
2. Physiological dead space.

### *Anatomical Dead Space (150 ml)*

It is the volume of air present in the 'conducting zone' of the respiratory passage which is from nose and mouth up to terminal bronchioles. It is the respiratory system volume exclusive of alveoli. Here there is no exchange of gases.

***Normal value***

Anatomical dead space value is approximately the body weight in pounds. For example, in a man who weighs 150 lb (68 Kg), only the first 350 ml of the 500 ml inspired with each breath at rest mixes with the air in the alveoli, i.e. the 150 ml of the expired gas is from the dead space.

### *Physiological Dead Space/Total Dead Space*

It includes anatomical dead space plus volume of air in the alveoli which does not take part in exchange of gases (i.e wasted alveolar ventilation). It is the volume of gas not equilibrating with blood.

***Note:*** Clinically anatomical and physiological dead spaces are same in healthy subjects. If ventilation and perfusion are not in equilibrium, then only they differ in volume.

### *Variations*

***Physiological***

a. *Sex:* Dead space is more in males.
b. *Age:* Dead space increases as age increases (inflated lungs pull the airways, increasing the airway diameter).
c. *Body height:* Dead space is directly proportional body height.

***Pathological***

a. *Emphysema*—loss of elasticity of lungs decreases elastic recoil. Produces hyperinflation of lungs which causes increase in dead space.
b. *Bronchiectasis*—it is associated with dilated bronchi leading to increase in dead space.

## Alveolar Ventilation

It is the amount of air ventilating the alveoli per minute.
Alveolar ventilation =
(Tidal volume – Dead space) × Respiratory rate
i.e. Alveolar ventilation = (500 – 150) × 12 = 4.2 L /min.

### *Physiological Significance of Alveolar Ventilation*

Respiration involves the gaseous exchange of $O_2$ and $CO_2$ by diffusion between the alveoli and pulmonary capillary blood, so maintenance of volume of alveolar ventilation is very important. In tachypnea (rapid shallow respiration) alveolar ventilation decreases, though the pulmonary ventilation remains normal, as a result less air is available for exchange. In slow, deep respiration both alveolar and pulmonary ventilation are normal.

### *Ventilation-Perfusion (V/P) Ratio or Ratio*

It is the ratio of alveolar ventilation to pulmonary blood flow.

As, alveolar ventilation = 4.2 L/min, pulmonary blood flow = 5.5 L/min

$$V/P = 4/5 = 0.8$$

The total ratio is not important, more important is that whether this ratio is present uniformly throughout the lungs for proper oxygenation.

### *Factors Affecting V/P Ratio*

***Physiological causes***

Effect of gravity—V/P ratio are high in the apical portions of the lung.

***Pathological causes***

All the factors which cause uneven alveolar ventilation or non-uniform blood flow to pulmonary circulation will alter the V/P ratio. For example:

- Bronchial asthma, pneumothorax , emphysema (causes of uneven alveolar ventilation).
- Fallot's tetrology, pulmonary embolism (causes of non-uniform pulmonary blood flow).

### *Clinical Significance*

It is said that the high V/P ratio at the apices account for the predilection of tuberculosis (TB) for this area because high alveolar $pO_2$ provides a favorable environment for the growth of tuberculosis bacteria.

## Physiological Shunt and its Significance

When VA/Q, i.e. the ratio of alveolar ventilation to blood flow is below normal, there is inadequate ventilation to provide the $O_2$ needed to fully oxygenate the blood flowing through the alveolar capillaries. Therefore, a certain fraction of the venous blood passing through the pulmonary capillaries does not become oxygenated. This fraction is called shunted blood.

1. Although some of the bronchial vessels (bronchial arteries, branches of the thoracic aorta) enters the bronchial veins, some enters the pulmonary capillaries and veins, bypassing the right ventricle.
2. Blood that flows from the coronary arteries into the left side of the heart.

In this two exceptions, a physiological shunt is created and the blood in the systemic arteries has a $pO_2$ (Fig. 3.14) about

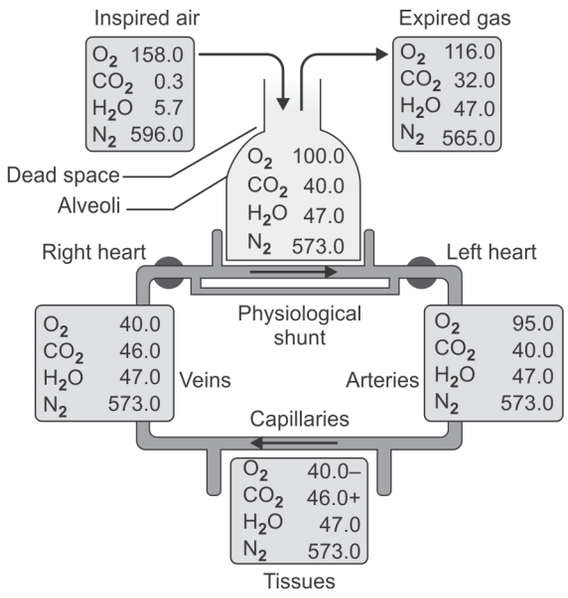



**Fig. 3.14:** Partial pressures of gases (mm Hg) in various parts of respiratory and in the circulatory system

2 mm Hg lower than that of blood which has equalibrated with alveolar air. The greater the physiologic shunt, the greater the amount of blood that fails to be oxygenated as it passes through the lungs.

## TRANSPORT OF GASES

### Oxygen Transport

Oxygen is transported in the blood in two forms.
1. In dissolved form.
2. In combination with hemoglobin (Hb).

#### *In Dissolved Form*

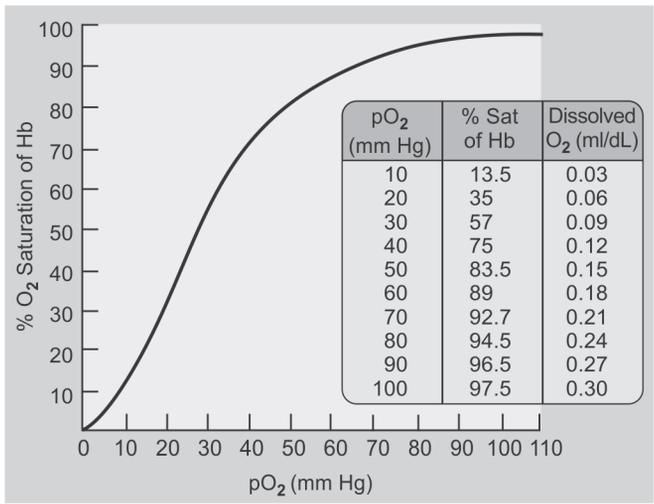
In dissolved form the amount of oxygen transported is 0.3 ml/100 ml of blood per 100 mm Hg $pO_2$. The dissolved $O_2$ obeys the Henry's law, i.e. amount dissolved is proportional to the $pO_2$. Dissolved $O_2$ asssumes its practical importance in case of hyperbaric $O_2$ therapy when this amount can be increased by giving $O_2$ at high pressure as in the treatment of CO poisoning, gas gangrene (here Hb gets denatured).

#### *In Combination with Hemoglobin*

Each Hb molecule has four heme groups which have an iron in ferrous form. The sixth valency bond of each $Fe^{2+}$ combines with 1 mole (2 atoms) of $O_2$. Therefore, 4 moles (8 atoms) of $O_2$ combine with 1 mole of Hb. The $O_2$ carrying power of Hb is given by $O_2$-Hb dissociation curve (ODC curve). It is a curve relating percentage $O_2$ saturation of the Hb to the $pO_2$. The curve has a characteristic sigmoid shape due to shifting affinity of Hb for $O_2$.

In deoxy-Hb, the globin portion is tightly bound in a tense (T) configuration thereby reducing the affinity of the molecule for $O_2$. Combination of molecule with $O_2$ releases the bonds holding the globin units, producing a relaxed (R) configuration This results in the exposure of more $O_2$ binding sites and thereby the affinity of Hb molecule with $O_2$ increases. Since the 4 atoms of $Fe^{2+}$ do not combine with $O_2$ simultaneously we do not get a vertical line. The combination is a step wise process and the affinity for $O_2$ is different at different steps. The combination of 1st heme in the Hb molecule with $O_2$ increases the affinity of 2nd heme for $O_2$ and so on.

This shifting affinity of Hb for $O_2$ due to T-R interconversion produces the characteristic sigmoid curve (Fig. 3.15). This phenomenon is referred to as Heme-Heme Interaction.




| $pO_2$ (mm Hg) | % Sat of Hb | Dissolved $O_2$ (ml/dL) |
|---|---|---|
| 10 | 13.5 | 0.03 |
| 20 | 35 | 0.06 |
| 30 | 57 | 0.09 |
| 40 | 75 | 0.12 |
| 50 | 83.5 | 0.15 |
| 60 | 89 | 0.18 |
| 70 | 92.7 | 0.21 |
| 80 | 94.5 | 0.24 |
| 90 | 96.5 | 0.27 |
| 100 | 97.5 | 0.30 |

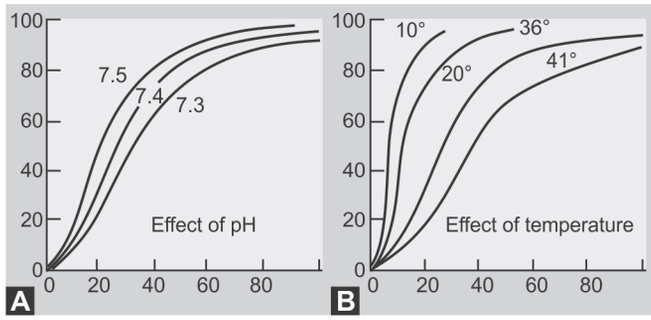
**Fig. 3.15:** Oxygen-hemoglobin dissociation curve

#### *Physiological Advantages of S-Shaped Curve*

- It allows greater uptake of $O_2$ at lungs despite great variation in alveolar air $pO_2$ (from 95 to 60 mm Hg).
- When $pO_2$ is below 60 mm Hg, a small fall in $pO_2$ causes significant reduction in percent saturation of Hb. This means that peripheral tissue can withdraw large amount of $O_2$ for a small drop in tissue capillary $pO_2$. This behavior of Hb enables uptake of $O_2$ in lung where $pO_2$ is high and release of $O_2$ into tissue where $pO_2$ is low.

***Note***

1. *$O_2$ content:* It is the actual amount of $O_2$ present in the sample of blood (19.4 ml /100 ml, when 97.5% saturated).
2. *$O_2$ carrying capacity:* The maximum amount of $O_2$ that a particular amount of blood can combine with at full saturation. A 1 gm Hb can combine with 1.34 ml of $O_2$ (at max $pO_2$ of approx 120 mm Hg). Since the average Hb concentration is 15 gm%, therefore 100 ml of blood can carry, $1.34 \times 15 = 20.1$ ml (at full saturation).
3. Percentage saturation of Hb is given by the formulae = ($O_2$ content/$O_2$ capacity) × 100. Normally it is 97.5%.
4. *Utilization coefficient:* The percentage of the blood that gives up its $O_2$ as it passes through the tissue capillaries is called utilization coefficient. Normal value: 25%. During strenuous exercise, the utilization coefficient increases up to 75–80%. In some area where blood flow is extremely slow or metabolic rate is very high, utilization coefficient is approximately 100%.




**Figs 3.16A and B:** Effect of pH and temperature on oxygen-hemoglobin dissociation curve

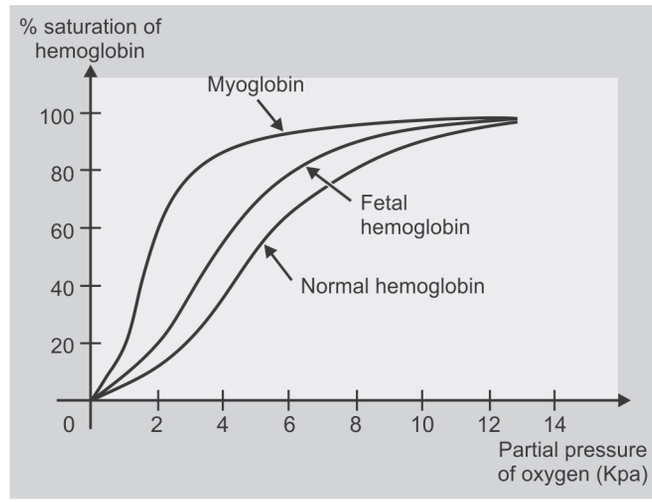



**Fig. 3.17:** Dissociation curve for myoglobin, fetal Hb and normal Hb

## *Factors Affecting $O_2$-Hb Dissociation Curve*

***Shift to right***

A shift to right occurs if affinity of Hb for $O_2$ decreases.

*Causes*

1. Fall in blood pH/increase in $H^+$ (Fig. 3.16A).
2. Increase in $CO_2$ (Respiratory/Metabolic cause).
3. Increase in temperature (Fig. 3.16B).
4. Increase in the concentration of 2,3 DPG.

The 2,3 DPG is a product of glycolysis. It is a highly charged anion that binds to - β chains of deoxy-Hb. It competes with $O_2$ for the binding sites on the Hb molecule and therefore at a given $pO_2$ the percent saturation of Hb with $O_2$ will be reduced in the presence of 2,3 DPG.

## *Bohr Effect*

Increased $CO_2$ content of blood helps to release more $O_2$ from Hb. This is called Bohr effect. It can also be explained as the decrease in the $O_2$ affinity of Hb when the pH of blood falls. The Bohr effect is useful during physical exercise, when more $CO_2$ is produced and more $O_2$ is delivered to tissues ie an active tissue gets more $O_2$.

***Shift to left***

A shift to left occurs when the affinity of Hb towards $O_2$ increases.

*Causes*

1. Decrease in body temperature.
2. Increase in blood pH (decrease in $CO_2$).
3. Fetal Hb (HbF).
4. Myoglobin.
5. Decrease in concentration of 2,3 DPG.
6. Carbon monoxide (CO).

Affinity of fetal Hb (HbF) for 2,3 DPG is considerably less than that of HbA (poor binding of 2,3 DPG by γ polypeptide chain). So HbF shifts the curve to the left, i.e. a lower $pO_2$ is required to bind a given amount of $O_2$. Thus, the affinity of HbF to combine with $O_2$ is more than that of HbA.

Myoglobin contains only 1 heme group with 1 polypeptide chain, i.e. 1 atom of iron per molecule (MW=1/4 MW of Hb). Its dissociation curve is rectangular hyperbola. It takes up $O_2$ from Hb in the blood and releases $O_2$ only at low $pO_2$ values, i.e. rate of association of myoglobin with $O_2$ is very fast. It does not show Bohr effect (Fig. 3.17).

CO shifts the curve to left due to inhibition of synthesis of 2, 3 DPG. Affinity of 'CO' to combine with Hb is 200 times more than that of $O_2$. Due to larger proportions of carboxy-hemoglobin (COHb) formed Hb is unavailable for $O_2$ carriage.

## *Significance of $P_{50}$*

$P_{50}$ means the $pO_2$ at which the Hb is half (50%) saturated with $O_2$. Normal value is 26 mm Hg, at $pCO_2$ 40 mm Hg, pH 7.4 and temperature 37°C. It helps to determine the Hb affinity for $O_2$. Hb affinity for $O_2$ is an inverse function of $P_{50}$ value, i.e. the higher the $P_{50}$, the lower the affinity of Hb for $O_2$.

## $CO_2$ Transport

$CO_2$ is produced due to tissue activity and it enters the blood due to:

- Difference in $pCO_2$ between arterial blood and tissues (arterial blood $pCO_2$ = 40 mm Hg, tissues $pCO_2$ = 46 mm Hg).
- High diffusion coefficient of $CO_2$ as compared to $O_2$ (20 times more than that of $O_2$).

$CO_2$ is carried in three forms:

1. In dissolved form (0.3 ml%).
2. As carbamino compounds (0.7 ml%).
3. As bicarbonate (3 ml%).

### In Dissolved Form

$CO_2$ is transported as dissolved form in both plasma and RBC. The venous blood, with $pCO_2$ 46 mm Hg contains about 2.7 ml/100 ml of $CO_2$ in dissolved form. The arterial blood with $pCO_2$ 40 mm Hg contains 2.4 ml/100 ml of $CO_2$ in dissolved form. Thus only 0.3 ml of $CO_2$ is transported in dissolved state per 100 ml of blood from tissues to the lungs. This represents about 7% of all $CO_2$ that is transported.

### As Carbamino Compounds

After entering the blood, some of the $CO_2$ combines with proteins in blood, both in plasma and cells.

***In plasma***

$CO_2$ combines directly with plasma proteins to form carbamino proteins. This is a slow reaction and only 0.1 ml% of $CO_2$ is transported in this form.

$$CO_2 + PrNH_2 \longrightarrow PrNHCOOH$$

***In RBC***

$CO_2$ combines with amino group of Hb to form carbamino Hb. This is a fast reaction and 0.6 ml% of $CO_2$ is transported in this form.

$$CO_2 + HbNH_2 \longrightarrow HbNHCOOH$$

Approximately 23% of the total $CO_2$ (0.7 ml%) is transported in the blood in the form of carbamino compounds.

### As Bicarbonates

It accounts for about 70% of the total $CO_2$ (3 ml%) of total $CO_2$ transported from the tissues to the lungs. These bicarbonates are formed in the RBC and then diffuse into plasma. This is because RBC has the required enzyme carbonic anhydrase (CA). After entering the blood most of the $CO_2$ enters the RBC, where in the presence of CA, it rapidly reacts with water to form carbonic acid. Carbonic acid dissociates into bicarbonate ions and hydrogen ions.

$$CO_2 + H_2O \xrightarrow{CA} H_2CO_3 \longrightarrow H^+ + HCO_3^-$$

RBC membrane is relatively impermeable to cations. So $H^+$ combine with Hb. This enables the reaction to proceed in the forward direction and prevent the backward reaction. The $HCO_3^-$ (70%) diffuse out of RBCs into plasma. Some $HCO_3^-$ remains in the RBCs as well.

***Chloride shift (Fig. 3.18)***

When the $HCO_3^-$ diffuses out of RBCs into the plasma, the inside of the cell become less negatively charged. To maintain electrical neutrality $Cl^-$ ions diffuse from plasma into the RBC to replace the $HCO_3^-$. The movement of $Cl^-$ into the RBC is called chloride shift or Hamburger phenomenon. This process is mediated by a membrane protein called band 3 protein. As a result of chloride shift, the total number of ions inside the RBCs increases, so the osmotic pressure inside the RBCs becomes higher than that of plasma. This draws water and the RBCs become slightly larger. Thus PCV of venous blood is slightly higher (3%) than that of arterial blood.

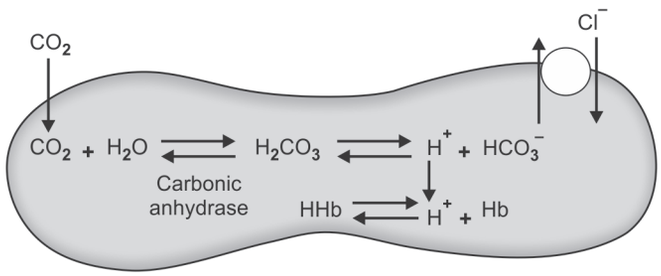



**Fig. 3.18:** Chloride shift

### Summary of $CO_2$ Transport

Thus, out of about 52 ml% of $CO_2$ in venous blood, 4 ml% is given out in the lungs and the arterial blood contains about 48 ml%. Out of this 4 ml% 0.3 ml% is contributed by dissolved form, 0.7 ml% by carbamino compounds and 3 ml% by bicarbonate (Table 3.2).

### $CO_2$ Dissociation Curve (Fig. 3.19)

$CO_2$ dissociation curve is obtained by plotting the relationship between $CO_2$ and total $CO_2$ content of the blood. The graph shows that the relationship between the two is nearly linear over wider range of $pCO_2$ (compared to $O_2$-Hb dissociation curve which is sigmoid in shape). The $pCO_2$ of arterial and venous blood varies practically within a narrow range of 40-45 mm Hg. Binding of $O_2$ to Hb reduces its affinity for $CO_2$ from blood, shifting the $CO_2$ dissociation curve to right. This effect is called ***Haldane effect.***

Figure 3.20 demonstrates the significance of Haldane effect on the transport of $CO_2$ from the tissues to the lungs. Figure 3.20 shows small portions of two $CO_2$ dissociation curves.

i. When the $pO_2$ is 100 mm Hg, which is the case in blood capillaries of lungs.
ii. When $pO_2$ is 40 mm Hg, which is the case in tissue capillaries.

**Table 3.2: Amount of $CO_2$ held by different vehicles**

| *Forms* | *Venous blood* | *Arterial blood* |
|---|---|---|
| Dissolved form | 2.7 ml% | 2.4 ml% |
| Carbamino compound | 3.7 ml% | 3 ml% |
| Bicarbonate | 45.6 ml% | 42.6 ml% |
| Total | 52 ml% | 48 ml% |

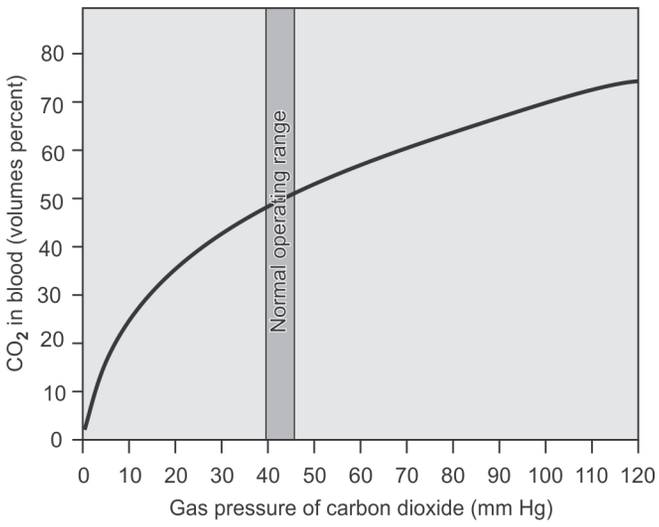



**Fig. 3.19:** $CO_2$ dissociation curve

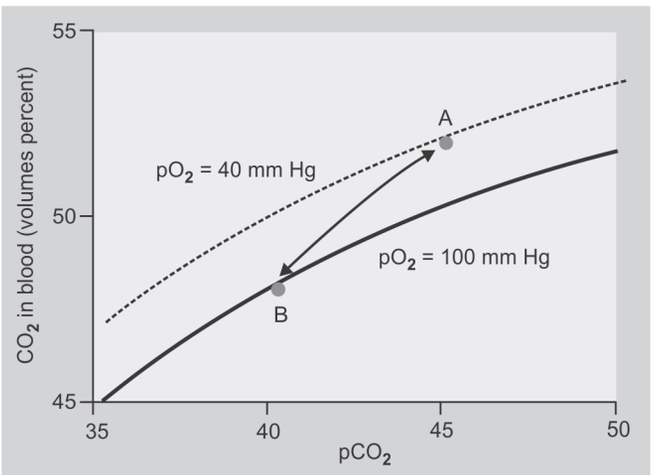



**Fig. 3.20:** Significance of Haldane effect on transport of $CO_2$ from tissue to the lungs

- Point A shows that the normal $pCO_2$ of 46 mm Hg in tissues causes 52 ml% of $CO_2$ to combine with the blood. On entering the lungs, $pCO_2$ falls to 40 mm Hg and the $pO_2$ rises to 100 mm Hg.
- If the $CO_2$ dissociation curve did not shift because of Haldane effect, the $CO_2$ content of the blood would fall only to 50 ml%. However, the increase in $pO_2$ in lung lowers the $CO_2$ dissociation curve from top to lower curve in the figure, so that the $CO_2$ content falls to 48 ml% (point B).

Thus, the Haldane effect doubles the amount of $CO_2$ released from the blood in the lungs.

### *Mechanism of Haldane Effect*

The combination of $O_2$ with Hb in the lungs causes the Hb to become a stronger acid. This displaces $CO_2$ from the blood and into the alveoli in two ways:

i. The more highly acidic Hb has less tendency to combine with $CO_2$ to form carbaminohemoglobin, thus displacing much of the $CO_2$ that is present in the carbamino form from the blood.
ii. The increased acidity of Hb also causes it to release an excess of $H^+$, and these bind with $HCO_3^-$ to form $H_2CO_3$ Then this dissociates into $H_2O$ and $CO_2$, and the $CO_2$ is released from the blood into the alveoli and finally into the air.

## REGULATION OF RESPIRATION

Spontaneous respiration is produced by rhythmic discharge of motor neurons that innervate the respiratory muscles. This discharge is totally dependent on nerve impulses from brain. During regulation of respiration, pulmonary ventilation is adjusted according to metabolic demands of the body. The metabolic demands are: (1) Supply of adequate $O_2$ to tissues, (2) Removal of $CO_2$ formed during metabolism, (3) Maintenance of optimum pH of blood.

Unlike all other organ system, respiration demonstrates automaticity as well as self modulation, i.e. we breath without thinking, but can willingly modify the breathing pattern. Rate, depth and rhythm of respiration is controlled by group of neurons situated reticular formation of brainstem. The collection of these neurons are called *respiratory center*. The rhythmic discharge from the brain that produces spontaneous respiration is regulated by two mechanisms: (1) Nervous regulatory mechanism and (2) Chemical regulatory mechanism.

### Respiratory Centers

The rhythmic discharge is initiated by a group of pacemaker cells in the brainstem referred to as *Pre-Botzinger complex of neurons (PBZ)*. They are situated in either sides of medulla. These neurons discharge spontaneously and rhythmically. They produce rhythmic discharges in phrenic motor neurons. All the neurons regulating respiration project into PBZ (Fig. 3.21).

The respiratory centers are situated in the reticular formation of the brainstem and depending upon the situation in the brainstem, they are classified into medullary and pontine center. There are two centers in each group. Medullary centers include two group of neurons: the dorsal respiratory group (DRG), and ventral respiratory group (VRG) which generate

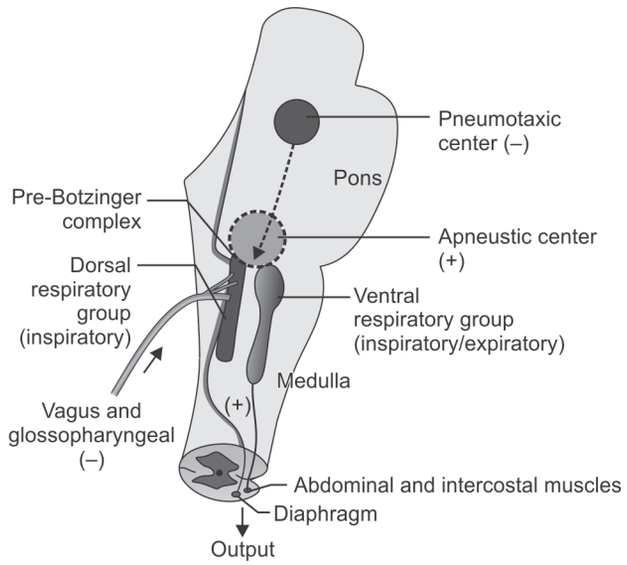



**Fig. 3.21:** Respiratory neurons in the brainstem

the basic respiratory rhythm. The pontine centers include the apneustic center (APN) and pneumotaxic center (PNC), both of which modify the activity of medullary respiratory centers. Pontomedullary respiratory center neurons are of two types—I and E neurons. I neurons are active during inspiration and E neurons are active only during forceful expiration.

### Dorsal Respiratory Group Neurons

Most of the neurons are located within the nucleus tractus solatarius (NTS) and some in the adjacent reticular substance. The basic rhythm of respiration is generated mainly in the (DRG). They contain mainly I neurons. DRG send fibers to phrenic motor neurons which innervate diaphragm. NTS is the sensory termination of both vagal and glossopharyngeal nerve which transmit sensory signals into respiratory center from peripheral baroreceptors, chemoreceptors and pulmonary receptors.

***Note***

***Inspiratory ramp signal***

The nervous signal that is transmitted to the inspiratory muscles, mainly diaphragm is not an instantaneous burst of action potentials. It begins weakly and increases steadly in a ramp manner for about 2 sec. Then it ceases abruptly for the next 3 sec. During this period expiration occurs. At the end of 3 sec, the inspiratory ramp signals reappear in the same pattern and the cycle is repeated.

### Ventral Respiratory Group Neurons

Ventral group is a long column of neurons that extends through nucleus ambiguus and nucleus retroambiguus in the ventrolateral medulla. They contain both I and E neurons. I neurons are situated in its midportion whereas E neurons at caudal and rostral end. Normally, this center is inactive during quiet breathing and it becomes active during forced breathing or when the inspiratory center is inhibited.

The rhythmic discharge of the neurons in the medullary respiratory center is spontaneous, but is modified by: (i) neurons in the pons (ii) by afferents in the vagus nerves from receptors in the airways and lungs.

### Pneumotaxic Center

Situated in dorsal part of upper pons in nucleus parabrachialis and Kolliker-fuse nuclei. It contains both I and E neurons. Main function of PNC is to switch off inspiration so that duration of inspiration is controlled. Indirectly PNC increases respiratory rate by limiting duration of inspiration, i.e. when the duration for inspiration is reduced, naturally the expiration time is also reduced so that respiratory rate increases.

### Apneustic Center

Situated in the reticular formation of lower pons. It is made up of diffusely located neurons in the region of nucleus pontocaudalis and rostral part of nucleus gigantocellularis. This center is always excitatory to medullary inspiratory center and it increases the depth of inspiration.

### Neural Regulation

Two separate mechanisms: (i)Voluntary control (ii)Automatic control.

### Voluntary Control

Normally respiration is involuntary action. Voluntary control is possible, but only to a limited extent. Breathing can be voluntary inhibited only for a short period of time. It becomes voluntary in spite of all our efforts to hold our breath. The point at which breathing can no longer be inhibited is called *breaking point*. Duration of breaking point is 40–80 sec. Breaking is due to rise in $pCO_2$ and fall in $pO_2$. Breaking point can be delayed by removing carotid body, breathing 100% $O_2$ before breath holding, hyperventilation. Breathing point is reduced in exercise or $CO_2$ rich air.

Center of the pathway for voluntary control is in cerebral cortex. Impulses are sent to respiratory motor neuron via corticospinal tract. These nervous pathways bypass the medullary respiratory neurons. As automatic control is through neurons of pons and medulla, pathway for voluntary and automatic control are separate. Automatic control of respiration is sometimes destructed without loss of voluntary control. This clinical condition is called *Ondine's curse*. This is seen in patients with poliomyelitis.

### *Automatic Control*

Automatic control of respiration is mainly through respiratory centers. The nerve fibers from the respiratory centers leave brainstem and descend in anterior part of lateral columns of spinal cord. These nerve fibers terminate in the motor neurons in the anterior horn cells of cervical and thoracic segments of spinal cord. From the motor neurons of spinal cord, two sets of nerve fibers arise which are:

a. Phrenic nerve fiber that supplies diaphragm.
b. The intercostals nerve fibers (supply intercostals). Impulses from higher centers and various reflexes influences respiratory centers.

***Control from higher centers***

Respiration is modified during deglutition, chewing, speaking, crying, singing, etc. This modification is done with the help of cerebral cortex, hypothalamus and limbic system.

***Reflex Control***

a. *Hering-Breuer reflex:* The impulses from the lungs bring about a respiratory reflex called *Hering-Breuer Reflex*. This reflex prevents over distention of lungs during inspiration and collapse of lungs during expiration. This is not important in the normal adults in the range of normal TV breathing. Important in neonates and infants.

   There are some stretch receptors on the muscular portions of the wall of bronchi and bronchioles of lungs. Overstretching of the lungs during inspiration stimulate the stretch receptors and impulses are carried by vagal afferent fibers to DRG and inspiration stops and expiration starts. This reflex is a protective reflex because, it restricts the inspiration and limits the overstreching of lung tissues. This is called *Hering-Breuer Inflation Reflex.* However, this reflex does not operate during quiet breathing. It operates, only when the tidal volume reaches above 1500 ml.The reverse of this reflex is called *Hering-Breuer Deflation Reflex.* When the inspiratory center is inhibited the inspiration stops and expiration occurs. During expiration as the stretching of lungs is abolished, the deflation of lungs occurs.
b. *J receptor mediated reflex:* 'J' receptors are juxtacapillary receptors. These receptors are the sensory nerve endings of the vagus. The fibers from these receptors are nonmyelinated and belong to C type. The 'J' receptors are situated in alveolar interstitium close to the pulmonary capillaries. The 'J' receptors are stimulated by certain chemicals released in the interstitium during pulmonary edema, pulmonary embolism, pulmonary congestion. The stimulation of the 'J' receptors produces a reflex response, which is characterized by a period of apnea followed by rapid breathing, bradycardia, hypotension and weakness of skeletal muscles.

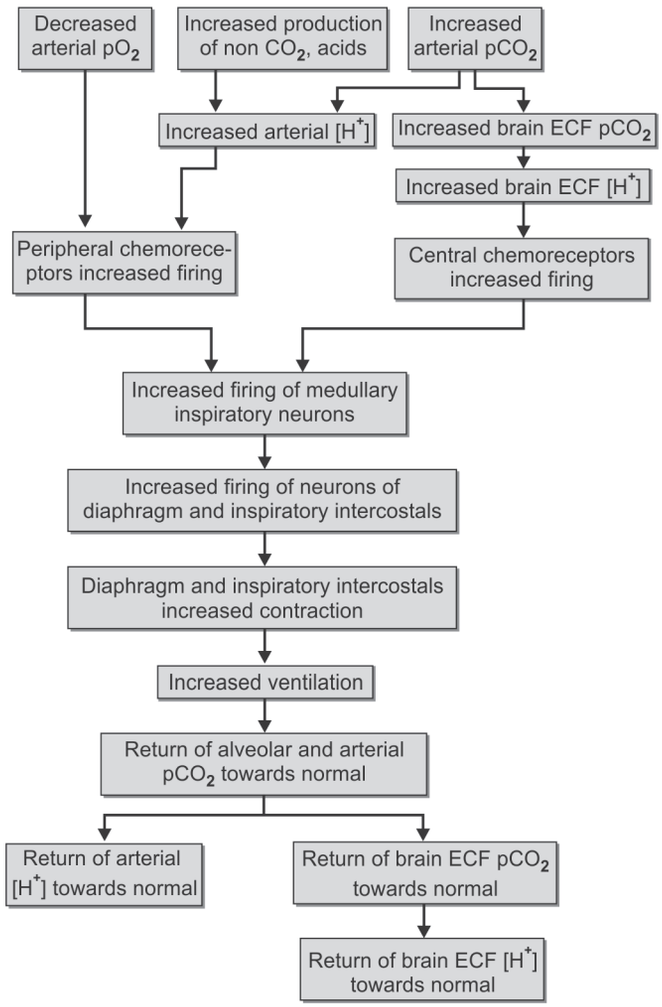
   J receptors may have a physiological role in severe exercise. Severe muscular exercise → very mild degree collection of fluid in the alveoli → irritation of J receptors → muscle weakness → stoppage of exercise = breaking (compulsory stoppage) of exercise.
c. *Lung irritant reflex:* It is a protective reflex. Receptors are located in between epithelial cells of tracheobronchial tree. Stimulus is exposure to irritant fumes/dust. Stimulation of irritant receptors produces reflex bronchospasm (manifested as cough and sneeze) so that irritant fumes cannot reach the alveoli.
d. *Reflexes from muscle spindles of diaphragm and other inspiratory muscles:* In case of insufficient air entry in the lungs as in case of airway obstruction, the muscle spindle act in such a way that inspiratory muscles continue to contract more forcefully and this will help to overcome the obstruction.
e. *Reflexes from limbs, joints:* Movements of limbs cause stimulation of proprioreceptors (muscle spindle and golgitendon organ). This lead to increased rate and depth of respiration. The reflex is active during exercise.
f. *Baroreceptor reflex:* Rise in BP → arterial baroreceptors stimulated → afferent impulses teminates at VMC and respiratory center → the I neurons are inhibited → stoppage of inspiration.
g. *Chemoreceptor reflex*
h. *Cough reflex:* This is a protective reflex. Cough begins with deep inspiration followed by forced expiration against closed glottis. This increases intrapleural pressure above 100 mm Hg. The glottis is suddenly opened producing an explosive outflow of air.
i. *Sneezing reflex:* It is a similar expiratory effort with a continuously open glottis.
j. *Deglutition reflex:* During swallowing of the food, there is temporary arrest of respiration called deglutition apnea. This occurs during pharyngeal stage (2nd stage of respiration) and it prevents the entry of food particles into the respiratory tract. The nerve involved in this reflex is glossopharyngeal nerve.
k. *Others:* Rise in body temperature causes hyperventilation. Sharp acute pain increases the rate of respiration temporarily.

## Chemical Regulation

The chemical mechanism of regulation of respiration is operated through the chemoreceptors. These receptors are stimulated by any change in the concentration of $O_2$, $CO_2$, $H^+$ and other drugs, chemical hormones. Chemoreceptors are of 2 types:

i. Central chemoreceptors
ii. Peripheral chemoreceptors.

**Flow chart 3.1:** Chemical regulation of respiration




## Central Chemoreceptors

Central chemoreceptors are situated in the ventral part of medulla. They are distinct and separate from pontomedullary respiratory center. Stimulus is increase in $pCO_2$.

### Mechanism of Stimulation of Chemoreceptors

$CO_2$ from the arterial blood crosses blood-brain barrier and enters the CSF and brain interstitial fluid (Flow chart 3.1)

$CO_2$ cross the cell membrane, combine with $H_2O$ to form $H_2CO_3$ which splits into $H^+$ and $HCO_3^-$ (carbonic anhydrase mediated). It is this $H^+$ ion which stimulates respiration. Once stimulated sent impulse to pontomedullary respiratory center and influence rate and rhythm of respiration.

## Peripheral Chemoreceptors

They are carotid body and aortic body. There are two carotid bodies, one on either side of midline near bifurcation of common carotid artery. These contain chemoreceptors which are sensors of arterial $O_2$ tension, $CO_2$ tension and blood pH. Usually two or more aortic bodies are present near the arch of aorta. From carotid body impulses are transmitted via Hering nerve and from aortic body through vagus. Each carotid and aortic body contains islands of two types of cells – Type I and Type II cells.

### Type I Cells

Type I cells are also called glomus cells, these islands are surrounded by fenestrated sinusoidal capillaries. They are closely associated with cup-like endings of afferent nerve (glossopharyngeal). These cells have dense core granules. Granules contains catecholamine (dopamine). Neurotransmitter released at the junction of afferent nerve and receptor cell is dopamine.

Glomus cells are stimulated mainly by hypoxia, these cells have $O_2$ sensitive $K^+$ channels whose conductance is decreased proportionate to degree of hypoxia. This reduces $K^+$ efflux and depolarizes the cell → lead to $Ca^{2+}$ influx → fusion of the released $Ca^{2+}$ with neurotransmitter in receptor membrane → release of neurotransmitter into the synaptic cleft → dopamine bind with dopamine receptors on the postsynaptic membrane → AP in the afferent nerve (glossopharyngeal, vagus) → impulse transmitted to respiratory center.

### Type II Cells

They are also called glial/supporting cells.

## Chemoreceptor Reflex

*Afferent nerve:* Glossopharyngeal and vagus.

*Receptor:* Carotid and aortic body.

*Center:* Respiratory center.

*Efferent nerve:* Nerves supplying muscles of respiration, diaphragm, intercostals.

*Effector:* Respiratory muscles causing increase in their activity (contraction).

***Note***

1. Anemic hypoxia will not stimulate chemoreceptors. Blood flow in each carotid body is 2000 ml/100 g tissue per min (highest and in brain only 54 ml/100 g/min; kidney 420 ml/100 g/ml). As the blood flow per unit area is enormous, $O_2$ needs can be met by dissolved $O_2$ alone. In anemia

**Table 3.3: Different types of hypoxia**

| *Type* | *Example* | *$PAO_2^*$* | *$PaO_2^\dagger$* | *$O_2^\ddagger$ content* | *A-V different* |
|---|---|---|---|---|---|
| Hypoxic | High altitude sickness | ↓ | ↓ | ↓ | ± |
| Anemic hypoxia | Severe anemia | ± | ± | ↓ | ± |
| Stagnant hypoxia | Left ventricular failure | ± | ± | ± | ↑ |
| Histotoxic hypoxia | HCN poisoning | ± | ± | ± | ↑ |

*where $PAO_2$ = $pO_2$ of alveolar air
†$PaO_2$ = $pO_2$ of arterial blood
‡A-V difference = arterial and venous $O_2$ difference ($O_2$ utilization)

and CO poisoning, dissolved $O_2$ is normal and $O_2$ in combination with Hb varies.

2. Increase in $H^+$ ion concentration in blood cannot activate central chemoreceptors ($H^+$ cannot cross BBB).

## APPLIED PHYSIOLOGY

### Hypoxia

Hypoxia is $O_2$ deficiency at the tissue level. It is a more relevant term than anoxia, where rarely no $O_2$ is left in the tissues.

Hypoxia is divided into four types (Table 3.3):

1. Hypoxic hypoxia (anoxic anoxia).
2. Anemic hypoxia.
3. Stagnant/ischemic hypoxia (blood flow to the tissues is low, adequate $O_2$ not delivered).
4. Histotoxic hypoxia (because of the action of a toxic agent, tissue cells cannot make use of the $O_2$).

#### *Hypoxic Hypoxia*

It is characterized by a low arterial $pO_2$ when $O_2$ carrying capacity of blood and rate of blood flow to tissues are normal or elevated.

Hypoxic hypoxia is a problem in normal individuals at high altitude and is a complication of pneumonia and a variety of other diseases of respiratory system.

***Causes for hypoxic hypoxia***

a. *Low $O_2$ tension in the inspired air:* The $O_2$ tension in the inspired air reduces at high altitude or while breathing air in closed space and also breathing a gas mixture containing low $pO_2$.
b. *Decreased pulmonary ventilation:* Pulmonary ventilation decreases in the following conditions:
   i. Airway obstruction as in asthma
   ii. Depression of respiratory centers by drugs such as morphine.
   iii. Weakness/paralysis of respiratory muscles.
c. *Inadequate oxygenation of blood in lungs:* Oxygenation of blood in the lungs reduces by the following conditions:
   i. Impaired alveolar diffusion as in emphysema.
   ii. Presence of nonfunctioning alveoli as in fibrosis
d. *Cardiac disorders:*
   i. Venous arterial shunts (deoxygenated blood mixes with oxygenated blood)
   ii. Congestive heart failure.

#### *Anemic Hypoxia*

Here the arterial $pO_2$ normal, but amount of Hb to carry $O_2$ is reduced. It is a condition in which $O_2$ carrying capacity of blood is reduced. The $O_2$ availability is normal, but the blood is not able to take up sufficient amount of $O_2$ due to anemic condition.

***Causes of anemic hypoxia***

Anemic hypoxia can be due to two reasons:

a. *Quantitative deficiency of Hb:* For example: Anemia, here the $O_2$ carrying capacity is decreased due to actual deficiency of Hb.
b. *Qualitative deficiency of Hb:* For example: Altered Hb such as methemoglobin.

   Here the Hb content is normal, but due to its altered nature it cannot carry $O_2$. This also includes CO poisoning. The affinity of Hb for CO is 210 times its affinity for $O_2$ and COHb liberates CO very slowly. The difficulty is that when COHb is present the dissociation curve of the remaining $HbO_2$ shifts to the left, decreasing the amount of $O_2$ released. The characteristic feature of anemic hypoxia is that $pO_2$ of the arterial blood is normal, whereas the $O_2$ carrying capacity of blood is reduced.

#### *Stagnant Hypoxia*

In this type of hypoxia blood flow to the tissues is so low that adequate $O_2$ is not delivered to them despite a normal arterial $pO_2$ and Hb concentration. So A-V $O_2$ concentration difference increases, thereby the reduced Hb increases.

Hypoxia due to slow circulation is a problem in organs such as the kidneys and heart during shock. The liver and possibly the brain are damaged by stagnant hypoxia in congestive heart failure.

***Causes of stagnant hypoxia***

The velocity of blood flow decreases in the following conditions: Congestive cardiac failure, hemorrhage, surgical shock, vasospasm, thrombosis and embolism.

### Histotoxic Hypoxia

Hypoxia in which the amount of oxygen delivered to the tissues is adequate, but because of the action of a toxic agent the tissue cells cannot make use of the $O_2$. It occurs due to inhibition of tissue oxidative processes and most commonly as a result of cyanide poisoning. Here the cyanide inhibits cytochrome-oxidase and possibly other enzymes. When cytochrome-oxidase enzymes are inhibited, oxidation stops in the tissues $\rightarrow$ $O_2$ from the capillary blood is not extracted $\rightarrow$ $pO_2$ of venous blood remains high. So A-V $O_2$ difference decreases. Methylene blue or nitrites are used to treat cyanide poisoning. They act by forming methemoglobin, which then reacts with cyanide to form cyanmethemoglobin (nontoxic compound).

## Effects of Hypoxia

### On Blood

Hypoxia stimulates juxtaglomerular apparatus of kidney, increasing the secretion of erythropoietin. Erythropoietin stimulates the red bone marrow, RBC count increases with an increase in reticulocyte count ($O_2$ carrying capacity of blood is improved).

### On CVS

Hypoxia (except anemic hypoxia) stimulates peripheral chemoreceptors which in turn stimulate cardiac and vasomotor centers, thereby there is an increase in the HR, force of contraction, CO and systemic arterial blood pressure.

### On Respiration

All types of hypoxia except anemic hypoxia stimulate peripheral chemoreceptors to increase respiration. The rate of increase in ventilation is in proportion to the severity of the hypoxia of the peripheral chemoreceptors.

### On CNS

In mild hypoxia, the symptoms are similar to alcohol intoxication (depression, general loss of self control, headache, loss of time sense). In severe hypoxia, there is sudden loss of consciousness, if not treated immediately coma occurs which leads to death.

## Treatment for Hypoxia ($O_2$ Therapy)

The best treatment for hypoxia is $O_2$ therapy, i.e. treating the affected person with $O_2$. Pure $O_2$ or $O_2$ combined with another gas is administered. Depending on the basic physiological principles of different types of hypoxia the valuability of oxygen therapy in various types can be understood.

### Atmospheric Hypoxia (Hypoxic Hypoxia)

$O_2$ therapy can completely correct the depressed $O_2$ level in the inspired gases and therefore provide 100% effective therapy.

### Hypoventilation Hypoxia

Here with $O_2$ therapy the amount of $O_2$ entering the alveoli with each breath can be increased. But this provides no benefit for the excess blood $CO_2$ also caused by hypoventilation.

In hypoxia caused by anemia, abnormal Hb, transport of $O_2$, circulatory deficiency or physiological shunt, oxygen therapy is of much less value because normal $O_2$ is already available in the alveoli.

In hypoxia caused by inadequate tissue use of $O_2$ (histotoxic hypoxia), $O_2$ therapy is of practically no value because:

i. Here neither $O_2$ pick up by the lungs or transport to the tissues is deficient.
ii. The defect is in the tissue metabolic system so it cannot utilize the $O_2$ being delivered.

## Dyspnea

Dyspnea is difficult or labored breathing in which the subject is conscious of shortness of breath or it is an abnormal uncomfortable awareness of breathing.

A normal individual is not conscious of respiration until ventilation is doubled and breathing becomes uncomfortable. Real dyspnea (uncomfortable breathing) occurs when pulmonary ventilation is tripled or quadrupled, i.e. when an imbalance between demand for ventilation and actual ventilation is achieved.

The basic mechanisms of dyspnea are:

1. Hypercapnea and hypoxia: Hypoxia and hypercapnea result in increased rate and depth of breathing regardless of the patient's subjective sensation.
2. Increased effort of breathing or increased work of breathing. For example, in bronchial asthma where airway resistance is increased and compliance is reduced.
3. Current hypothesis is that dyspnea occurs when there is a mismatch between incoming afferent information to the brain and outgoing motor signals from brain to respiratory muscles.

### Causes

***Diseases of respiratory system***

a. Obstruction to any part of respiratory passage: Increase work of breathing. For example, bronchial asthma.
b. Diseases of lungs and pleura: Pneumonia, pulmonaryedema, fibrosis, pleural effusion and pneumothorax.
c. Interference with respiratory movement:

- Weakness or paralysis of respiratory muscles
- Pain due to injury to chest wall, ribs
- Deformities of spine
- Impaired movements of diaphragm.

***Diseases of CVS***

a. Chronic CCF: Initially dyspnea only on exertion, later even at rest.
b. Paroxysmal nocturnal dyspnea: Pulmonary edema of LVF.

***Disorders of metabolism***

a. Metabolic acidosis
b. Diabetic acidosis
c. Uremia.

***Other causes:*** Anemia, cerebral hemorrhage and psychogenic.

### *Dyspneic Index/Breathing Reserve Percentage*

It is the percentage of respiratory capacity not being used at a given RMV or pulmonary ventilation. Normal dyspneic index at rest is >90%.

Breathing reserve = MVV – RMV = 100 – 10 = 90 L
DI = MVV – RMV/MVV × 100
Where, MVV – Maximal voluntary ventilation
RMV – Residual minute volume

This means that breathing can be increased by 90 L, i.e. from 6–8 to 100 L or more. Dyspnea is there when this index is less than 70%, which is called *dyspneic point*. An example taken from a patient of emphysema will clarify it. The MVV has decreased from 100 L/min to 40 L/min, while RMV has increased 10 L/min to 20 L/min (due to respiratory stimulation by increased $pCO_2$ and low $pO_2$). DI = 40 – 20/40 × 100 = 50%.

This means that dyspneic point has been crossed, so that the patient is experiencing dyspnea.

## Orthopnea

It refers to the dyspnea in lying position. Dyspnea increases when the person lies down and improves when the person sits up. This is usually seen in patients with cardiac failure. Improvements of dyspnea occurs in sitting position as the abdominal viscera do not press upon the diaphragm during sitting, so that the diaphragm can descend easily. Effect of gravity is that as the person lies down, the venous return to the heart increases and the symptoms of orthopnea flare up. When the person sits up, as a result of gravity the venous return to the heart decreases and the symptoms of orthopnea decreases.

## Hypercapnia

Hypercapnia is retention of $CO_2$ in the body. In these patients $pCO_2$ is markedly elevated, there is severe respiratory acidosis and plasma $HCO_3^-$ may be very high which partially compensates for the acidosis. Essential mechanisms underlying hypercapnia is inadequacy of alveolar ventilation for the amount of $CO_2$ produced.

### *Causes*

1. Increased $CO_2$ production: In febrile patients 13% increase in $CO_2$ production for each 100°C rise in temperature. High carbohydrate diet increases $CO_2$ production.
2. Malfunction of respiratory pump: Hypercapnia is associated with hypoxia.
3. Inefficiency of gas exchange (Increased dead space or V/P mismatch).

In hypoxia due to poor diffusion through respiratory membrane, serious hypercapnia does not occur because $CO_2$ difuses 20 times rapidly as $O_2$.

### *Symptoms*

1. Alveolar $pCO_2$ > 60–75 mm Hg; breathing becomes rapid and deep.
2. Alveolar $pCO_2$ > 80–100 mm Hg; symptoms due to depression of CNS, i.e. confusion, decreased sensory perception and eventually coma.
3. Alveolar $pCO_2$ > 120–150 mm Hg; anesthesia and death of the patient.

## Hypocapnia

The chronic effects of hypocapnia are seen in neurotic patients who chronically hyperventilate themselves. Hypocapnia has a direct vasoconstrictor effect on cerebral vessels. So cerebral blood flow is reduced, thereby leading to cerebral ischemia that lead to dizziness and paresthesia.

If a person voluntarily hyperventilates, excess amount of $CO_2$ is washed out and $pCO_2$ decreases. This depresses respiration and leads to apnea. During this period of apnea $CO_2$ is accumulated and a fall in $pO_2$ occurs. This stimulates respiration and normal respiration is resumed.

If $H^+$ is normal and if there is prolonged hyperventilation, increased $CO_2$ is washed out and $H^+$ becomes less than normal and the condition is called respiratory alkalosis.

When $H^+$ is low or pH is high, the proteins are ionized. Ionised $Ca^{2+}$ in blood combine with protein and $Ca^{2+}$ gets converted to the bound form. When ECF concentration of $Ca^{2+}$ falls below normal, the nervous system becomes progressively more excitable leading to increased permeability to $Na^+$ allowing easy initiation of action potentials. This may lead to symptoms of hypocalcemia and tetany.

## Asphyxia

It is produced by occlusion of airways. This results in hypoxia (lack of $O_2$) and hypercapnia (excess of $O_2$). Asphyxia occurs in strangulation, acute tracheal obstruction due to foreign

body in trachea or larynx, traumatic compression of chest by fall of heavy objects (trapped in building collapse). When a newborn does not begin to breath soon after birth, it develops asphyxia called asphyxia neonatorium.

Effects of asphyxia is described under three stages.

1. *Stage of exaggerated breathing:* Due to stimulation of respiratory centers by $CO_2$ breathing become deeper, more frequent and more labored.
2. *Stage of convulsion:* Due to spread of stimulation to centers in brain and spinal cord generalized convulsions appear. There is tachycardia, vasoconstriction, rise of BP and lack of consciousness.
3. *Stage of collapse:* Due to paralysis of respiratory centers convulsions cease abruptly and respiration becomes gasping in character. Pupils dilate, pulse becomes feeble, reflexes are absent. Finally death occurs by the failure of vital centers.

***Note:*** In the earlier stages of asphyxia the knee-jerks are exaggerated, but when the third stage is reached they are entirely lost.

## Cyanosis

It is a clinical condition characterized by bluish discoloration of skin and mucous membrane, best seen in people with white complexion. Cyanosis is caused when more than 5 gm of reduced Hb is present in the local blood. Thus in anemia where Hb is less than 5 gm%, no cyanosis is seen (enough reduced Hb is not formed to produce blue color). But in cases of polycythemia vera (excess RBC), the great excess of available Hb that can become deoxygenated leads frequently to cyanosis. Cyanosis does not occur in histotoxic hypoxia. Cyanosis is of two types:

a. Central cyanosis
b. Peripheral cyanosis.

### *Central Cyanosis*

Central cyanosis is due to heart or lung disease and is associated with hyperkinetic circulation (tachycardia, increase in BP, warm periphery). It occurs mainly due to the shunting of blood from the right to left side of the heart, i.e. bypassing the lung. Therefore, the oxygenation of Hb is hampered resulting in the rise of reduced Hb on the blood. This condition is characterized by blue extremities which are warm due to hyperdynamic circulation. The site for central cyanosis is tongue and lip. It also occurs in different lung diseases where pulmonary gas exchange is affected.

### *Peripheral Cyanosis*

It is due to local causes. Here, there is severe vasoconstriction due to sympathetic stimulation. Vasoconstriction in the periphery leads to reduction of blood flow in the tissue while $O_2$ demand of the tissues remains the same, thus the concentration of reduced Hb rises. The site for peripheral cyanosis is toes and finger tips. This can occur in peripheral circulatory failure resulting in cold blue extremities.

***Note:*** A discoloration of the skin and mucous membrane similar to cyanosis is produced by high circulating levels of methemoglobin.

## Special Types of Respiration

### *Cheyne-Stoke's Breathing*

When respiration shows alternate waxing and waning of tidal volume, it is called Cheyne-Stoke's breathing (Fig. 3.22). Physiological causes are voluntary hyperventilation, high altitude, during sleep in some normal individuals (especially infants). Pathological causes include chronic heart failure, brain damage, uremia and poisoning by narcotics.

***Explanation***

*Voluntary hyperventilation:* Voluntary hyperventilation for two minutes produces apnea followed by respiration. This cycle keeps on repeating but with a decreasing duration of apnea until the respiration comes to normal.

*Mechanism:* Hyperventilation cause increased alveolar $pO_2$ or decreased $pCO_2$. Decreased alveolar $pCO_2$ cause apnea. Apnea results in:

i. $CO_2$ accumulation in the body with gradual increase in alveolar $pCO_2$. As long as increase in alveolar $pCO_2$ remains below 40 mm Hg (threshold level) apneic spells are there.
ii. Fall in alveolar $pO_2$ to 60 mm Hg (hypoxia) via peripheral chemoreceptors stimulate the respiratory center producing hyperventilation.

*Heart failure:* It occurs mainly in left ventricular failure and is associated with pulmonary congestion producing hypoxia leading to the stimulation of respiratory center and thus ventilation increases. In heart failure, the circulation is slowed down from lungs to brain, therefore when such individuals hyperventilate, it takes longer than the normal time for the

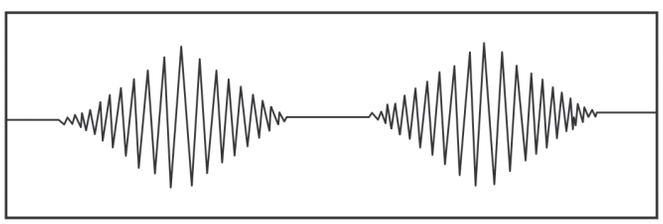


**Fig. 3.22:** Cheyne-Stoke's breathing



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blood to reach the brain. When this blood reaches the brain, low $pCO_2$ inhibits the respiratory center producing 'apnea'.

*Brain damage:* If there is damage of supra medullary inhibitory pathway, the medullary chemoreceptor becomes more sensitive to the action of $CO_2$. Thus pulmonary ventilation increases, so $CO_2$ is washed out and alveolar $pCO_2$ falls, producing apnea. As a result, $CO_2$ accumulate, alveolar $pCO_2$ rises and respiration gets stimulated.

***Effects of periodic breathing***

a. Fall in arterial $pCO_2$ causes severe vasoconstriction of cerebral blood vessels, as a result, cerebral blood flow decreases producing dizziness.
b. Hyperventilation leads to respiratory alkalosis.

### *Biot's Respiration*

This is a type of periodic breathing in which there are 3–4 cycles of normal respiration followed by abrupt onset of apnea and again abrupt onset of normal respiration (Fig. 3.23). It is seen in case of meningitis, severe brain damage, etc.

### *Kussmaul Breathing*

It is also known as acidotic breathing/air hunger. It occurs in case of metabolic acidosis as in diabetic ketoacidosis, renal failure, etc. The respiration is characterized by rapid and deep breathing (due to stimulation of respiratory center by increased $H^+$). The main action of $H^+$ in the blood is via peripheral chemoreceptors. But $H^+$ ions can slowly cross the blood-brain barrier when the concentration is high and persistent, in that case the central chemoreceptors are also stimulated. It's aim is to wash out $CO_2$ and thereby to correct the acidosis. Here, the blood $pCO_2$ level is low.

## Artificial Respiration

In acute asphyxia due to drowning, CO or other forms of gas poisoning, electrolution and anesthetic accidents, where breathing has ceased artificial respiration may be life saving. It should always be attempted, because respiration stops before the heart stops.

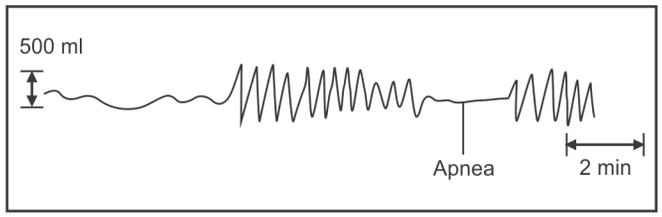



**Fig. 3.23:** Biot's breathing

### *Mouth-to-Mouth Breathing (Figs 3.24 A to C)*

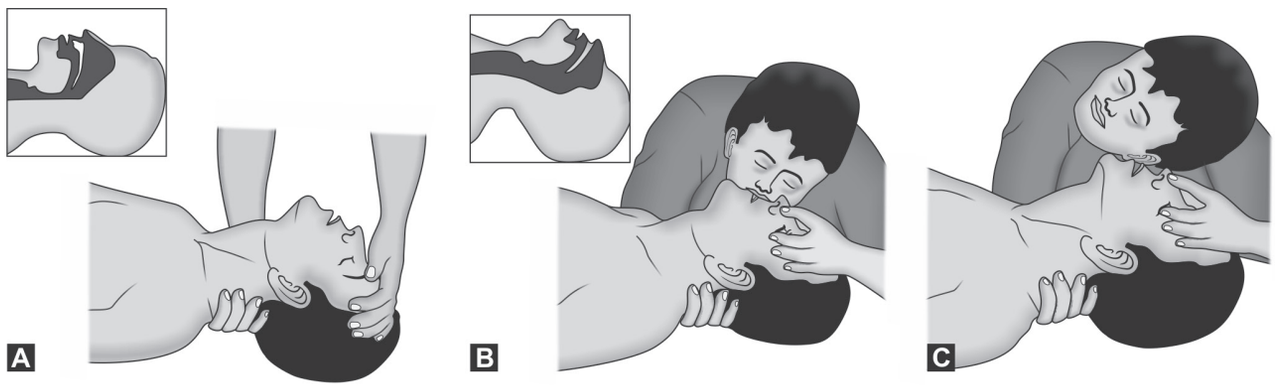
There are numerous methods of artificial respiration, but the method presently recommended to produce adequate ventilation in all cases is mouth-to-mouth breathing. It works by expanding the lungs.

***Method***

1. In this form of resuscitation, the operator 1st places the victim in the supine position and opens the airway by placing a hand under the neck and lifting, while keeping pressure with the other hand on the victim's forehead. This extends the neck and lifts the tongue away from the back of the throat.
2. Now the victim's mouth is covered by the operator's mouth while the fingers of the hand already on the forehead occlude the nostrils.
3. About 12 times a minute, the operator blows into the victim's mouth a volume twice the tidal volume, then permits the elastic recoil of the victim's lungs to produce passive expiration (by unsealing mouth and nose). The victim's neck is kept extended. Rescuer should listen and feel for expiratory airflow.

***Note***

a. Any gas blown into the stomach can be expelled by applying upward pressure on the abdomen from time to time.




**Figs 3.24A to C:** Steps of mouth-to-mouth breathing

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b. In apneic individuals in whom no heartbeat is detectable, mouth-to-mouth breathing should be alternated with cardiac massage.

### *Mechanical Ventilation*

For treatment of chronic weakness of the respiratory muscles, airtight devices that cover the chest are available. By means of a motor, negative pressure is applied to the chest at intervals, drawing air into the lungs. In cases of acute respiratory failure and other conditions in which alveolar-capillary exchange is affected patients are intubated and pulses of air or mixtures of respiratory gases are delivered by machines. Various pressure adjustments are done to maintain a positive end-expiratory pressure (PEEP) to aid movement of $O_2$ into the blood and prevent atelectasis. However, excessive pressure can rupture the alveoli. For this and other reasons, mechanical ventilation should be discouraged as soon as possible.

## Acclimatization

Various physiological readjustments and compensatory mechanisms in the body that reduce the effects of hypoxia in permanent residents at high altitude is called 'acclimatization' at high altitudes. Acclimatization is possible by the following compensatory mechanisms:

### *Increase in Pulmonary Ventilation*

In acclimatized subjects, the sensitivity of respiratory center to 'hypoxia' increases. Therefore even with slight decrease of arterial $pO_2$, pulmonary ventilation increases and alveolar $pCO_2$ falls. This increase in pulmonary ventilation is maintained by active regulation of pH of CSF and blood to normal levels.

### *Decreased Affinity of Hb for $O_2$ under Hypoxic Conditions*

When a person is exposed to hypoxia at high altitude within hours there will be increased amount of 2,3 DPG. This shifts $O_2$-Hb dissociation curve to right, releasing more $O_2$ from Hb.

### *Rise in Hb Concentration*

Erythropoietin secretion increases promptly on ascent to high altitude. 'Hypoxia' is a powerful stimulus for erythropoietin secretion and thus activates erythropoiesis. This increase in circulating RBC triggered by erythropoietin begins in 2–3 days and is sustained as long as the individual remains at high altitude.

### *Changes at Tissue Level to Reduce the Effect of Hypoxia*

Compensatory changes also occur in the tissues.

i. Increase in the number of mitochondria which are the sites of oxidative reactions.
ii. Increase in cytochrome oxidase.
iii. Increase in myoglobin which facilitates the movement of $O_2$ in tissues.

### *Increased Vascularity of Hypoxic Tissues*

Hypoxia increases tissue capillary density, i.e. more capillaries open up. Hypoxia also causes vasodilatation. Therefore, more $O_2$ can be supplied to tissues.

### *Increased Diffusion Capacity of Lungs for $O_2$*

This occurs due to:

i. Increase in the number of pulmonary capillaries secondary to increase in pulmonary artery pressure.
ii. Pulmonary vasodilatation.
iii. Increase in pulmonary blood flow.

***Note***

1. *Mountain sickness:* When a person ascends to high altitude he suffers from mountain sickness. It starts approx 8–12 hours after arrival at high altitude and lasts for about 4–8 days. It is characterized by nausea, vomiting, headache, insomnia, dyspnea and irritability. The exact cause of mountain sickness is not known, but it appears to be associated with cerebral edema or alkalosis.
2. When a person ascends to high altitude, the availability of $O_2$ in the inspired air decreases but the amount of $CO_2$ increases. So, in order to get adequate $O_2$ supply to the tissues, there is an increase in the rate of respiration. But consequently as the respiration rate increases, there is more entry of $CO_2$ with the inspired air. Therefore to facilitate the removal of $CO_2$ and to permit the entry of $O_2$ into the tissues, the respiration becomes periodic. This is why periodic breathing is seen in unacclimatized persons at high altitude.

## Dysbarism

Dysbarism is also known as Caisson's disease, decompression sickness, divers' palsy, the bends. A person after staying for sometime in higher barometric pressure if suddenly exposed to a low barometric pressure, suffers from a group of symptoms called 'dysbarism'. When the individual ascends rapidly to sea level after sufficient exposure to high atmospheric pressure deep in the sea, $N_2$ is decompressed and escapes from the tissues at a faster rate. Being gas it forms bubbles while escaping rapidly from the tissues. The gases block the blood vessels producing tissue ischemia and sometimes the tissue death.

Caisson is an iron chamber used to lower individuals to work deep under the sea, they suffered from dysbarism and thus it is also called as Caisson's disease. This problem is also

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faced by professional divers and tunnel workers who are exposed to high barometric pressure.

### *Symptoms*

1. Pain in joints and muscles of legs or arms. The joint pain accounts for the term 'bends' that is often applied to this condition.
2. *The chokes:* The chokes refers to serious shortness of breath which is often followed by severe pulmonary edema and, occasionally death.
3. Neurological symptoms like dizziness, paralysis of muscles, or collapse, paresthesia and unconsciousness may occur due to blockage of blood vessels of brain and spinal cord.
4. Paralysis of muscles may occur temporarily due to the presence of $N_2$ bubbles in the myelin sheath of motor nerves. This is called *diver's palsy*.
5. Coronary ischemia or MI may occur due to blockage of coronary capillaries by the $N_2$ bubbles.

### *Principle*

When a person stays in a higher barometric pressure, his blood is equilibrated to the air of that pressure. So, all the gases dissolved in blood increase proportionately including $N_2$. Now when the person is suddenly exposed to low barometric pressure, these gases are liberated from the blood. $CO_2$ poses no problem as it can diffuse quickly and $O_2$ can be utilized by the tissues. But $N_2$ bubbles cannot be got rid of easily and they obstruct the blood vessel to produce the symptoms stated above.

### *Prevention*

Diver or caisson workers should come to the surface slowly.

### *Treatment*

Tank decompression is most important method in treating people in whom symptoms of decompression develops. In this case ,the diver is recompressed immediately to a deep level. Then decompression is carried out over slowly to normal atmospheric pressure.

***Note***

1. Risk of decompression sickness can be reduced by breathing mixture of $O_2$ and helium during the dive.
2. $N_2$ bubbles may not appear for many minutes to hours because sometimes the gas can remain dissolved in the supersaturated state for hours before bubbling.
3. Recovery is often complete, but there may be residual neurologic sequele as a result of irreversible damage to the nervous system.

### Hiccup

Hiccup is a spasmodic contraction of the diaphragm and other respiratory muscles that produces an inspiration during which the glottis closes suddenly. The glottic closure is responsible for the characteristic sensation and sound. Hiccups occur in the fetus *in utero* as well as throughout extrauterine life. Most attacks of hiccups are usually of short duration and they often respond to breath-holding or other measures that increases arterial $pCO_2$.

## RESPIRATORY CHANGES IN EXERCISE

Many cardiovascular and respiratory mechanisms must operate in an integrated fashion if the $O_2$ needs of the active tissue are to be met and the extra $CO_2$ and heat removed from the body during exercise.

The circulatory changes maintains adequate circulation in the rest of the body while increased extraction of $O_2$ from the blood in exercising muscles ensures adequate ventilation This provides extra $O_2$ and eliminates extra $CO_2$ and some amount of heat.

### Changes in Ventilation

During exercise, the amount of $O_2$ entering the blood in the lungs is increased because the amount of $O_2$ added to each unit of blood and the pulmonary blood flow per minute are increased. The $pO_2$ of blood flowing into the pulmonary capillaries falls 40–25 mm Hg and thereby an increased alveolar capillary $pO_2$ gradient is created and more $O_2$ enters the blood. Blood flow per minute is increased from 5.5 L/min to as much as 20–35 L/min and thereby the total amount of $O_2$ entering the blood and $CO_2$ extraction are increased markedly. The increase in $O_2$ uptake is proportional to the work load up to a maximum. Above this maximum, $O_2$ consumption level falls off and the blood lactate level continues to rise. The lactate comes from muscles where aerobic resynthesis of energy stores cannot keep pace with their utilization and an $O_2$ debt occurs.

***Note***

***Oxygen debt***

In any type of muscular exercises, $O_2$ requirement increases. Consumption of $O_2$ ($VO_2$) increase during 2–4 min of exercise and then reaches a plateau. So in the beginning (during adaptation phase), an $O_2$ deficit is established. This deficit is caused by the lag in circulatory adjustments during the start of exercise. During this period, muscles stores of ATP are used. This deficit is repaid in the form of $O_2$ debt (Fig. 3.25). Oxygen debt may be defined as the amount of excess $O_2$ that is consumed during recovery after an exercise. Physical performance is inversely related to $O_2$ deficit.

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**Table 3.4: Respiratory changes during exercise**

| | *At rest* | *During exercise* | *Cause and control* |
|---|---|---|---|
| 1. Pulmonary ventilation (PV) | Frequency of breathing = 12/min<br>TV = 500 ml<br>PV = 6 l/min | Frequency of breathing = 40–45/min<br>TV increases from 10–15% to 50% of VC<br>PV = 100 l/min | PV increase in parallel to increase in $O_2$ consumption and increase in $CO_2$ output<br>PV is increased due to:<br>1. Stimulation of respiratory center from motor cortex<br>2. Stimuli from proprioceptors of moving muscles, tendon and joints<br>3. Stimulation of carotid bodies<br>4. Increase in body temperature stimulates respiratory center<br>5. Increase in lactic acid and plasma $K^+$ level in blood<br>*Note:* During heavy exercise, PV increase is not proportional to increase in $O_2$ consumption and increase in $CO_2$ output. This is due to anaerobiosis of working muscles, which contributes to the extra drive to respiratory center. |
| 2. Diffusion capacity of $O_2$ ($DO_2$) | $DO_2$ = 20–30 ml/min/mm Hg | $DO_2$ increase above 3 times | $DO_2$ increase is due to:<br>1. Increase in blood perfusion around air sacs in the lungs<br>2. Opening of more capillaries.<br>Both increase surface area of contact between alveoli and capillaries |
| 3. Oxygen consumption | $VO_2$ = 250 ml/min | Increased to 15–20 times resting value | Due to:<br>1. Three times increase in A-V $O_2$ difference.<br>2. Five times increase in $O_2$ delivery to tissues<br>Increased $O_2$ delivery to tissues is due to: increase in CO, alveolar ventilation, capillary density, RBC count |

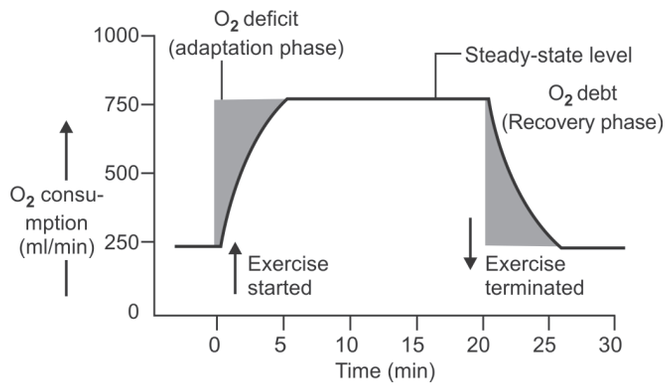


**Fig. 3.25:** Oxygen debt

$O_2$ deficit is decreased by warm up and training. $O_2$ debt is meant for:

1. Reoxygenation of myoglobin.
2. Regeneration of depleted stores of ATP and creative phosphate.
3. Removal accumulated lactic acid from muscle tissues (lactic acid $O_2$ debt).
4. Resupply of dissolved $O_2$ in tissue fluids and blood.

Ventilation increases abruptly with the onset of exercise, followed after a brief pause by a further, more gradual increase. With moderate exercise, the increase is mostly due to an increase in the depth of respiration and when the exercise becomes more strenous this is accompanied by an increase in the respiratory rate.

Ventilation abruptly decreases when exercise ceases, followed after a brief pause by a more gradual decline to pre-exercise values. The abrupt increase in the ventilation at the start of exercise is presumably due to psychic stimuli and afferent impulses from proprioceptors in the muscles, tendons and joints. The increase in ventilation is proportionate to the increase in $O_2$ consumption. Exercise increases the plasma $K^+$ level and this increase may stimulate the peripheral chemoreceptors responsible for stimulation of respiration.

In addition, the sensitivity of the neurons controlling the response to $CO_2$ is increased and there will be increased fluctuations in the arterial $pCO_2$ therefore $CO_2$ is responsible for the increase in ventilation although $O_2$ seems to play some role.

When exercise becomes more vigorous, buffering of the increased amounts of lactic acid that are produced liberates more $CO_2$ and this further increases ventilation.

With respect to respiratory system, there are changes in (Table 3.4):

1. Pulmonary ventilation
2. Diffusion capacity of $O_2$ in lungs
3. Oxygen consumption.



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Chapter

# 4 Cardiovascular System

Cardiovascular system comprises of heart and blood vessels. The function of CVS is to supply $O_2$, nutrients and other essential substances to the tissues of the body and to remove $CO_2$ and other metabolic endproducts from tissues.

## ORGANIZATION OF THE VASCULAR SYSTEM

The functions of the circulation are achieved because the vascular system consists of the following type of blood vessels:

### *Windkessel Vessels/Distensible Vessels*

These vessels are highly elastic (Windkessel means elastic reservoir). For example, aorta, pulmonary artery and their larger branches.

### *Resistance Vessels*

These vessels contain less elastic tissue, but more smooth muscles. They can change the diameter by contraction or relaxation of smooth muscles. This changes the resistance and thus influences flow through these vessels. So these vessels are called resistance vessels. For example, arterioles, metaarterioles and precapillary sphincters.

### *Capacitance Vessels*

These vessels are thin walled and highly distensible. So they have the ability to store large amount of blood and hence called capacitance vessels. For example, veins.

### *Exchange Vessels*

These are the vessels are thin walled and have fenestrations and helps in the exchange of materials between blood and interstitial fluid. For example, capillaries.

### *Shunt (Thoroughfare) Vessels*

These are vessels which bypass the capillaries. For example, arteriovenous anastomosis.

### Windkessel Effect

As the heart contracts intermittently, the pressure and blood flow in the large arteries is pulsatile (During systole volume of blood pumped is maximum and in diastole it is minimal). However the flow of blood through other blood vessels is continuous. It is because of the behavioral pattern of aorta and other large vessels.

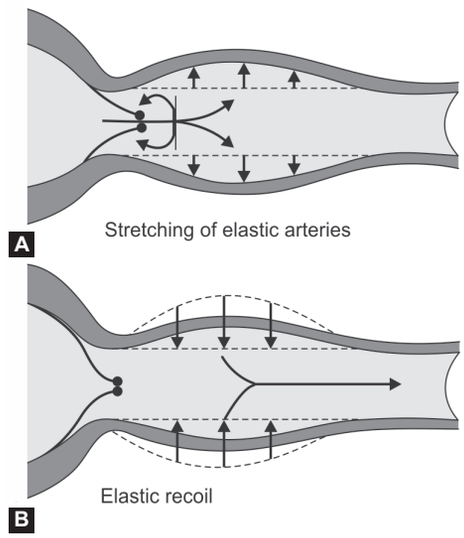
During ventricular systole, blood enters large arteries with considerable force and this blood can be accommodated by distensible nature of blood vessels. During diastole, force is absent and volume of blood entering vessels is zero, but since vessels recoil due to elastic property, the BP is retained and the blood is pumped to periphery. This recoil effect is called Windkessel effect and the vessels exerting this effect is called Windkessel vessels (aorta, pulmonary artery and their large branches; Figs 4.1A and B).

## HEMODYNAMICS

The flow of blood through the vascular system is governed by a group of physical laws.

### *Bernoulli's Principle*

It states that, in a tube or blood vessel, the sum of the kinetic energy (KE) of flow and the pressure energy is constant. Therefore, when fluid flows through the narrow portion of tube, KE of flow increases as the velocity increases and the




**Figs 4.1A and B:** Windkessel effect

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pressure energy is reduced (distending pressure decreases). Thus greater the velocity of flow in a vessel, the lesser will be the lateral pressure distending its walls.

### *Law of Laplace*

It is the relationship between distending pressure and tension on the wall in a hollow viscous object. It states that distending pressure (P) in a distensible hollow object is equal to the tension in the wall (T) divided by two principal radii of curvature of object (R1 and R2). So, P = T/ R1 + T/ R2.

In a sphere, such as lung alveoli R1 = R2; therefore,
P = 2T/R.

In a cylinder such as blood vessel, as one radius is infinite; therefore P = T/R.

#### *Physiological Significance of Law of Laplace*

Smaller the radius of blood vessel, lesser the tension in the wall necessary to balance the distending pressure. This is why the thin walled and delicate capillaries are less prone to rupture.

### Types of Blood Flow

There are two types of blood flow: (1) Laminar (streamline) and (2) Turbulent blood flow (Fig. 4.2).

#### *Laminar (streamline) Blood Flow*

In laminar flow, blood flows in large number of layers at a steady rate with each layer remaining at the same distance from the vessel wall. For example, characteristic of most part of the vascular system.

#### *Turbulent Blood Flow*

Here blood flows in all directions in the vessel and continuously mixing within the vessel. Thus there is a greater energy loss compared to laminar flow. For example, ventricles and aorta.

### *Reynold's Number*

Turbulence is given by Reynold's number (Re),

$$Re = V\rho\, d/\eta$$

Where,

V = Velocity of flow in cm/sec
ρ = Density of blood
d = Diameter of blood vessel
η = Viscosity of blood in poise

**Fig. 4.2:** Types of blood flow

When Re less than 1000, flow is always laminar. As the value increases the probability of turbulence also increases. Turbulence develops when Re exceeds 2000. In anemia viscosity is decreased and a systolic murmur is heard while auscultating heart.

## PROPERTIES OF CARDIAC MUSCLE

***Electrical Properties***

- Excitability (Bathmotropism)
- Autorhythmicity (Chronotropism)
- Conductivity (Dromotropism).

***Mechanical Properties***

Contractility (Inotropism).

***Other Properties***

- Refractory period
- Frank-Starling law.

### Excitability

The cardiac muscles are excitable and respond to proper stimuli with the production of action potentials. In heart two types of tissues are present.

a. *Conducting tissue:* They initiate and conduct impulses (SAN, AVN, internodal tract, bundle of His and Purkinje fibers).
b. *Contractile tissue:* They contracts in response to the impulse conducted (myocardial cells forming walls of cardiac chamber).

### *Action Potential*

Action potential (AP) can be defined as sequence of changes in the membrane potential in an excitable cell due to opening and closure of different ion channels after the application of a threshold stimulus. Action potential in cardiac muscles is of two types:

a. Fast response action potential
b. Slow response action potential

***a. Fast response action potential***

This type of action potential is seen in working myocardium (atria, ventricles) and in Purkinje fibers (Fig. 4.3). It is characterized by:

*Rapid depolarization:* When the firing level is reached, there is a very rapid change of membrane potential producing a sharp upstroke called '0' (zero) phase. The resting membrane potential (RMP) of ventricular musculature is about –90 mV. In this phase the membrane potential crosses the zero line (positive overshoot). The inside of the cell becomes +ve with respect



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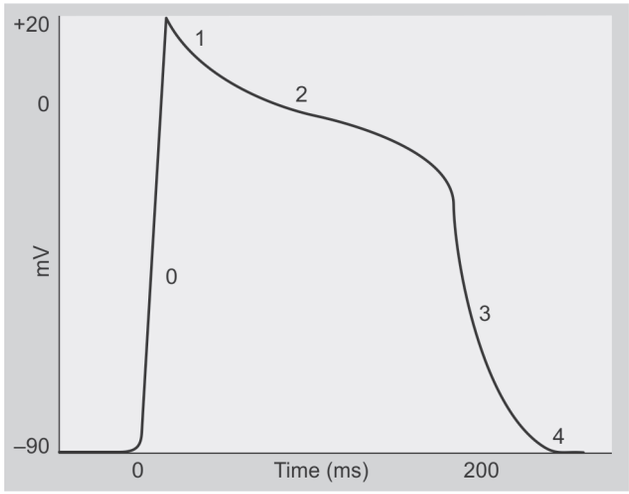


**Fig. 4.3:** Phases of action potential in a myocardial muscle fiber

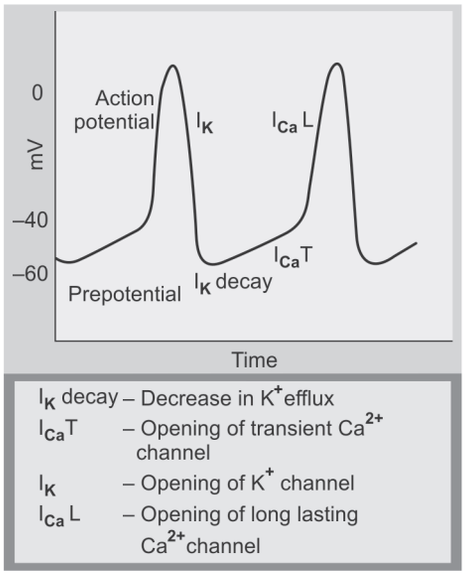


**Fig. 4.4:** Membrane potential of a pacemaker tissue

to outside and the cell is fully depolarized. The initial depolarization is due to $Na^+$ influx through rapidly opening $Na^+$ channels.

*Initial rapid repolarization:* After '0' phase there is a slight fall of membrane potential towards the zero potential line. This phase is named as phase '1'. This phase is due to closure of fast $Na^+$ channels and opening of $K^+$ channels ($K^+$ efflux begins).

*Plateau phase:* After phase '1', the membrane potential is maintained for sometime at that level, i.e. the repolarization is prolonged. This phase is named as phase '2'. It is due to opening of slow $Ca^{2+}$ channels along with $K^+$ efflux. Thus, potential change due to $K^+$ efflux is neutralized.

*Late rapid repolarization:* Then there is a rapid repolarization at phase '3'. This is due to closure of slow $Ca^{2+}$ channels and $K^+$ efflux.

*Base line (polarized state):* In the last phase (phase '4') the RMP is restored by the activation of $Na^+$–$K^+$ pump (causing $K^+$ efflux).

***b. Slow response action potential***

This type of action potential is seen in the pacemaker tissues (Fig. 4.4). Before the sharp upstroke (seen in myocardial cells) there is a gradual slope. In sinoatrial node (SAN) and atrioventricular node (AVN) the depolarization in the beginning is gradual and RMP automatically approaches to –60 mV. This phase of gradual slope is called pacemaker potential.

When this pacemaker potential reaches a value of –60 mV, firing occurs. Now there develops sharp upstroke. There is no plateau in the AP of SAN and AVN.

*The ionic basis of slow response AP:*

- At the peak of each impulse (end of depolarization) $K^+$ efflux brings about repolarization. Then there is a gradual decrease in $K^+$ efflux followed by the opening of transient $Ca^{2+}$ channels and there is $Ca^{2+}$ influx. This accounts for prepotential.
- When the membrane potential reaches the firing level, there is opening of long-lasting $Ca^{2+}$ channels and there is $Ca^{2+}$ influx. When the membrane potential reaches +35 mV, there is closing of $Ca^{2+}$ channels and opening of $K^+$ channels.

***Note:*** Electrical and mechanical response overlap in cardiac muscle in contrast to skeletal muscle (Fig. 4.5).

## Autorhythmicity

The property of spontaneous pre-potential followed by AP is called autorhythmicity. The RMP of working myocardial cells is about –90 mV and is stable. In conducting tissues, RMP is about –60 mV and it is unstable.

Because of continuous change in membrane permeability, their membrane potential declines towards the firing level spontaneously after each action potential. When the firing level is reached an action potential is triggered. This slow depolarization between action potential is called prepotential/pacemaker potential/diastolic depolarization.

*The ionic basis of prepotential:* At the peak of each impulse (at the end of depolarization) $K^+$ efflux brings about repolarization. Then there is a gradual decrease in $K^+$ efflux followed by the opening of transient $Ca^{2+}$ channels (Fig. 4.4).

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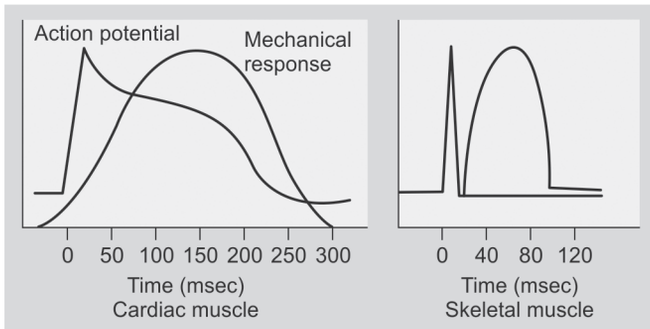


**Fig. 4.5:** Action potential in cardiac muscle and skeletal muscle compared

### *Effect of Vagal (Cholinergic) Stimulation on Membrane Potential*

When cholinergic fibers to nodal tissue are stimulated heart rate decreases (Fig. 4.6). ACh released at the nerve endings increases $K^+$ conductance at nodal tissues (mediated via $M_2$ muscarinic receptors).

There is an increase in $K^+$ efflux at nodal tissues resulting in hyperpolarization. In addition, activation of $M_2$ receptors slows the opening of $Ca^{2+}$ channels. The result is a decrease in firing rate.

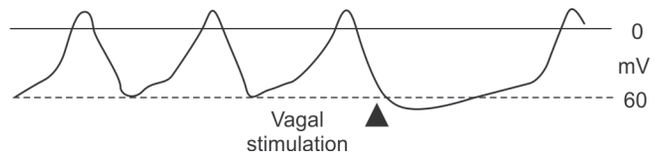


**Fig. 4.6:** Effect of vagal stimulation on membrane potential

### *Effect of Sympathetic (Noradrenergic) Stimulation on Membrane Potential*

When sympathetic cardiac nerves are stimulated heart rate increases (Fig. 4.7). Noradrenaline released makes membrane potential fall more rapidly (mediated via $\beta_1$ receptors). Noradrenaline facilitates the opening of $Ca^{2+}$ channel and thus rapidity of depolarization is increased.

***Note***

1. The discharge frequency is increased when the temperature rises. This explains tachycardia associated with fever.

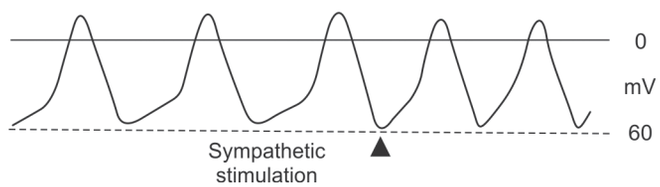


**Fig. 4.7:** Effect of sympathetic stimulation on membrane potential

2. Digitalis depresses nodal tissue and exerts an effect like that of vagal stimulation, particularly on AV node.

*Rate of impulse production*

| | | |
|---|---|---|
| SA node | : | 70 – 80/min |
| AV node | : | 40 – 60/min |
| Bundle of His | : | 30/min |
| Purkinje fibers | : | 15 – 40/min |
| Atrial muscle | : | 40 – 60/min |
| Ventricular muscle | : | 20 – 30/min |

## Conductivity

The property which enables myocardium to conduct electrical impulse is called conductivity. Human heart has specialized conductive system through which the impulse from SA node are transmitted to all parts of the body.

The conductive system of human heart (Figs 4.8 and 4.9) comprises of:

1. SA node
2. Internodal pathways
3. AV node
4. Bundle of His
5. Purkinje system

### *Sinoatrial Node*

Sinoatrial node (SA node) is a small, flattened, ellipsoid strip of specialized cardiac muscle. It is about 3 mm wide, 15 mm long and 1 mm thick. It is located at the junction of the superior vena cava with the right atrium. The SA

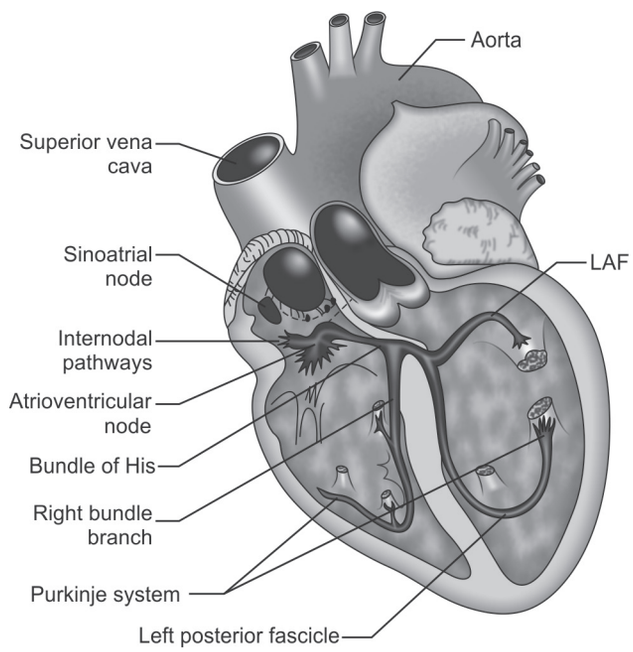


**Fig. 4.8:** Conduction system of heart



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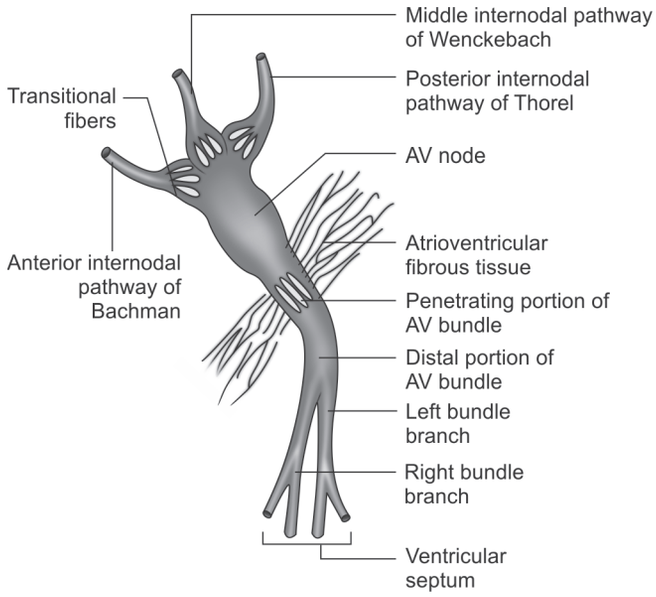


**Fig. 4.9:** Organization of atrioventricular node

nodal fibers connect directly with atrial muscle fibers, so that AP from the SA node immediately spreads to atrial wall. The SA node contains small round cells called P cells/ pacemaker cells.

The action potential is largely due to $Ca^{2+}$ with no contribution from $Na^{+}$ influx. Prepotential is most prominent in the SA node. Even though all parts of the conducting system can generate impulses, the rate of rhythmical discharge is faster than that of any other part of heart (70-80/min). The generated impulse spreads downwards and activates other parts of the heart. So depolarization of other parts of the conducting system occur before they discharge spontaneously and hence SA node is the pacemaker of normal heart.

### *Internodal Atrial Pathways*

The ends of sinus nodal fibers connect directly with surrounding atrial fibers. But conduction is more rapid in some bands of atrial fibers. These bands of fibers are called internodal atrial pathways. There are three bundles of atrial fibers:

1. Anterior internodal tract of Bachman
2. Middle internodal tract of Wenckebach
3. Postinternodal tract of Thorel

The rapidity of conduction is because they contain a specialized fast conducting fibers of Purkinje type.

### *Atrioventricular Node*

Atrioventricular node (AV node) is located in the right posterior portion of the interatrial septum. It is the only conducting pathway between atria and ventricles. This is because atrial muscle fibers are separated from the ventricular muscles by fibrous tissue ring (annuli fibrosii).

Atrioventricular node also contains P cells but fewer in number than SA node, so rate of impulse production is also less (40–60/min). Sometimes AV node can generate impulse when SA node is out of order or if the conduction from SA node is blocked. Other parts of the heart can generate this rhythm and they are called ectopic foci.

### *Atrioventricular Nodal Delay*

On reaching AV node, the speed of impulse is slowed down and then it is transferred to the bundle of His. Thus transmission of impulse suffers a delay of about 0. 1 sec called AV nodal delay.

This is important because :

- Atria gets enough time to empty blood into ventricles.
- Efficiency of ventricular pumping is increased.
- It prevents entry of too rapid impulses from atria into the ventricles.

***Causes***

- Number of gap junctions is less between successive cells, so the velocity of conduction is decreased.
- Presence of multiple branching system in AV node.
- Cells of AV node are made up of small diameter fibers in which velocity of conduction is less.

### *Bundle of His (AV Bundle)*

Atrioventricular node is continuous with bundle of His. Bundle of His originates from ventricular surface of AV node and runs along the right border of interventricular septum. It runs for a short distance and soon gives off a left bundle branch (at the top of interventricular septum) and continues as right bundle branch. The left bundle branch divides into an anterior fascicle and a posterior fascicle. All the branches run subendocardially on either side of septum. A special feature of AV bundle is one way conduction of impulse (except in abnormal states).

### *Purkinje System*

It is an extensive network formed of the Purkinje cells present subendocardially, which transfer impulse to working myocardial cells. They are fast conducting, very large fibers with extensive gap junction. So the cardiac impulse is instantaneously transmitted to entire ventricular musculature. The ends of the Purkinje fibers penetrate into the muscle mass and finally become continuous with cardiac muscle fibers.

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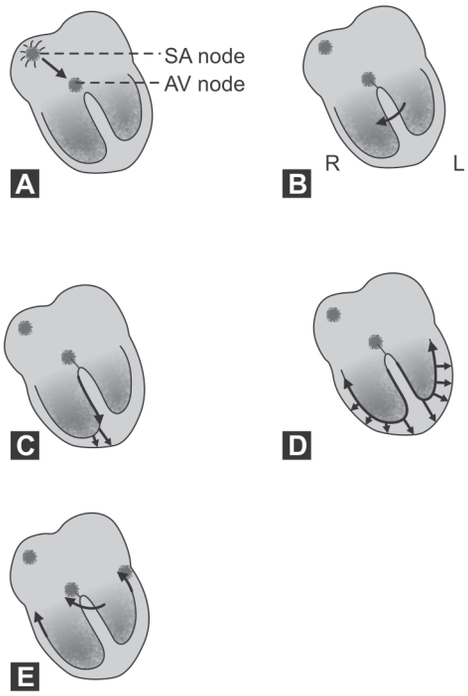
| Table 4.1: Conduction speeds in cardiac tissue | |
|---|---|
| *Tissue* | *Conduction rate (m/sec)* |
| SA node | 0.05 |
| Atrial pathways | 1 |
| AV node | 0.05 |
| Bundle of His | 1 |
| Purkinje system | 4 |
| Ventricular muscle | 1 |

The conduction speeds in cardiac tissues are given in Table 4.1.

### *Spread of Electrical Activity (Figs 4.10A to E)*

- Depolarization initiated in the SA node spreads radially through the atria. It then converges on the AV node. Atrial depolarization is completed in 0.1 sec.
- Conduction of AV node is slow and so there is a delay of 0.1 sec called AV nodal delay.
- From the top of the septum, wave of depolarization spreads in the rapidly conducting Purkinje fibers to all parts of ventricle in 0.08-0.1 sec. It then spreads down the septum to the apex of heart. The wave then returns along ventricular walls to the AV groove (proceeds from endocardial to epicardial surface).




**Figs 4.10A to E:** Normal spread of electrical activity in the heart: (A) Atrial activation; (B) Septal activation from left to right; (C) Activation of anteroseptal region of the ventricular myocardium; (D) Activation of major portion of ventricular myocardium from endocardial surfaces; (E) Late activation of posterobasal portion of the left ventricle and the pulmonary conus

- The last parts of the heart to be depolarized are the posterobasal portion of the left ventricle, pulmonary conus and uppermost portion of septum.
- After complete activation of the whole heart the myocardium remains depolarized for sometime and repolarization starts. Repolarization begins at the apex of the heart and then proceeds towards the atrioventricular groove and ultimately the whole heart is repolarized. Repolarization takes place from epicardium to endocardium.

## Contractility

It is ability of the tissue to shorten in length (contraction) after receiving a stimulus. Isometric as well as isotonic contraction are seen in the heart.

***Factors that influence contractility*** (Table 4.2).

| Table 4.2: Factors that influence contractility | |
|---|---|
| *Increased contractility* | *Decreased contractility* |
| Sympathetic stimulation | Parasympathetic stimulation |
| Increased $Ca^{2+}$ | Hypercapnia |
| Xanthine | Quinidine, barbiturates |
| Glucagon | Myocardial damage |
| Thyroid hormones | Acidosis |

### $V_{max}$

Velocity of contraction is maximum when after load is zero. The maximum velocity which will develop when after load is zero is called $V_{max}$ (Fig. 4.11). It is increased when contractility is increased and is reduced when contractility is decreased. It is not changed when the initial length of muscle fiber is changed.

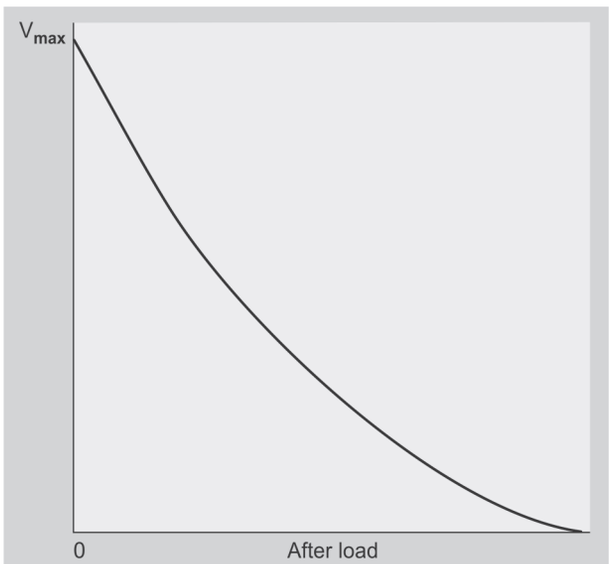



**Fig. 4.11:** Force velocity relationship



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***Note***

1. *Preload:* Degree to which myocardium is stretched before it contracts and it is equal to End-diastolic volume (EDV). Here the load acts before the muscle starts contracting.
2. *After load:* Resistance against which blood is expelled from the heart. Here the load acts on the muscle after it has started contracting.

### *Extrasystole and Postextrasystolic Potentiation*

- In a regularly beating heart if an extra stimulus is delivered so that it falls earlier than the usual timing, but after the refractory period then the heart responds to this stimulus by a weak extra contraction called extra systole.
- Now the next regular impulse comes but it finds the heart refractory due to extrasystole, so there is no contraction and the gap produced is called compensatory pause.
- The subsequent regular impulse comes and the heart responds to it stronger than normal contraction due to postextrasystolic potentiation. The cause for this postextrasystolic is increased availability of intracellular $Ca^{2+}$.

## Refractory Period

It is period in which the muscle does not show any response to a stimulus. Normal refractory period of ventricles is 250–300 msec and that of atria is 150 msec. Refractory period is of two types–absolute and relative (Fig. 4.12).

### *Absolute Refractory Period (180–200 msec)*

Absolute refractory period is the period during which the muscle does not show any response at all, whatever may be the strength of the stimuli. During phases 0–2 and about half of phase 3 cardiac muscle is in its absolute refractory period.

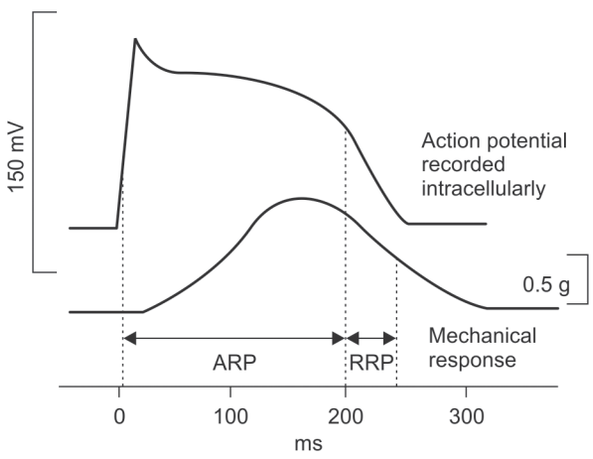



**Fig. 4.12:** Mechanical events in contractality (ARP: Absolute refractory period, RRP: Relative refractory period)

### *Relative Refractory Period (50 msec)*

The relative refractory period is the period during which muscle shows response, if the strength of the stimulus is increased to maximum. It remains relatively refractory until phase 4.

### *Significance*

Since absolute refractory period extends throughout contraction period, the following cannot be produced in cardiac muscle (1) Summation of contractions (2) Tetanus (3) Fatigue.

## Frank-Starling Law

This law states that, the force of contraction of the heart is directly proportional to the initial length of cardiac muscle fiber within physiological limits. Initial length of the muscle fiber = length of the fiber at the end of diastole = end diastolic fiber length. It may also be expressed as end-diastolic blood volume. When the ventricle is in early diastole, it is more compliant. (it is more distensible). The blood at this stage, enters the ventricle, but the tension (this is called passive tension) of the ventricle (intraventricular pressure) does not rise appreciably. Only when the ventricle is reasonably filled, from then, the passive tension (intraventricular pressure) begins to rise steeply. The developed tension (Fig. 4.13) increases as the diastolic volume increases until it reaches a maximum (ascending limb of Starlings curve), then tends to decrease (descending limb of Starling curve). The descending limb in human heart is seen only when cardiac muscles are ruptured. This law has an important role in the regulation of stroke volume and hence cardiac output.

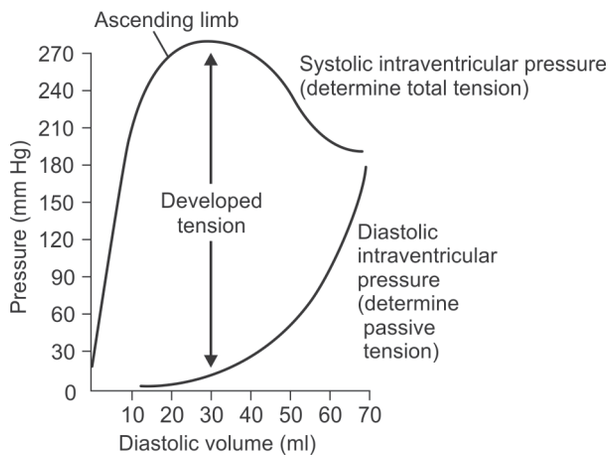



**Fig. 4.13:** Length-tension relationship in cardiac muscle

### *Factors Affecting End-diastolic Volume (Table 4.3)*

**Table 4.3: Factors affecting end-diastolic volume**

| *Factors increasing EDV* | | *Factors decreasing EDV* |
|---|---|---|
| Increased pumping action of skeletal muscle | | Sitting and standing posture |
| Increased blood volume | Myocardial stretching (EDV) | Decreased total blood volume |
| Sympathetic discharge | | Decreased ventricular compliance |
| Decreased intrathoracic pressure | | Increased venous resistance (Pericardial effusion) Increased intrathoracic pressure |

### *Physiological Significance*

1. The law explains why blood ejected by each of the ventricle per heart beat is same. If RV output is more than the left, blood accumulates in the left side leading to greater force of contraction of left ventricle, thus increasing LV output.
2. It serves as a life saving device in cardiac failure. LV failure causes accumulation of blood in the LV, thereby decreases blood supply to vital organs. Soon accumulation of blood in the LV increases the initial length of muscle fibers leading greater cardiac output according to Frank-Starling mechanism. If accumulation of blood exceeds physiological limit, the law fail to operate leading to death.
3. When the peripheral resistance is increased, initially the heart is unable to pump all the blood it normally does. The accumulated blood in the ventricle stretches the muscle fibers leading to greater of contraction and thus stroke volume is restored to normal in spite of greater resistance to the flow.

## CARDIAC CYCLE

Cardiac events that occur from the beginning of one heart beat to the beginning of next are called cardiac cycle. Each cycle is initiated by spontaneous generation of action potential in SA node. The orderly depolarization triggers a wave of contraction and relaxation. With an average heart rate of 75/min, duration of one cycle will be 0.8 seconds (Fig. 4.14). Cardiac cycle include electrical as well as mechanical event. Electrical events are followed by mechanical events.

*The mechanical events are:*

- Pressure changes in atria are ventricles.
- Pressure changes in aorta, pulmonary artery are jugular vein.

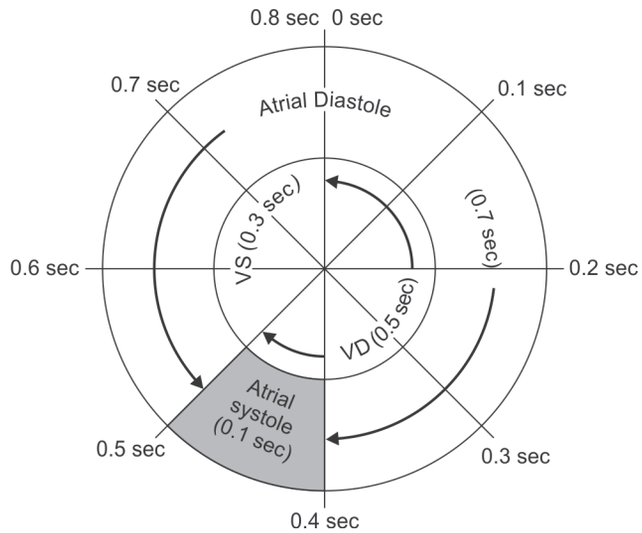



**Fig. 4.14:** Atrial and ventricular events of cardiac cycle

- Volume changes in atria are ventricles.
- Movements of heart and production of heart sounds.

### Phases of Cardiac Cycle

1. Atrial systole (0.1 sec)
2. Ventricular systole (0.3 sec)
3. Ventricular diastole (0.5 sec)
4. Atrial diastole (0.7 sec)

### *Atrial Systole*

Atrial systole can be taken as the initial phase of cardiac cycle. Before atrial contraction, AV valves are open, semilunar valves are closed and blood flows continuously from great veins to atria and from atria to ventricles. seventy percent of ventricular filling occurs before atrial contraction. Atrial systole contributes only 30% of ventricular filling. Atria simply acts as booster pumps that increase the effectiveness of ventricular filling Atrial systole causes an elevation of atrial pressure which is recorded as 'a' wave in atrial pressure tracing. Here there is some regurgitation of blood into the great veins which is minimized by constriction of vena cava during contractrion of atrial muscles. Atrial systole starts after 'P' wave in ECG.

### *Ventricular Systole*

Atrial systole is followed immediately by ventricular systole. It is divided into three phases:

1. **Isovolumetric (Isometric) ventricular contraction (0.05 sec) [ICP]**
   - After the onset of ventricular contraction, the pressure in the ventricle rises abruptly. This causes increase in

ventricular pressure above atrial pressure which causes closure of AV valve thereby the first heart sound.

- The semilunar valves are already closed so the ventricle is a closed chamber now. Ventricular muscles are contracting, but there is no change in the length of muscle fiber (isometric contraction). There is no change in volume also, so this phase is called isovolumetric contraction phase. During this phase, there is sharp rise in intraventricular pressure.
- The AV valves bulge into atria which causes a slight increase in atrial pressure and this recorded as 'c' wave in atrial pressure tracing. The intraventricular pressure rises sharply and when it exceeds aortic and pulmonary arterial pressure semilunar valves open.

**2. Maximum (rapid) ejection phase (0. 1 sec) (MEP)**

- When the semilunar valves are open, initially the pressure gradient is more and the blood enters rapidly into the aorta and pulmonary artery, so this phase is called rapid ejection phase. Although the duration of rapid ejection phase is less, seventy percent of ejection occurs during this. Aortic pulmonary arterial pressure increases as the blood enters them. There is marked reduction in ventricular volume.

**3. Reduced/slow ejection phase (0. 15 sec) (REP)**

- Thirty percent of ventricular ejection occurs during this phase. Ventricular pressure begins to fall are when it becomes less than aortic and pulmonary arterial pressure, momentum keeps blood flow for sometime ventricular volume continues to fall.

### *Ventricular Diastole*

*It includes four phases:*

**1. Protodiastole phase (0.04 sec) (PDP)**

- Ventricle starts relaxing, ventricular pressure reduces rapidly below aortic and pulmonary arterial pressure. When the momentum of flowing blood is overcome, semilunar valves close. So protodiastole is the short interval between ventricular diastole and closure of semilunar valves. The closure of valves is sharp and this leads to rebound of blood column, which is represented as a sharp deflection called incisura in aortic pressure tracing.

**2. Isovolumetric relaxation phase (0. 06 sec) (IRP)**

- It starts from closure of semilunar valves. AV valves are already closed and ventricle is again a closed chamber. As there is no change in volume it is called isovolumetric relaxation. There is sudden reduction in pressure and when it becomes less than that of atrial pressure, AV valves open. As AV valves open there is rapid entry of blood into ventricles and it marks the end of isovolumetric relaxation.

**3. Ventricular diastole proper (0.3 sec)**

i. *First rapid filling phase (0.1 sec) (Ist RFP)*
   - As AV valves open, blood flows rapidly into ventricles. It is due to more pressure gradient and ventricular volume increases. Atrial pressure will decrease, but it is still higher than ventricular pressure (results in the production of 3rd heart sound).

ii. *Reduced filling phase/Diastasis (0.2 sec)*
   - Ventricular inflow velocity decreases, volume increases gradually. Blood flows into the atria through superior vena cava and inferior vena cava and pulmonary veins. From atria blood flows into the ventricles, all these act as a single chamber.

**4. Last rapid filling phase (0.10 sec) (IInd RFP)**

- It corresponds to atrial systole. Due to atrial contraction, velocity of flow into ventricles again increases. Thirty percent of ventricular filling is contributed by atrial contraction (this coincide with 4th heart sound).

### Pressure Changes in Atria (Right Atrial/Left Atrial/JVP)

Atrial pressure changes (Fig. 4.15) can be studied by pressure changes in the internal jugular vein, which is similar to atrial pressure tracing as it is a retrograde transmission of atrial pressure changes.

Atrial pressure rises during atrial systole and continue to rise during isovolumetric ventricular contraction when AV valve bulges into atria. When AV valves are pulled down by contrating ventricles during ejection phase, atrial pressure falls rapidly. The pressure then rises, until AV valves are again open. Then pressure in atria decreases. Atrial pressure changes are transmitted to great veins, producing three positive (a, c, v) and two negative waves (x,y).

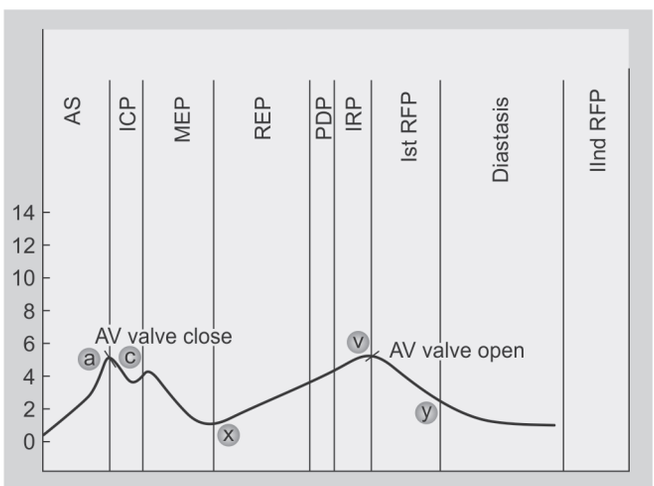



**Fig. 4.15:** Intra-atrial pressure changes during cardiac cycle/jugular venous pulse

### *'a' Wave*

- It is due to atrial systole. Pressure in the jugular vein also increases as some blood regurgitates during atrial systole.
- In addition, venous inflow stops and the resultant rise in venous pressure contributes to a wave.

### *'c' Wave*

It is manifested due to rise in atrial pressure produced by the bulging of AV valve into atria during isovolumetric contraction.

### *'x' Wave*

- It is the 1st negative wave.
- Due to downward movement of AV ring during ejection.

### *'v' Wave*

It is due to passive increase in pressure due to venous return.

### *'y' Wave*

Due to emptying of atria as AV valve opens.

### *Jugular Venous Pulsation*

Jugular venous pulsations is different from arterial pulsation in neck by following ways:

1. Jugular venous pulsations is less sharp and less palpable and the pulsations 'c' and 'v' can be made out.
2. There is slight change in JVP during respiratory cycle, but no such changes for arterial pulsation.
3. Jugular venous pulsations can be abolished by slight pressure at the root of the neck.
4. If pressure is applied in the abdomen the level of JVP rises.
5. Jugular venous pulsations is better seen than felt.

### *Abnormalities of JVP*

1. Elevated in congestive heart failure.
2. Large 'a' wave is got when there is abnormal resistance to atrial contraction also when there is narrowing (stenosis) of AV valves.
3. Giant 'a' wave/Canon wave occurs when there is atrioventricular dissociation. Here atria contracts against closed ventricle and the condition is complete heart block.
4. Giant 'c' wave is seen in tricuspid insufficiency.

## Pressure Changes in Ventricles

### *Left Ventricular Pressure Changes (Fig. 4.16)*

- A small rise in pressure (up to 10 mm Hg) is seen in the ventricle during atrial systole (AS).
- At the end of AS, pressure decreases to 2–3 mm Hg.

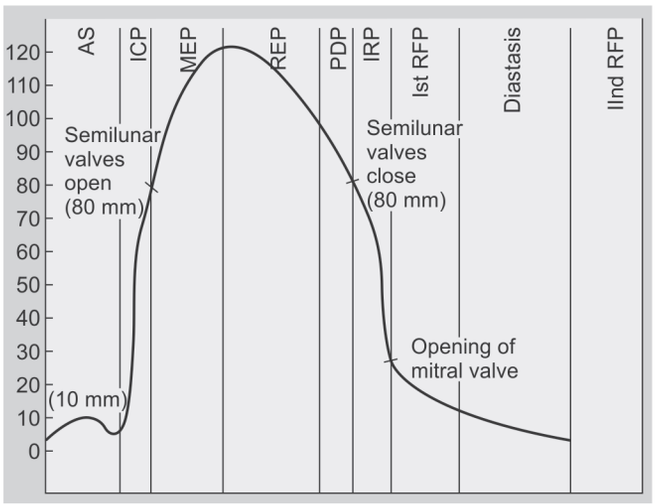



**Fig. 4.16:** Left ventricular pressure changes

- In the ICP the pressure increases (80 mm Hg) and towards the end of this phase the semilunar valve opens. Further contraction is isotonic and the pressure reaches a maximum of 120–130 mm Hg.
- In the REP pressure starts decreasing, but it is higher than aortic pressure.
- In the PDP pressure again decreases and becomes less than aortic pressure resulting in closure of semilunar valves.
- In IRP there is a rapid fall in pressure. At the end of this phase pressure becomes less than that of atria, resulting in opening of AV valves.
- In the later stages, pressure falls to base line (1–3 mm Hg).

### *Right Ventricular Pressure Changes*

- When compared to LV pressure changes, RV pressure is less in the different phases of cardiac cycle.
- In the ICP, the pressure in the RV is 10 mm Hg and in the MEP the pressure attained is 20–25 mm Hg.

## Pressure Changes in Aorta (Fig. 4.17)

- Since pumping of blood by ventricle is intermittent, the aortic pressure fluctuates between systolic pressure of 120 mm Hg and diastolic pressure of 80 mm Hg.
- During AS and ICP there is no change in aortic pressure.
- In MEP blood is ejected into the aorta and the wall of aorta stretches due to elasticity. Aortic pressure reaches a peak of 120 mm Hg.
- In the REP amount of blood ejected into aorta becomes lesser and lesser. The peripheral run off into the smaller vessels become more and the aortic pressure starts to fall.

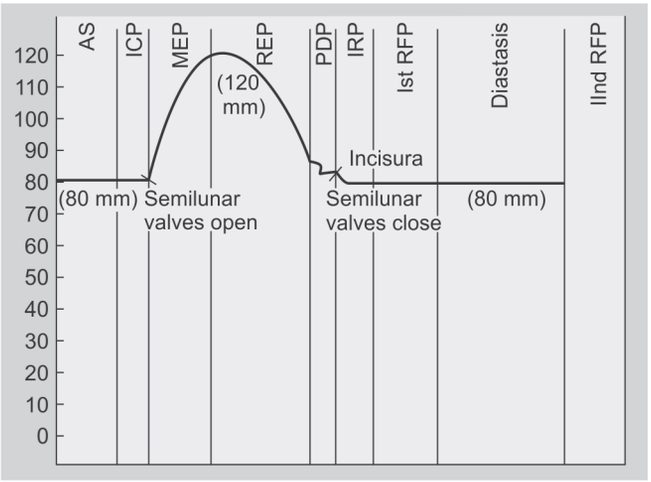



**Fig. 4.17:** Pressure changes in aorta

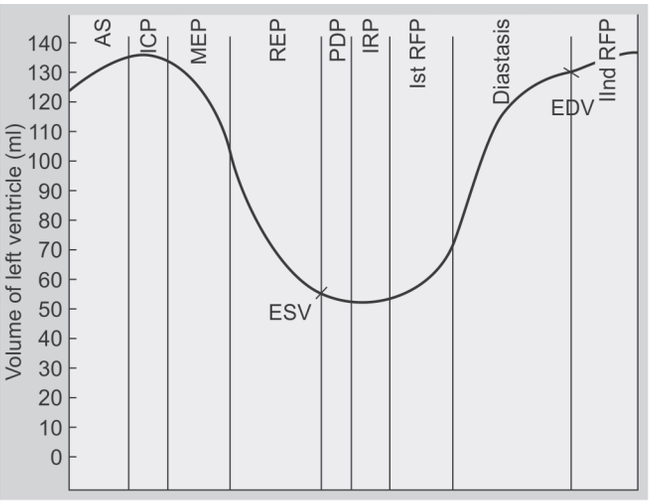



**Fig. 4.18:** Volume changes in ventricles

- During PDP ventricular pressure becomes less than that of aortic pressure. So there is a tendency of blood to flow back into left ventricle marked by a depression incisura. At the end of this phase semilunar valves close.
- Closure of semilunar valve (forming dicortic nocth) causes a momentary increase in aortic pressure and the blood strikes against semilunar valve causing vibrations in the blood column called after vibrations in the recording. This occurs in IRP.
- The aortic pressure falls through out the ventricular diastolic phase. Due to elastic recoil of vessels the pressure will not fall beyond 80 mm Hg.

### Pressure Changes in Pulmonary Artery

Pressure changes are similar to aorta except that the pressure value is less. Maximum is 25 mm Hg and minimum is 10 mm Hg.

### Volume Changes in Ventricles (Fig. 4.18)

- During atrial systole the ventricular volume increases.
- During ICP there is no change in the volume since all the valves are closed.
- During MEP, volume decreases rapidly.
- During REP, decrease in volume is less.
- During IRP there is no change in volume.
- Rapid increase in volume occurs during RFP and a slow rise during diastasis.
- The rest of the filling is during AS.
- The amount of blood in the ventricle at the end of each diastole is called EDV (end diastolic volume) and is approximately 120–130 ml/each ventricle.

## ARTERIAL PULSE

As blood is forced into aorta during systole it sets up a pressure wave that travels along the artery with expansion of arterial wall and the expansion is palpable as a pulse. The rate at which the wave travels is 4 m/s in aorta, 8 m/s in small arteries and 16 m/s in arterioles. Pulse is felt in the radial artery at the wrist about 0.1 sec after the peak of systolic ejection into the aorta.

Arterial pulse can be measured by a sphygmograph and pulse recording is called sphygmogram. The normal pulse is called catacrotic pulse.

Arterial pulse tracing (Fig. 4.19) shows a sharp ascending limb (upstroke) – anacrotic limb and a slower downstroke – catacrotic limb with a dicrotic notch. Dicrotic notch is caused by vibrations set up when the aortic valve closes suddenly at the end of systole.

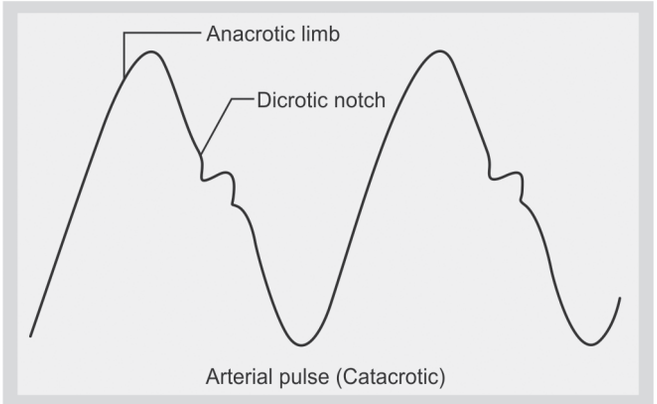



**Fig. 4.19:** Radial pulse tracing

While examining pulse, the rate, rhythm, volume, character, condition of vessel wall, radiofemoral delay, other peripheral pulses, pulse deficit are observed. Arterial pulsation can be also felt in facial artery, common carotid artery, axillary artery, brachial artery, femoral artery popliteal artery, posterior tibial artery and dorsalis pedis artery.

### Types of Pulse

1. **Collapsing/Water hammer pulse:** This is seen in aortic insufficiency. Here there is rapid upstroke and rapid downstroke without dicrotic notch. For example, aortic regurgitation.
2. **Slow rising/hypokinetic/small volume pulse:** Here the volume ejected will be less. For example, aortic stenosis.
3. **Pulsus alternans:** Here there will be alternate small and large volume pulse. For example, left ventricular failure.
4. **Bisferiens pulse:** It is a combination of slow rising and collapsing pulse. For example, aortic stenosis with aortic regurgitation.

## HEART SOUNDS

When the valves open, no audible sounds are produced. Sounds are produced when the valves close. Two heart sounds are heard normally through a stethoscope. Closure of valves lead to vibration of valves, which causes vibration of adjacent column of blood and wall of heart which in turn is transmitted to chest wall.

### *First Heart Sound (0.15 sec)*

It is produced due to closure of AV valves. It has two components–mitral and tricuspid.

It marks the beginning of ventricular systole. When the ventricles contract, the intraventricular pressure increases and becomes more than the atrial pressure. This will lead to AV valve closure.

***Features***

- Low pitched, soft (valves are thin and filmy)
- Prolonged lub sound
- Frequency : 25–45 Hz
- Heard in mitral and tricuspid area.

### *Second Heart Sound (0.12 sec)*

It is produced due to closure of semilunar valves. It has two components–aortic and pulmonary.

***Features***

- Short, high pitched
- Dup sound
- Frequency–50 Hz (high frequency is due to greater elasticity of semilunar valves)
- Heard over aortic and pulmonary areas.

In some persons second sound may be split due to asynchronous closure of aortic and pulmonary valves. Usually aortic valve closes first because of lower pressure in pulmonary artery and lower ejection time and split is wide during inspiration. During inspiration venous return increases due to more –ve intrathoracic pressure. So stroke volume of right ventricle increases and duration of right ventricular systole prolongs.

### *Third Heart Sound (0.1 sec)*

It is produced due to rapid filling of ventricles. It can be occasionally seen in young adult.

***Features***

Soft, low pitched.

### *Fourth Heart Sound*

Not heard normally and is heard best with the bell piece of stethoscope. It is heard just before 1st heart sound. It is produced due to rapid ventricular filling due to atrial contraction and occurs when atrial pressure is high.

### Murmurs and Bruits

Murmurs are abnormal sounds heard over the heart and produced due to turbulence created at or near a valve or due to abnormal communication within the heart or between great vessels.

The major cause of cardiac murmur are diseases of heart valves. Bruits are abnormal sounds heard over vessels.

Normally the flow is streamline or laminar which is silent. When the flow exceeds a critical velocity the flow become turbulent and produce sound. When a valve is narrowed/stenosed, velocity of flow increases and the flow becomes turbulent. When a valve is incompetent, blood flows backward through this incompetent valve which is called regurgitation or insufficiency.

## ECG

The electrical activities of myocardium is graphically recorded using surface electrodes. The biphasic recording thus obtained is called as electrocardiogram. It is possible because body acts as a volume conductor. Procedure is called electrocardiography and the equipment is called electrocardiograph (invented by William Einthoven). ECG provides useful information about: (a) heart rate (b) cardiac rhythm (c) cardiac hypertrophy (d) conduction abnormalities (e) ischemia and infarction (f) electrolyte changes.

### *Volume Conductor*

The electrical activities of heart can be recorded from electrodes placed on various specific site, distant from the heart. Electrolytes present in the body fluids aids the conduction of electrical activity so body acts as a volume conductor.

### *Spread of Cardiac Impulse*

Refer page number 61.

### *Dipole and Vector*

The wave of depolarization travels in a particular direction. The outer surface of depolarized part is –ve, while the outer surface of part yet to be depolarized is +ve, thus a dipole is created. The dipole has a particular direction (–ve to +ve) and a particular magnitude. The magnitude and direction of dipole can be expressed by a vector known as dipole vector.

Heart is a functional syncitium, many small dipoles form in a particular direction. The sum of all of them is called the resultant of dipole. The resultant of dipole changes in direction and magnitude from moment to moment. Summated resultant vectors over a period of time are taken into account and these are called average vector. ECG is analyzed on the basis of number of average vectors during the passage of cardiac impulse. As the wave of depolarization spreads along the heart the following average vectors (Fig. 4.20) appears sequently.

1. The vector of atrial depolarization is directed downwards and to the left.
2. The ventricle has four main vectors.
   i. First ventricular vector (due to ventricular depolarization). It is directed obliquely downwards from left to right (as the left wall of interventricular septum is depolarized first and the wave of depolarization passes across the septum from left to right).
   ii. Second ventricular vector (due to the passage of cardiac impulse towards apex). It is directed downwards.
   iii. Third ventricular vector (due to depolarization of left ventricle). It is directed downwards and to the left because wave of depolarization proceeds from subendocardium to epicardium. It is largest because left ventricle has the largest muscle mass.
   iv. Fourth ventricular vector (due to depolarization of the bases). It is directed upwards towards the base and small in size.

**Fig. 4.20:** Shaded areas of the ventricles are depolarized. Nonshaded areas are still polarized

The resultant of all the four vectors is called mean electrical axis of heart. Normally, it is directed downwards and to the left and makes an angle of about 59° with the horizontal (angle may vary between –30 and +110).

Ventricular repolarization takes place from epicardium to endocardium. So T wave caused by ventricular repolarization is upright.

### *ECG Paper*

ECG is recorded on a mm square graph paper, moving at a speed of 25 mm/sec. It is divided into 1 mm square by thin lines. Every 5th line is thick both horizontally and vertically.

Vertical lines are time calibration lines, 1 mm = 0.04 sec on X axis. So time duration between two thick lines is 0.2 sec. Vertical amplitude of a wave is measured in mm, so a deflection of 10 mm represents 1 mV.

## ECG Leads

*There are 12 leads in the ECG:*

1. Bipolar limb leads/Standard limb leads: Lead I, Lead II, Lead III.
2. Augmented unipolar leads: aVR, aVL, aVF.
3. Unipolar chest leads: V1 to V6.

### *Bipolar Limb Leads*

When both the electrodes of a lead are active and a potential difference between them is recorded, the lead is then called bipolar lead. Each bipolar lead has one +ve and one –ve electrode.

When the vector is directed towards +ve electrode, positive/upward deflection is obtained and vice versa.

Einthoven selected three points in the body:

1. Left shoulder
2. Right shoulder
3. Left midinguinal point.

When the above points are joined together an equilateral triangle is obtained. Heart is assumed to be in its center and this triangle is called *Einthoven's triangle*. The positions of +ve and –ve electrodes of the bipolar leads are shown in the (Fig. 4.21).

If the electrical potential at left arm, right arm and left leg are designated as VL, VR, VF respectively, voltage recorded in:

LI = VL – VR

LII = VF – VR

LIII = VF – VL

LI + LII+ LIII = VL – VR+ VF – VR+ VF – VL ≠ 0

It would have been 0 if right arm is +ve and left foot is –ve. Einthoven deliberately changed the polarity of Lead II, in order to get upward deflection in all the three leads.

Then LII = VR – VF.

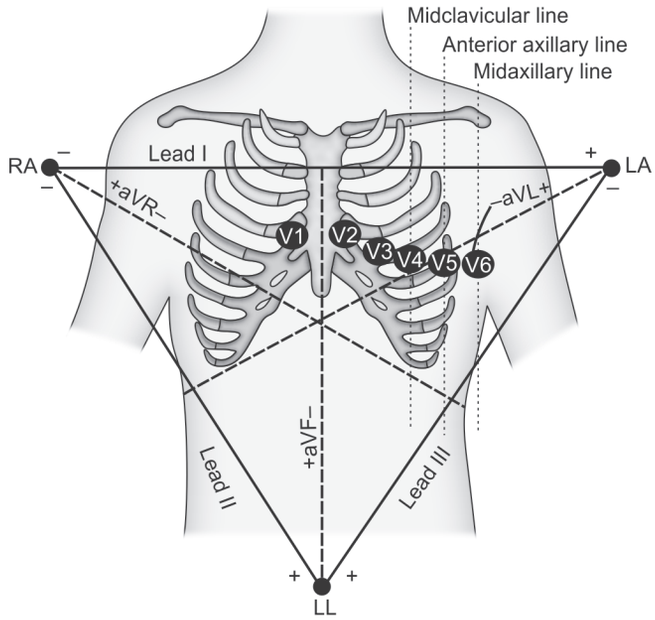



**Fig. 4.21:** Einthoven's triangle, position of various leads

Now, VL – VR + VR – VF + VF – VL = 0
i.e. LI + LIII – LII = 0 (LI + LIII= LII)

At any given instant (moment), the sum of potentials in Lead I and Lead III equals the potential in lead II. This is called ***Einthoven's Law.*** So the maximum amplitude is obtained in LII.

## *Unipolar Leads*

Unlike bipolar leads, unipolar lead has only one active electrode called exploring electrode. Other electrode is kept at zero potential and is called as indifferent electrode. So unipolar leads records the absolute electrical potential under the exploring electrode.

Depending on whether the lead is placed on the chest or the limbs, unipolar leads are classified as unipolar limb leads and unipolar chest leads.

### *Unipolar Limb Lead*

An electrode is placed on the distal part of any limb (Rt arm, Lt arm, Lt foot) and the other electrode should be at zero potential. Indifferent electrode is designated as V. So the leads are designated as VL, VR, VF. Indifferent electrode is made by connecting the 3 limbs (Rt arm, Lt arm, Lt foot) through a high resistance of 5000 Ohm to a common terminal called Wilson's terminal.

These unipolar limb leads gives waves of very small amplitude, so these leads were augmented by removing the contribution of the respective limb to the central terminal

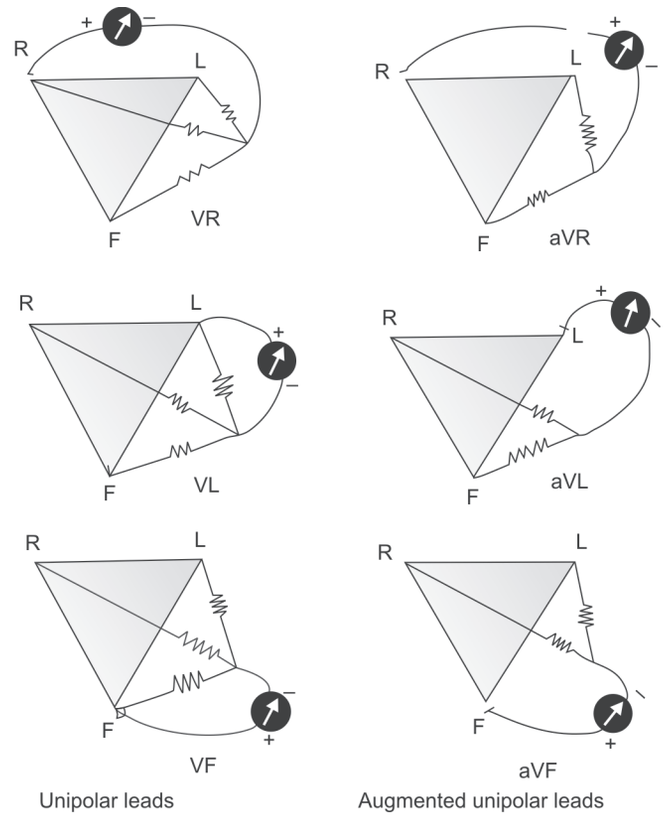



**Fig. 4.22:** Augmentation of leads

(Fig. 4.22). This arrangement has increased amplitudes of the waves (aVR = 3/2 VR) and these are called as augmented limb leads. The augmented limb leads are aVR, aVL, aVF.

### *Unipolar Chest Leads*

These are named as V1, V2, V3, V4, V5, V6. The position of exploring electrodes (Fig. 4.21) of the various chest leads are as follows :

| | |
|---|---|
| V1 | Right 4th intercostal space (ICS) near the sternal border |
| V2 | Left 4th ICS near the sternal border |
| V3 | In the midpoint between V2 and V4 |
| V4 | Left 5th ICS on the midclavicular line |
| V5 | Left 5th ICS on the anterior axillary line |
| V6 | Left 5th ICS on the mid axillary line |

***Wilson central terminal***

According to Kirchoff's law VR + VF + VL = 0. But it is not exactly zero as.

- Triangle is not exactly equilateral.
- Heart is not exactly at the center.

To tide over this problem three resistance of 5000 Ohm is connected to electrode placed at three apical points and they

were connected to a common terminal called Wilson's central terminal. It funtions as zero potential indifferent electrode used in unipolar leads.

## Normal ECG

The waves associated with the electrical activity of the various parts of the heart tissue during each cardiac cycle are represented by letters P, Q, R, S, T, and U (Fig. 4.23).

### *P Wave*

- It is due to atrial depolarization.
- It represents the spread of impulse from SA node to atrial muscles.
- *Normal duration:* Less than 0.1 sec.
- *Normal amplitude:* Less than 0.5 mV (represents the functional activity of atrial muscles).
- Abnormal P waves are seen in atrial hypertrophy, hyperkalemia, etc.
- Saw tooth pattern of P wave are seen in atrial flutter.

### *P-R Segment*

Following the P wave, there is a brief isoelectric segment of 0.04 sec due to AV nodal delay.

### *QRS Complex*

- It is due to ventricular depolarization
- *Normal duration:* 0.08–0.10 sec
- *Normal amplitude:* 1–1.5 mV
- It is a complex wave as it consist of an initial downward deflection – Q wave, an upward deflection – R wave and a downward deflection - S wave.

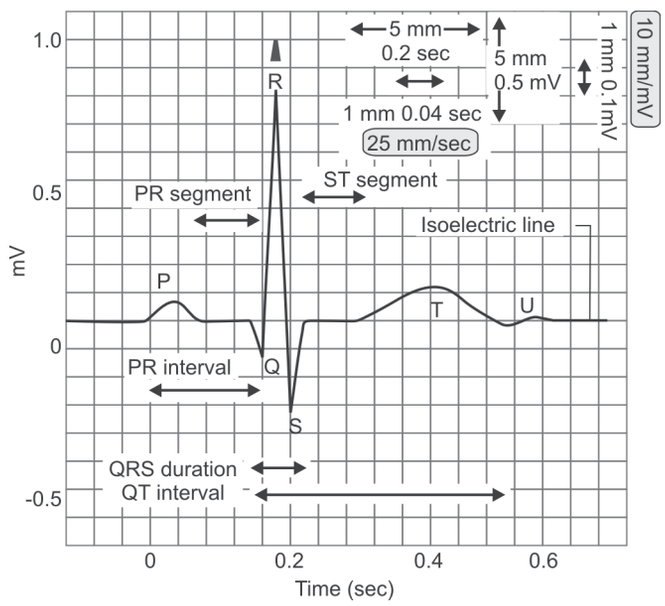



**Fig. 4.23:** Normal electrocardiogram; (lead II)

### *Q Wave*

- It is the 1st wave of ventricular depolarization, which is always –ve.
- It is due to depolarization of interventricular septum from left to right.

### *R Wave*

It is the 1st +ve wave of QRS complex. It is the main wave of ventricular depolarization and the tip of R wave is sharp and pointed.

### *S Wave*

It is the –ve wave that follows R wave and ends at J point also marks the termination of QRS complex.

### *S-T Segment*

- Following QRS complex there is a long isoelectrical segment.
- It represents the duration from end of ventricular depolarization to beginning of ventricular repolarization and its duration is 0.32 sec.
- In ventricular hypertrophy QRS amplitude increases.
- In MI, ST segment is elevated in leads overlying the area of infarct and ST segment is depressed in the reciprocal leads.

### *J Point*

Junction between end of S wave and beginning of ST segment.

### *T Wave*

- It is an upward deflection due to ventricular repolarization.
- Duration of T wave is longer as repolarization of ventricles takes longer time.

### *U Wave*

- Rarely we get U wave after normal ECG.
- It denotes delayed repolarization of papillary muscle.

### *PR Interval*

- It is the interval between beginning of P wave to the beginning of QRS complex.
- So this includes P wave and PR segment.
- Its normal duration is 0.12–0.2 sec.
- It indicates atrial depolarization and AV nodal delay.
- When Q wave is absent, it may be termed as PR interval and when Q wave is present it is termed as PQ interval.
- P-R interval is prolonged in heart block and hypokalemia.
- P-R interval is decreased in WPW syndrome and LGL syndrome.

### *QT Interval*

- It is the interval between beginning of QRS complex and the end of T wave.
- This includes QRS complex, ST segment and T wave.
- This denotes the time taken for ventricular depolarization and repolarization.
- Normal duration is 0.35–0.43 sec.

### *ST Interval*

- It denotes the duration between end of S wave and end of T wave.
- ST interval = ST segment + T wave.

### ***Pattern of ECG in Other Leads***

The pattern is same in LI, LII and LIII, but the amplitude is maximum in LII. In aVR – P, R, T waves are found to be inverted. This is because the depolarization curve is moving away from exploring electrode. In V1, small R and deep S wave is seen but as electrode position is changed from V1 to V5, height of R increases, but the depth of S decreases from V1 to V5. In V5 and V6 R wave is more prominent (Fig. 4.24).

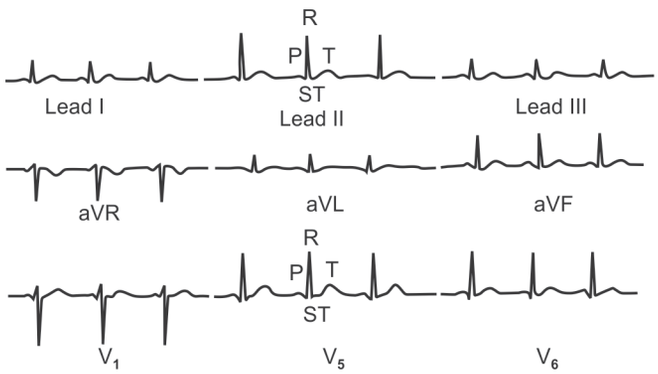



**Fig. 4.24:** Pattern of ECG in other leads

## Examination of ECG

Heart rate =

$$\frac{1500}{\text{No. of small squares between two R waves}}$$

or

$$\frac{300}{\text{No. of big squares between two R waves}}$$

Rhythm can be assessed in the ECG by comparing length of R-R interval.

## HEART BLOCK

Defined as the disturbance in the normal transmission of impulses generated in SAN. Normal P-R interval is 0.12 sec, when it exceeds 0.20 sec the condition is called heart block.

### *Causes*

i. MI
ii. Inflammation
iii. Excessive vagal stimulation.

### Types

#### *Sinoatrial Nodal Block*

Here the level of block is within the substance of SAN. After an interval of approximately two cardiac cycle the heart resumes its normal action as some new pacemaker other than SAN takes over (Fig. 4.25). The impulse originate spontaneously in the AV node. Rate of QRS - T complex is altered.

#### *AV Nodal Block*

Here there is disturbance of conduction between atria and ventricles. It is of two types:
Incomplete heart block
Complete heart block.

***Incomplete (partial) heart block (Fig. 4.26)***

It is of two types:

*Ist degree*

In Ist degree block PR interval is prolonged (above 0.2 sec), but all atrial impulse reach ventricle. All P waves are followed by QRS complex.

*IInd degree*

Here also the PR interval is above 0.2 sec, but all atrial impulses are not conducted to ventricles. All QRS complexes are preceded by P waves, but all the P waves are not followed by QRS complexes. It is of three types:

i. *2:1 heart block:* Here every two P waves are followed by QRS complex.
ii. *3:1 heart block:* Here every three P wave is followed by QRS complex.

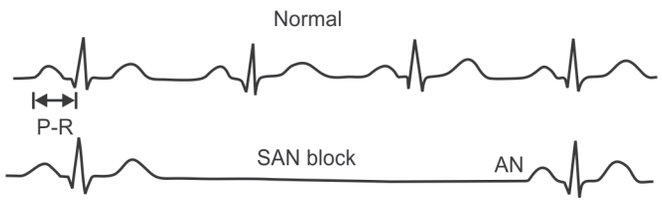



**Fig. 4.25:** Sinoatrial nodal block

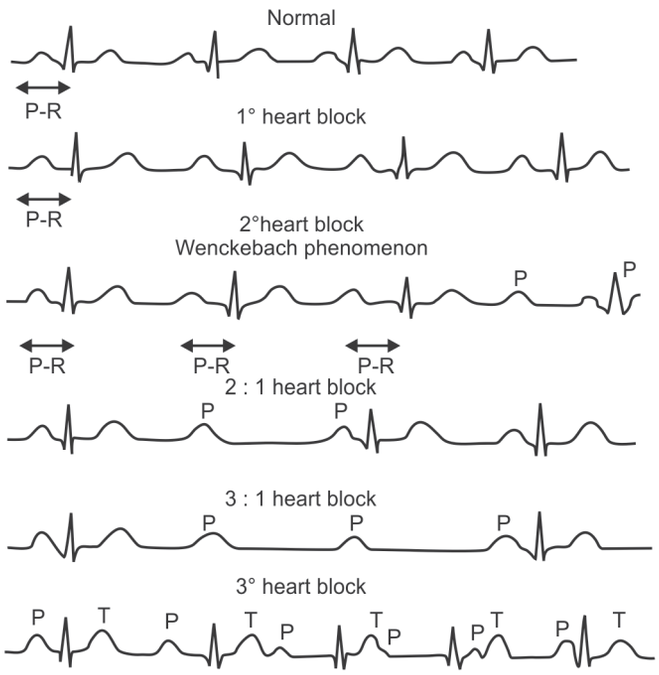



**Fig. 4.26:** AV nodal block

iii. *Wenckebach phenomenon:* In this condition PR interval is prolonged progressively until one impulse fails to be transmitted to the ventricles. It is a cyclical phenomenon.

***Complete heart block (3rd degree heart block)***

Here no impulse is transmitted from atria to ventricles. There is complete atrioventricular dissociation.

Atria contract at its own rate and ventricle contract independently at its own rate and rhythm (Idioventricular rhythm). When complete heart block occurs suddenly, the ventricles takes some time before it can beat at its own rhythm. During this time there is cerebral hypoxia (as there is no cardiac output). This will lead to syncope and fainting attack called **Stokes Adam's syndrome.**

## *Bundle Branch Block (BBB) (Fig. 4.27)*

Here there is block of one of the branches of bundle of His. So excitation process passes normally down to bundle on the intact side and then sweeps back through the muscles to activate the ventricle on the blocked side. It may be right BBB, left BBB and hemiblock (fascicular block). When block occurs in the anterior or posterior fascicles of the left bundle branch, it produces hemiblock.

***Note***

1. *WPW syndrome (Wolff-Parkinson-White syndrome):* Congenital anomaly where an accessory bundle of muscle fiber called bundle of Kent connects right atria to ventricles. As a result depolarization wave from the atria is transmitted to ventricle faster bypassing the AV node (So AV nodal delay absent and PR interval is shortened). Here wide, slurred QRS complex is obtained. Normally beat conducts down the AV node. But here impulse is transmitted retrograde to the atrium due aberrant bundle. A circus movement is thus established (Fig. 4.28).
2. *Lown-Ganong-Levine syndrome:* Here depolarization passes from the atria to the ventricles via an aberrant bundle. The impulses bypasses the AV node, but enters the intraventricular conducting system distal to the node QRS complex is normal and PR interval is shortened.
3. *Myocardial infarction (MI):* When the blood supply to part of the myocardium is interrupted, there are profound changes in the myocardium that lead to irreversible changes and death of muscle cells. This phenomenon is called myocardial infarction. ECG is very useful for diagnosing ischemia and area of infarction.

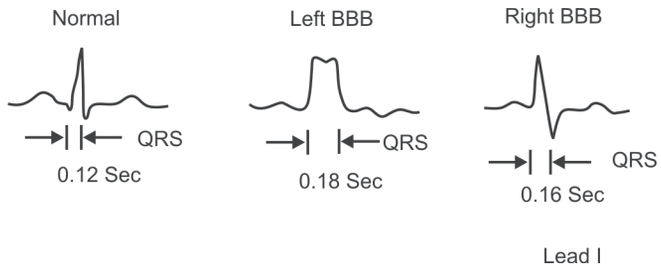



**Fig. 4.27:** Bundle branch block

*Diagnosis of MI (ECG findings):*

- Elevation of ST segment in the leads overlying the area of infarct.
- Depression of ST segment in the reciprocal leads.
- Pathological Q wave
- T wave inversion

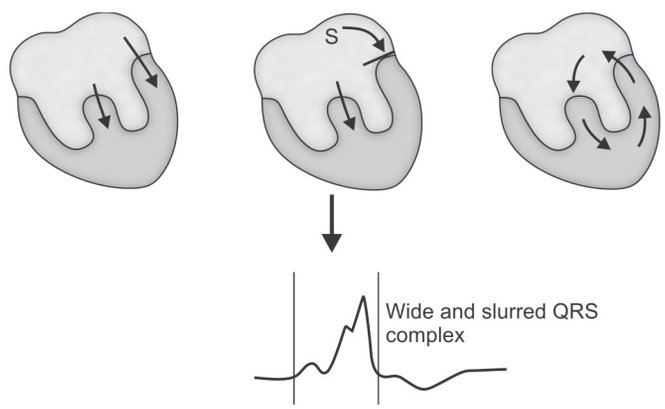



**Fig. 4.28:** Wolff-Parkinson-White syndrome

*Sick sinus syndrome:* Disease processes affecting the sinus node lead to marked bradycardia accompanied by dizziness and syncope.

### *ECG Changes in Electrolyte Concentration*

***Hypokalemia (Figs 4.29A)***

*Mild:* Prominent U wave.

*Severe:*

i. Prolongation of PR interval
ii. Prominent U wave
iii. Depression of ST wave
iv. Inversion of T wave.

***Hyperkalemia (Fig. 4.29B)***

*Mild:* Tall slender T wave.

*Severe:*

i. Tall slender T wave
ii. Broad and slurred QRS complex.

***Hypocalcemia***

i. Prolonged QT interval
ii. Ventricular fibrillation.

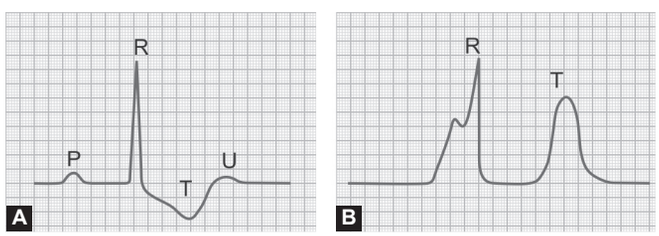
## CARDIAC OUTPUT

Amount of blood pumped out of each ventricle per minute is called cardiac output (CO). Normal value – 5 liters in a normal adult.

- Cardiac output = Stroke volume × Heart rate.
- Stroke volume is the amount of blood pumped out of each ventricle per beat (normal – 70 ml).
- Heart rate is defined as the number of beats per min (normal – 75/min).
- Cardiac index is the cardiac output in liter per min per $m^2$ of body surface (normal – 3. 2 L/min/$m^2$).

### *Estimation of Cardiac Output by Fick's Method*

Fick's principle states that the amount of a substance taken up from blood is equal to the arteriovenous difference of the substance times the blood flow. Fick's principle is modified to measure cardiac output.




**Figs 4.29A and B:** (A) Hypokalemia (B) Hyperkalemia

If we take,
Qx = amount of substance taken up or given out
Ax = arterial concentration in ml/100 ml of blood
Vx = venous concentration in ml/100 ml of blood
CO = amount of substance taken up or given out by organ per unit time divided by arteriovenous concentration difference.

$$\text{That is CO} = \frac{Qx}{Ax - Vx}$$

### Variation in Cardiac Output

#### *Physiological Increase*

1. Exercise
2. Anxiety
3. Excitement
4. Pregnancy

#### *Physiological Decrease*

1. Standing from lying position
2. In females

#### *Pathological Increase*

1. Anemia
2. Hyperthyroidism
3. Hypoxia
4. Fever
5. Beriberi

#### *Pathologically Decrease*

1. Hypothyroidism
2. MI
3. Valvular heart disease
4. Hemorrhage
5. Cardiovascular shock

### Regulation of Cardiac Output

Cardiac output is determined by stroke volume and heart rate (Stroke volume × Heart rate). Hence all the factors that regulate SV and HR regulates CO.

## STROKE VOLUME

Stroke volume depends on three factors:

a. Preload
b. Afterload
c. Contractility.

### Regulation of Stroke Volume

By two important regulatory mechanism—heterometric and homometric regulation.

### Heterometric Regulation

By factors that change the length of cardiac muscle fiber and this is affected by factors which act within the heart. So this is also called **intrinsic regulation.** This is based on Frank-Starling's law. Thus it is independent of chemical or nervous factors. As mentioned earlier, force of contraction is dependent on preloading and afterloading.

***Preload***

In the ventricle, the preload is the amount of blood present in it before it has started contracting (EDV). So within the physiological limit, more the EDV more will be the CO (Starling's law). Factors affecting EDV are:

a. *Venous return:* When venous return increases EDV increases. It in turn depends on:
   i. *Blood volume:* When BV increases, VR increases, EDV increases, SV increases, so CO increases.
   ii. *Venous tone:* Increase in venous tone leads to increased pooling of blood in periphery, VR increases, so EDV increases.
   iii. *Skeletal muscle pump:* Veins are surrounded by skeletal muscles and when they contract they reduce the capacity of venous reservoir by squeezing veins and diverting the blood to heart. EDV increases, so CO increases.
   iv. *Intrathoracic pressure:* An increase in the normal negative intrathoracic pressure increases the pressure gradient along which blood flows to heart; so more blood is sucked into the thorax, venous return increases. It is important during inspiration as intrapleural pressure falls.
   v. *Posture of body:* Venous return is maximum in lying posture. During standing, there is venous pooling which in turn increases venous return.
b. *Atrial contraction:* When atria contracts more effectively EDV increases.
c. *Intrapericardial pressure:* As intrapericardial pressure increases, there is a limit for the ventricle to expand and so filling is increases.
d. *Ventricular compliance:* If expansibility is less, EDV increases.

***Afterload***

For left ventricle, after load is the blood pressure in the aorta. When afterload is more, ventricles have to work more. It is called as aortic impedence or aortic resistance. When after load increases CO decreases.

### Homometric Regulation

By changing the factors that change the contractility of myocardium and it is independent of cardiac muscle fiber length. It is regulated by factors which operate outside the heart like neural and chemical factors, so it is also called extrinsic regulation.

***Neural***

When there is sympathetic stimulation, there is an increase in the force of contraction (via $\beta_1$ adrenergic receptors–activation of adenylcyclase → increased cAMP → intracellular calcium channel remain open for more time). Parasympathetic stimulation produces –ve effect.

***Chemical***

1. Xanthine like caffeine, theophiline inhibit the break down of cAMP. So more $Ca^{2+}$ is available.
2. Glucagon increases cAMP, so more $Ca^{2+}$ available.
3. Thyroid hormone increase cAMP.
4. Drugs like barbiturates and quinidine decreases force of contraction.
5. Hypoxia, hypercapnia, acidosis are the other chemical factors which decrease force of contraction.

## HEART RATE

Normally ranges from 60–100/min. It is also called sinus rhythm as it originates from SA node.

### Physiological Increase

1. Muscular exercise
2. Inspiration
3. After a meal
4. Excitement, anger and painful stimuli.

### Physiological Decrease

1. Expiration
2. Sleep
3. In trained athlete

### Pathological Increase

1. Hyperthyroidism
2. Circulatory shock
3. Congestive cardiac failure
4. Fever
5. Sympathomimetic drugs (adrenaline, isoprenaline)

### Pathologic Decrease

1. Heart block
2. Myxedema

## Control of Heart Rate

Heart rate is not under voluntary control. Regulation of heart rate can be explained under:

1. Neural regulation
2. Chemical regulation
3. Thermal regulation.

### *Neural Regulation*

Neural control is by autonomic nervous system (ANS) and by medullary centers.

#### *Autonomic Regulation (Role of Cardiac Innervation)*

***Sympathetic supply***

Sympathetic fibers are cardioacceleratory nerves. They originate from lateral horn of upper thoracic spinal cord. Lateral horn is known as spinal center of sympathetic system. The neurons in the lateral horns are influenced by impulses from medulla, which inturn is influenced by impulses from cerebral cortex, hypothalamus, limbic system and various peripheral afferent.

Preganglionic fibers from spinal cord end in stellate ganglion. Postganglionic fibers arise from stellate ganglion and innervate heart and vascular smooth muscles in the heart. Sympathetic fibers supply atrial muscles, SA node, AV node, purkinje system and ventricular muscles. The transmitter released at the postganglionic sympathetic nerve ending is norepinephrine. It mediates its action through β receptors.

*Effect of stimulation of sympathetic fibers*

- Increase HR (+ve chronotropic effect)
- Increase force of contraction (+ve inotropic effect)
- Increase conductivity (+ve dromotropic effect)
- Increase excitability (+ve bathmotropic effect).

***Note:*** Normally a moderate tonic discharge is present in cardiac muscle from sympathetic (sympathetic tone) but not as powerful as that of parasympathetic and this tone is responsible for maintaining normal heartbeat.

***Parasympathetic supply***

Parasympathetic supply to the heart is mainly through vagus nerve. It is cardioinhibitory. They arise from dorsal motor nucleus and nucleus ambiguus in medulla. From these nuclei fibers arise and descend through the main trunk of vagus till it reaches neck where the fibers of heart are separated and mixed with sympathetic fibers to form superficial and deep cardiac plexus. These give rise to superior and inferior cardiac nerves and these nerves supply nodal tissue and atrium.

Ventricles do not receive any parasympathetic innervations. Neurotransmitter released at postganglionic nerve endings is acetylchoine (ACh) (via nicotinic and muscarinic receptor). Right vagus innervate SA node and thus it controls heart rate. Left vagus innervate AV node, thus it controls conduction through AV node.

***Effect of stimulation of parasympathetic fibers***

- Decrease HR (-ve chronotropic effect)
- Decrease force of contraction (-ve inotropic effect)
- Decrease conductivity (-ve dromotropic effect)
- Decrease excitability (-ve bathmotropic effect).

***Note:*** Normally, a constant stream of impulses pass through vagus, which is inhibitory to heart (vagal tone).

Stimulation of right vagus decreases heart rate, left vagus stimulation delay the conduction through AV node. Strong stimulation of vagus decreases heart rate and finally the heart stops and it is called **vagal inhibition.** But after a few seconds, heart escapes from the inhibitory effect of vagus, this is called **vagal escape** and starts producing impulses of its own at a rate of 1–90/min called **idioventricular rhythm.**

#### *Medullary Regulation*

By denervating both sympathetic and parasympathetic, HR is found to be 100/min. This shows that sympathetic and parasympathetic innervation of heart plays an important role in maintaining normal HR and this activity is modified by higher centers which include centers in medulla, mainly the vasomotor area, hypothalamus and limbic system.

Medullary cardiovascular centers include vasomotor center and cardiac vagal center. This medullary center is influenced by cerebral cortex, hypothalamus, limbic system, peripheral afferents or peripheral reflex.

***Vasomotor center (VMC) consists of***

a. *Sensory area:* Nucleus tractus solitarius (NTS).
   This area receives impulse via IX and X nerve from periphery, particularly from the baroreceptors. In turn, this area sends impulses to control the vasoconstrictor and vasodilator areas.
b. *Depressor area:* Caudal and intermediate ventrolateral nucleus of medulla (CVLM and IVLM).
   This area is otherwise called vasodilator area. This area suppresses the vasoconstrictor area and causes vasodilation. It is concerned with cardioinhibition.
c. *Pressor area:* Rostral ventrolateral nucleus of medulla (RVLM).
   This area is otherwise called vasoconstrictor area. This area sends impulses to blood vessels through sympathetic vasoconstrictor fibers. So stimulation of this area causes vasoconstriction and rise in BP. This area is also concerned with acceleration of HR.

***Cardiac Inhibitory Center (CIC) consist of***

- Nucleus ambiguus (NA)
- Dorsal motor neuron/Dorsal motor nuclei.

There is a constant discharge of impulses from CIC through the vagus to the heart. This is responsible for the vagal tone of the heart.

## Factors Influencing VMC and CIC

### *Baroreceptor Reflex*

Baroreceptors are stretch receptors located on the walls of heart and blood vessels, they are stimulated by distension or stretch. Different types of baroreceptors includes sinoaortic reflex, atrial stretch receptor, Bainbridge reflex, left ventricular receptors.

***Sinoaortic reflex***

Receptors are mechanoreceptors and respond to pressure changes or stretch. They are free nerve endings and are located in carotid sinus and arch of aorta. They are also located in subclavian and other major arteries.

These receptors are stimulated when BP changes between 90–150 mm Hg. Baroreceptors of carotid sinus are supplied by Hering's nerve (branch of glossopharygeal nerve). Baroreceptors of arch of aorta are supplied by aortic branch of vagus nerve (Fig. 4.30).

When there is rise in BP, baroreceptors are stimulated. The nerve fibers from baroreceptors end in NTS of same side and opposite side. Neurotransmitter released is glutamate. Neurons originating from NTS is stimulated and these neurons end in depressor area (CVLM and IVLM). The neurotransmitter released here is excitatory (glutamate). These stimulate neurons from depressor area and the neurons originating from depressor area end in pressor area (RVLM). Here, the neurotransmitter released is GABA which is inhibitory. So when depressor area is stimulated, pressor area is inhibited. From pressor area fibers are given to intermediolateral horn. Impulse transmission to spinal sympathetic center is thus inhibited. Inhibition of the pressor area reduces the normal sympathetic vasoconstrictor tone, leading to vasodilation.

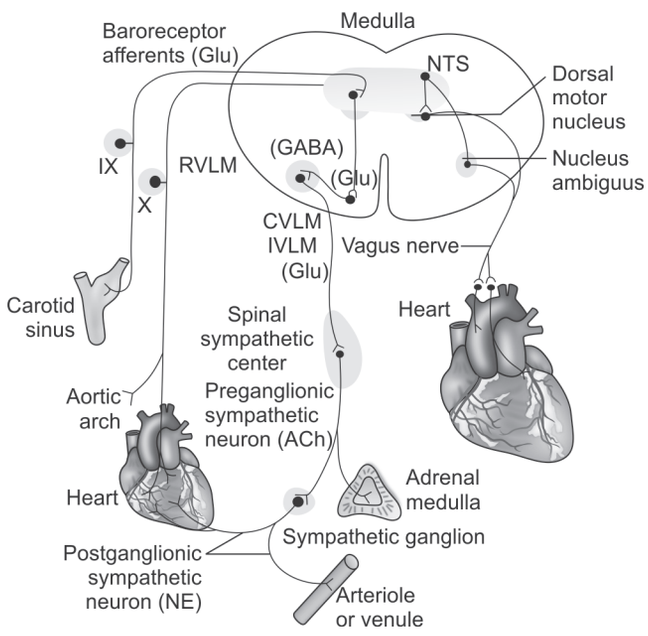



**Fig. 4.30:** Basic pathways involved in the medullary control of cardiovascular system

When NTS are stimulated impulses are also given to NA and dorsal motor neuron of vagus. That will lead to stimulation of vagus. When there is a rise in BP, there is increased parasympathetic and decreased sympathetic stimulation. The suppression of vasoconstrictor area reduces vasomotor tone (sympathetic tone). When vasomotor tone is reduced, there is vasodilatation which in turn leads to reduction in peripheral resistance. The simultaneous excitation of CIC reduces HR and force of contraction causing reduction in CO.

Both the factors, i.e. reduced peripheral resistance and reduced cardiac output ultimately decreases arterial BP. As the baroreceptor mechanism acts against the rise in arterial blood pressure it is called pressure buffer mechanism and the nerves from baroreceptors are called buffer nerves. When BP decreases, all the changes are reversed.

***Note***

i. From spinal sympathetic center sympathetic preganglionic fibers originate and these fibers end in sympathetic ganglia and adrenal medulla. When baroreceptors are not stimulated, spinal sympathetic center is not inhibited. Adrenal medulla is considered as a modified sympathetic ganglion. Adrenaline and noradrenaline are released from adrenal medulla. Adrenaline acts mainly on heart and nor adrenaline acts on smooth muscles or blood vessels to produce the pressor effects. From sympathetic ganglion postganglionic neurons originate and they innervate heart and blood vessels.

ii. *Mary's law:* It states that BP is inversely proportional to HR. This is mediated by baroreceptors, i.e. rise in BP will stimulate CIC and HR will decrease.

***Cardiopulmonary receptor***

This includes atrial stretch receptors, Bainbridge reflex and left ventricular receptors.

i. *Atrial stretch receptors:* These are stimulated by distension of atria. Increase in venous return leads to distension of atrial wall leading to increased discharge in receptors causing increase in HR. Increased HR causes vasodilatation which leads to fall in BP.

ii. *Bainbridge reflex:* Rapid infusion of blood or cold saline in anesthetized animals produces a rise in HR, if the initial HR is low. The receptors are tachycardia producing atrial receptors. The reflex competes with the baroreceptor mediated decrease in HR produced by volume expansion.

Afferent and efferent are through vagus and the center is at medulla. It is diminished or absent when the initial HR is high.

iii. *Left ventricular receptors:* When the left ventricle is distended, there is fall in BP and HR. It takes considerable distention to produce this response and its physiological significance is uncertain. However, they may play a role in the maintenance of vagal tone that keeps HR low at rest.

### Chemoreceptor

***From carotid body and aortic body***

Stimulated by fall in BP. Impulses are transmitted through IX and X cranial nerves. Impulses reach NTS and then it controls vasomotor center.

***Coronary chemoreceptors (Bezold Jarish reflex)***

In experimental animals, injection of serotonin, capsaicin, veratridine, etc. into the coronary artery supplying left ventricle cause apnea followed by rapid breathing, hypotension and bradycardia. The receptors are C fiber endings, the afferents are vagal and the center is medulla. They are also stimulated by occlusion of pulmonary artery or by substances released from damaged myocardium. In patients with MI, substances released from infarcted tissue stimulates C fiber ending of vagus and cause bradycardia, hypotension, apnea.

***Pulmonary chemoreceptors (J receptor mediated)***

The receptors are J receptors (juxtacapillary receptors). They are located in alveolar interstitium close to pulmonary capillaries. The effects are apnea followed by rapid breathing, hypotension and bradycardia.

***Miscellaneous***

Mild hypoxia and hypercapnia stimulate vasomotor center directly causing increased HR.

If hypoxia is severe it will depress the vasomotor center.

### Cushing Reflex

When intracranial pressure is increased, the blood supply to vasomotor area is decreased. This cause local hypoxia and hypercapnea. Vasomotor area is excited to increase BP which can increase blood supply to vasomotor area. When BP is increase there is reflex reduction in HR. This is the only condition in the body where we have increased BP associated with decreased HR.

***Note:*** The heart rate varies with the phases of respiration. It increases during inspiration and decreases during expiration. This phenomenon is called sinus arrhythmia. During inspiration, impulses in the vagi from stretch receptors in the lungs inhibit the CIC in the medulla oblongata. Thus, the tonic vagal discharge that keeps HR low, decreases and HR rises.

### Corticohypothalamic Pathways

Cerebral cortex and limbic system exerts strong influence on blood pressure and heart rate through medullary centers. Limbic system also influences through medullary center. Change in heart rate and BP during various emotional activities is due to influence of limbic system on medullary centers.

## Chemical Regulation

Norepinephrine has a direct chronotropic effect on heart, but its pressor action stimulates the baroreceptors leading to bradycardia. Thyroxine increases HR by increasing BMR and also by increasing the sensitivity of epinephrine and norepinephrine. Digitalis decreases HR.

## Thermal Regulation

Increased body temperature increases HR and vice versa.

## Summary of CO Regulation

$$CO = \text{Stroke volume} \times \text{Heart rate}$$

### Stroke Volume

1. Heterometric regulation
2. Homometric regulation.

***Heterometric regulation***

a. EDV-as EDV increases, SV increases and it in turn depends on:
   i. Venous return-blood volume, venous tone, skeletal muscle pump, intrathoracic pump, posture of body
   ii. Atrial contraction
   iii. Intra-pericardial pressure
   iv. Ventricular compliance.
b. Aortic resistance-if resistance is more SV is less.

***Homometric regulation (Table 4.4)***

**Table 4.4: Homometric regulation**

| *Neural* | *Chemical* |
|---|---|
| Sympathetic | Xanthines |
| Parasympathetic | Barbiturates |
| | Quinidine |
| | Digitalis |
| | Glucagon |
| | Hypoxia |
| | Hypercapnia |
| | Acidosis |
| | Calcium |
| | Thyroid hormones |

### Heart Rate

1. Neural regulation
2. Chemical regulation
3. Thermal regulation.

***Neural Regulation***

a. Autonomic regulation
b. Medullary regulation, which is influenced by :
   i. *Baroreceptors:* Sinoaortic reflex, atrial stretch reflex, Bainbridge reflex, LV receptors.
   ii. *Chemoreceptors:* From carotid body and aortic body, Bezold Jarish reflex, J receptor mediated, Cushings reflex.
   iii. Impulses from cerebral cortex, limbic system.

***Chemical Regulation***

Catecholamines, thyroxine, digitalis, hypercapnia, hypoxia.

***Thermal Regulation***

Temperature, exercise.

## BLOOD PRESSURE

Arterial blood pressure is defined as the lateral pressure exerted by column of blood on the wall of arteries. Systolic pressure is defined as the maximum pressure exerted in the arteries during systole of heart (normal value: 100–140 mm Hg). Diastolic pressure is the minimum pressure exerted in the arteries during the diastole of heart (normal value: 60–90 mm Hg). Pulse pressure is the difference between the systolic pressure and diastolic pressure (nomal value: 50 mm Hg). Mean arterial blood pressure is the average pressure throughout the cardiac cycle.

MAP = Diastolic pressure + 1/3 pulse pressure.

### Factors Affecting Arterial Blood Pressure

#### Age

Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) increases with age. Systolic blood pressure (SBP) increases more than DBP due to decreased distensibility of arteries. The DBP decreases with age after 50–60 years.

#### Sex

In females before menopause SBP is 4–5 mm Hg less than males of same age. In females after menopause SBP is 4–5 Hg more than males. This effect is due to estrogen which prevents atherosclerosis.

#### Body Built

In obese individuals brachial arterial pressure gives high readings because there is more tissue between the cuff and artery.

#### Climate

Exposure to cold via hypothalamus produces vasoconstriction and increases both SBP and DBP. Exposure to warmth via hypothalamus produces vasodilatation and decreases both SBP and DBP.

#### Diurnal Variation

Diurnal variation of 5–10 mm Hg is common in SBP, peak values observed during afternoon and lowest during early hours of morning. Reverse rhythm is observed in night workers.

#### Exercise

Blood pressure comes back to normal 5 minutes after the stoppage of exercise due to the relaxation of muscles which produces vasodilatation. Initial increase is due to sympathetic vasoconstriction.

#### Emotions

Excitement, fear, worry increase SBP due to increase in CO secondary to increased sympathetic activity.

#### Gravity

Pressure in any vessel below the heart is increased by the effect of gravity. Pressure in any vessel above the heart is decreased by the effect of gravity. Magnitude of gravitational effect at normal density of blood is 0.77 mm Hg/cm vertical distance fron heart.

#### Hereditary

Familial tendencies of hypotension/hypertension with SBP are common.

#### Meals

Changes in systemic BP due to:
a. Pressure over heart due to distended abdomen increases heart rate.
b. Increase epinephrine release from adrenal medulla.

Therefore, SBP increases 5–6 mm Hg up to 1 hour after meals, DBP remains same/decreases slightly due to vasodilatation in digestive organs.

### Sleep

Systolic blood pressure falls in early hours of sleep by 15–30 mm Hg, because of general vasodilatation of vessels in complete relaxed state. However, disturbed sleep increases SBP due to increased sympathetic discharge secondary to skeletal muscle tensioning.

### Posture

Changes in DBP are more with the change of body posture. In standing posture DBP increases; in sitting remains normal and decreases in lying posture.

***Mechanism***

*Upon standing:*

a. Peripheral pooling of blood in dependent parts → decrease in VR → decreased CO decrease in SBP → decrease in baroreceptor discharge → increase in DBP.
b. Increase in peripheral resistance → increase in DBP

Therefore, sudden standing increases DBP, if recorded within 30–60 seconds of change in posture after that it comes to normal via the operation of baroreceptor reflexes.

## Factors Determining BP

BP = Cardiac output × peripheral resistance.

### Role of Cardiac Output

Pumping action of heart is the main factor for controlling CO. Therefore, alteration of CO will alter arterial BP. CO = HR × stroke volume. Systolic pressure depends mainly upon stroke volume. Stroke volume in turn depends on preload, afterload and contractility.

### Role of Peripheral Resistance

This is the important factor which maintains diastolic pressure.

$$\text{Peripheral resistance} = \frac{8\eta l}{\pi r^4}$$

where,

$\eta$ = viscosity of blood
$l$ = length of vessel
$r$ = radius of the vessel.

### Peripheral Resistance

Peripheral resistance depends on:

***Viscosity of blood***

Arterial pressure is directly proportional to viscosity of blood. When viscosity of blood is more, the frictional resistance is more and this increases blood pressure.

***Radius of the vessel***

Peripheral resistance is inversely proportional to fourth power of radius. Even a slight change in diameter can produce great change in peripheral resistance. Changes in diameter is brought about by changes in sympathetic tone.

***Elasticity of vessel wall***

Blood pressure is inversely related to the elasticity of blood vessel. It is due to the elastic properties, the arteries can dilate and accommodate considerable amount of blood with relative rise of BP. At lower pressure (less than 30–40 mm Hg) elasticity does not come to play and blood vessels behave like a rigid tube.

***Velocity of blood flow***

The greater the velocity of flow in a vessel, the lower the lateral pressure distending its walls (according to Bernoulli's principle). When a vessel is narrowed, the velocity of flow in the narrowed portion increases and the distending pressure decreases.

## Regulation of Blood Pressure

Determinants can fix the level of BP, but when there is a fluctuation, it is brought back to normal level by various mechanisms available in our body. In short all the BP regulatory mechanisms are grouped under:

- Short-term regulatory mechanisms
- Intermediate regulatory mechanisms
- Long-term regulatory mechanisms.

### Short-term Regulatory Mechanisms (sec-min)

The short-term regulation or nervous regulation is rapid among all mechanism involved in the regulation of BP. The ANS participate in the short-term regulation through different reflex mechanisms. They include baroreceptor reflexes, chemoreceptor reflexes and Cushing's reflex.

### Baroreceptor Reflexes

***Sinoaortic reflex***

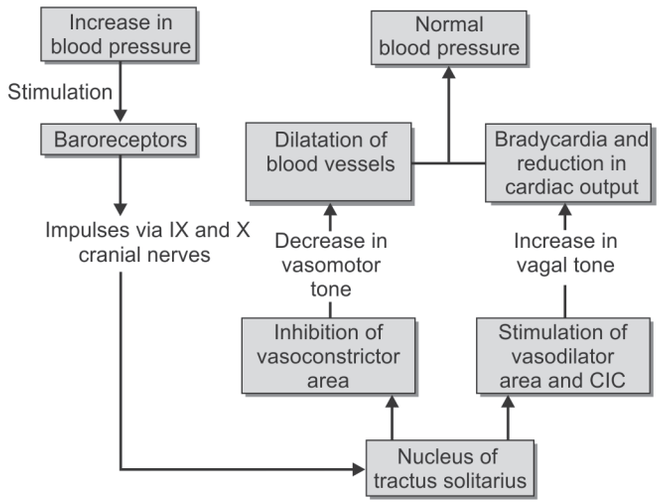
Refer page no 76.

The sequence of events are given in Flow chart 4.1:

***Other reflexes***

Atrial stretch receptors when stimulated will lead to fall in BP. Similarly, left ventricular stretch receptors when stimulated lead to fall in BP. Bainbridge reflex also have role in the regulation of BP but its main effect is on HR.

**Flow chart 4.1:** Regulation of blood pressure by baroreceptor mechanism




### *Chemoreceptor Reflex*

They give response to change in chemical constituents of blood. The receptors are carotid body and aortic body. They respond to hypoxia, hypercapnia, acidosis. When the mean pressure falls, it produces lack of $O_2$, excess of $CO_2$ and hydrogen ion concentration. When the arterial pressure falls below 80 mm Hg, chemoreceptors are stimulated. The chemoreceptors in the carotid body are supplied by glossopharygeal and those in the aortic body by vagal nerve fibers. The impulses reaches the medullary center, resulting in increased HR and BP.

### *Cushing Reflex*

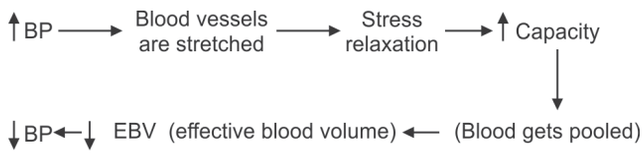
This response is also called CNS ischemic response as this reflex is due to ischemia of brain. The mechanism is given under factors influencing VMC and CIC.

## *Intermediate Regulatory Mechanism (min-hrs)*

They include stress relaxation of vasculature and capillary fluid shift mechanism.

### *Stress Relaxation of Vasculature*

Whenever the smooth muscle is stretched for prolonged time it goes into relaxation.




Reverse changes takes place when BP falls.

### *Capillary Fluid Shift Mechanism*

Whenever, there is an increase in BP more fluid is filtered through the capillary wall into the interstitial space. So blood volume decreases, resulting in decreased BP. Reverse changes takes place when BP falls.

## *Long-term Regulation (hrs-days)*

All the mechanism that tend to alter the blood volume participate in long-term regulation. The kidneys play an important role in the long-term regulation of BP. These mechanisms include renin angiotensin mechanism, renal body fluid system and hormonal mechanism.

### *Renin-Angiotensin Mechanism*

Whenever there is a fall in BP, there is decrease in blood flow to the kidney. This results in the release of renin from JG cells. It converts angiotensinogen to angiotensin I. This is converted to angiotensin II by angiotensin converting enzyme. Angiotensin II then acts to restore BP by:

- It acts directly on the kidneys to cause salt and water retention (by vasoconstriction).
- It causes adrenal glands to secrete aldosterone and the aldosterone in turn increases salt and water reabsorbtion by the kidney tubules.

All these ultimately lead to restoration of BP.

### *Renal Body Fluid System (By Regulation of ECF Volume)*

When the body contains too much extracellular fluid, the blood volume and arterial pressure rise. This rising pressure in turn has direct effect to cause the kidneys to excrete excess ECF, thus returning the pressure back to normal. Even a slight increase in BP can double water excretion, which is called *pressure diuresis.* Elevated BP can also leads to sodium excretion which is called pressure natriuresis. Reverse changes takes place when BP falls.

### *Hormonal Mechanism*

Hormones other than angiotensin also aids in the regulation of BP.

a. *Aldosterone:* It causes the retention of water and $Na^+$ thereby increases ECF volume leading to increase in BP.
b. *ADH (vasopressin):* Fall in BP causes increased production of ADH. It increases the reabsorption of water from renal tubules and collecting duct. ADH can also cause constriction of vascular smooth muscles.
c. *Atrial natriuretic peptide:* ANP causes dilation of blood vessels and decreases blood pressure.

d. *Catecholamines:* Released from adrenal medulla.
   - Epinephrine acts mainly on heart.
   - Norepinephrine acts on blood vessel.

e. *Urotensin:* II-present in cardiac and vascular tissue. It is the one of the most potent vasoconstrictor.

f. *Thyroid hormones:* Help in regulation of BP, mainly by their effect on metabolism. They also potentiate the effect on catecholamines on the vascular smooth muscle and the heart.
   - In hyperthyroidism - high BP
   - In hypothyroidism- low BP.

### Hypertension

Hypertension (HTN) refers to a condition in which value of systolic blood pressure is persistently more than 140 mm Hg and/or that of diastolic blood pressure is above 90 mm Hg. If there is increase only in systolic blood pressure, it is called systolic hypertension in which pulse pressure is raised.

#### *Types of Hypertension*

It is of two types: primary and secondary hypertension:

1. Primary hypertension also known as essential hypertension is characterized by a raised blood pressure without any underlying disease. Risk factors for primary HTN include: heredity, obesity, mental tension and smoking.
2. Secondary hypertension refers to a condition in which blood pressure is raised due to some other underlying disease. Common causes of secondary hypertension are:
   a. Cardiovascular diseases, e.g. atherosclerosis.
   b. Renal diseases, e.g. glomerulonephritis and tumor of juxtaglomerular cells leading to formation of excess of angiotensin II.
   c. Endocrinal disorders like hyperaldosteronism, phaeochromocytoma (tumor of adrenal medulla) and Cushing's syndrome (excessive secretion of glucocorticoids from adrenal cortex).
   d. Neurologic disorders which may produce hypertension include raised intracranial pressure.
   e. Pregnancy induced hypertension (PIH) is noticed in some of the pregnant women.

#### *Complications of Hypertension*

a. *Cardiac conditions:* Left ventricular hypertrophy, cardiac failure, ischemia, myocardial infraction
b. *CNS conditions:* Cerebral hemorrhage, stroke
c. *Retinal conditions:* Hypertensive retinopathy, papilloedema
d. *Renal conditions:* Renal failure.

#### *Treatment of Hypertension*

Primary HTN is treatable, but not curable.

a. Salt, calorie, cholesterol and saturated fat restricted diet
b. Avoid alcohol and smoking
c. Exercise and lifestyle changes
d. *Drugs:* There are two general classes of drugs for treating HTN:
   i. Vasodilator drugs (increase RBF)
   ii. Natriuretic/diuretic drugs (decreases the tubular reabsorption of salt and $H_2O$). Other drugs used for the treatment of HTN include anti-adrenergic drugs, ACE inhibitors and $Ca^{2+}$ channel blockers.

Secondary, HTN is not only treatable but sometimes also curable.

## CORONARY CIRCULATION

Coronary circulation means the circulation through the heart itself. Heart is supplied by two coronary arteries: left and right.

- In 50% of population right coronary artery carries major blood supply to heart.
- Twenty percent individuals left coronary artery is dominant.
- In the rest 30% both arteries are dominant (equally dominant).

The coronary sinus and anterior cardiac veins drain the blood ultimately into right atrium. Some quantity of blood enters directly into cardiac chambers via arteriosinusoidal vessels, arterioluminal vessels and the besian system of veins. Coronary blood flow in humans can be measured by Kety method or nitrous oxide technique (based on Fick's principle), radionuclides utilization technique, coronary angiography.

### Special Features of Coronary Circulation

1. It supplies the heart itself. Coronary blood flow at rest is 250 ml/min (5% of CO).
2. In majority of people one artery is dominant to other.
3. The vessels are subjected to force of myocardial contraction and are compressed during systole.
4. Unlike other vascular bed it is mainly perfused during diastole. (During diastole cardiac muscle relaxes and it will not obstruct blood flow through LV muscle capillaries).
5. $O_2$ extraction is highest in this bed. $O_2$ content of arterial blood is19 ml% and $O_2$ content of venous blood is 6.7 ml%. About 13 ml is utilized in heart (in other tissues 19 ml–14 ml about 5 ml utilized).
6. Coefficient of $O_2$ utilization is 70%, whereas it is about 20% in all other tissues. So increased blood flow is needed.

This is a disadvantage for persons with any block in blood vessels. On exertion, the part with decreased blood flow will get necrosis and MI occurs.

7. Collateral circulation is normally not very important but may develop in chronic CAD.
8. Diameter of muscle less, so high capillary density.
9. Change of blood flow in different phases of cardiac cycle (Figs 4.31 and 4.32).
10. Coronary circulation shows reactive hyperemia, which means increased blood flow to a part following a temporary obstruction of flow.
11. *Autoregulation:* Even if there is change in pressure (60–160 mm Hg) there is no change in coronary blood flow. This is achieved through autoregulation.
12. Metabolic factors are more important for controlling blood flow.

## Factors Regulating Coronary Blood Flow

### Rate of Metabolism

Local muscle metabolism (myocardium) is the primary controller of coronary flow. Higher the metabolic rate, higher is the $O_2$ demand and CBF increases. Due to increased metabolism there will be $O_2$ lack and increased concentration of $CO_2$, $H^+$, $K^+$, adenine, lactate, etc. and these produce vasodilation.

### Perfusion Pressure

More the perfusion pressure, more is the blood flow, but up to a limit only (due to autoregulation in coronary circulation). In the systemic pressure range of 60–150 mm Hg, CBF remains constant if cardiac activity remains constant. Coronary perfusion pressure mainly depends on DBP in the aorta.

### Effect of Ventricular Contraction

The vessels which are situated within the myocardium are compressed during myocardial contraction. During diastole, the cardiac muscle relaxes and no longer obstructs blood flow through the left ventricular muscle capillaries, so that blood flows rapidly during all of diastole (Fig. 4.31).

Since, the blood pressure between aorta (120 mm Hg) and LV (121 mm Hg) is very small during systole, therefore, blood flows to subendocardial portion of LV only in diastole (0 mm Hg). However, pressure difference is more in superficial portion of LV to permit some flow in this region throught the cardiac cycle; while blood flow to RV (25 mm Hg in systole and 0 mm Hg in diastole) and atria occurs both during systole and diastole (Fig. 4.32).

***Note:*** Because there is no blood flow during systole in subendocardial portion of LV, this portion of LV is more prone to MI.

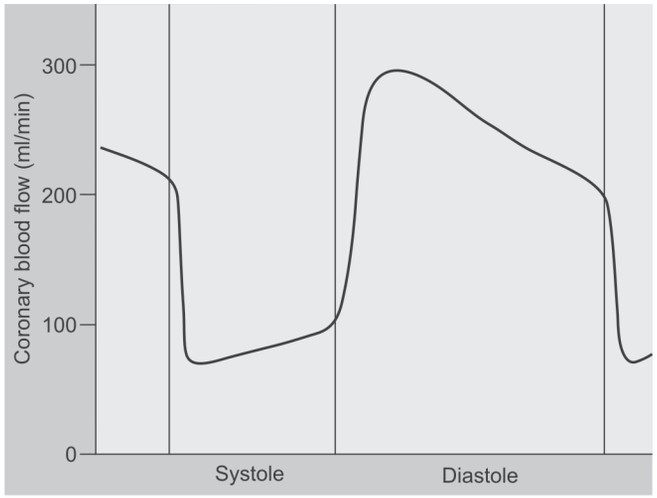



**Fig. 4.31:** Phasic changes in coronary blood flow

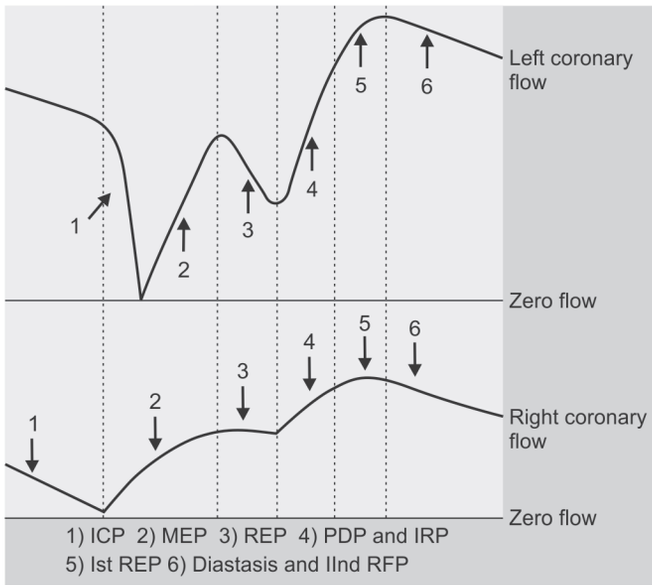



**Fig. 4.32:** Blood flow through coronary vessels during different phases of cardiac cycle

### Neural Influence

The stimulation of autonomic nerves influence coronary blood flow both directly and indirectly. The direct effects result from the action of neurotransmitter acetylcholine (parasympathetic) and norepinephrine, epinephrine (sympathetic) on the coronary vessels themselves. The indirect effect (important role) results from secondary changes in coronary blood flow caused by increased or decreased activity of heart. ACh has a direct effect to dilate coronary arteries, thus increases CBF.

Norepinephrine and epinephrine can have vascular constrictor or vascular dilator effects [depending on the presence or absence of constrictor (α) or dilator (β) receptors]. Both the receptors are present in coronary vessels. The sympathetic stimulation due to α receptors leads to vasoconstriction and decreased CBF. Similarly, sympathetic stimulation due to β receptors leads to vasodilation and increased CBF.

## CEREBRAL CIRCULATION

The principal arterial inflow to the brain in humans is via four arteries: Two internal carotid arteries and two vertebral arteries. The vertebral arteries unite to form the basilar artery. The basilar artery and the carotids form the circle of Willis. In human a relatively small fraction of the total arterial flow is carried by the vertebral arteries. Average blood flow rate in brain is about 750 ml/min of tissue.

### Features of Cerebral Circulation

1. The gray matter consumes a very high amount of $O_2$. It accounts for only 1% of total body weight but consumes about 20% of the total $O_2$ consumed in the body.
2. The total quantity of blood flowing to the brain is remarkably constant (In other circulations of the body, quantity of blood flow varies sharply due to factors such as exercise).
3. The brain keeps up its blood supply despite remarkable change in the perfusion pressure, as brain cannot survive anoxic assault.
4. The brain is inside a rigid cranial box (except in infants before anterior fontanelle closure), i.e. neither the blood nor the CSF can be compressed, so if the volume of CSF expands, the brain blood flow has to be reduced.

#### *Factors Determining the Blood Flow*

##### *Perfusion Pressure and Autoregulation*

The brain blood flow will not increase as mean arterial BP increases. Between 60 to about 150 mm Hg of mean BP, the blood flow is not affected This is autoregulation of brain blood flow. The principle factor in autoregulation is the accumulation of $CO_2$, although myogenic response to decreased distension may also have some role.

However, if the systemic BP falls very severely (below 60 mm Hg) as in severe cardiovascular shock there is an increased risk of cerebral anoxia.

##### *$CO_2$ Concentration*

When the $CO_2$ concentration of the local brain tissue rises, there is vasodilatation leading to increased blood flow.

##### *$O_2$ Tension*

High $O_2$ tension in the inspired air produces cerebral vasoconstriction so that the brain is protected from the dangers of $O_2$ poisoning.

##### *Anesthetics*

Majority of the anesthetics reduce the brain blood flow, e.g. halothane. They also decrease the cerebral metabolism.

##### *Sympathetic Stimulation*

Sympathetic stimulation produces cerebral vasoconstriction.

### Cerebrospinal Fluid

Cerebrospinal fluid (CSF) fills the ventricles and subarachnoid space. In humans, the volume of CSF is about 150 ml and the rate of CSF production is about 550 ml/day. The CSF turn over is about 3.7 times a day. The choroid plexus of the lateral ventricle (also 3rd ventricle) are the main sites of CSF formation.

A small part of CSF is probably also formed by the brain parenchyma. The process of CSF formation includes both filtration and secretion, however the CSF is not a pure ultrafiltrate of the plasma. The cells of choroids plexus also secrete in addition to filtration. The composition of lumbar CSF is essentially the same as that of brain ECF (15% of brain volume). The constituents of CSF are $Na^+$ (148 mEq/L), $K^+$ (2.9 mEq/L), $Cl^-$ (120–130 mEq/L), glucose (50-75 mg/dL), protein (15-45 mg/dL). pH is 7.3.

#### *Circulation*

The CSF, thus formed comes out of the lateral ventricle → enters the 3rd ventricle through the foramen of Monro → passes through the aqueduct of sylvius → enters the 4th ventricle → escapes mainly through the foramina of Luschka and Magendie → occupies the subarachnoid space and is distributed all over the brain. A small part of CSF enters the central canal (Fig. 4.33).

#### *Absorption*

At the sagittal sinus, finger like projections, called arachnoid villi, are seen to project from the arachnoid matter. These arachnoid villi come in contact with the venous blood of sagittal sinus. The membranous structure which separates the CSF within the arachnoid villi and the venous blood of

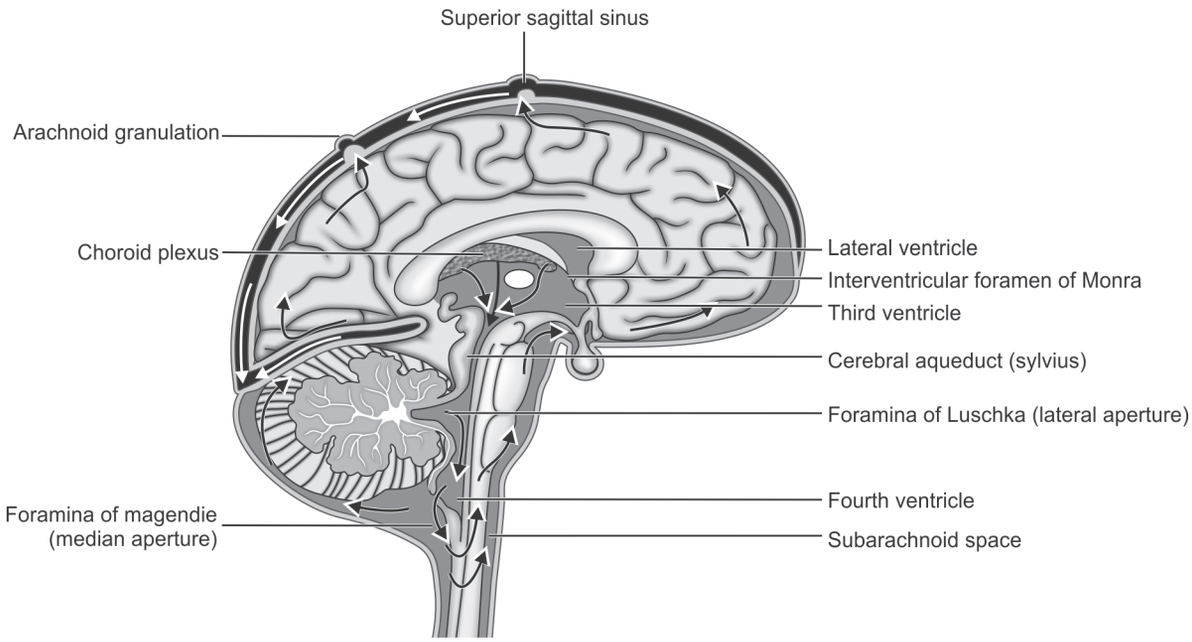



**Fig. 4.33:** Lateral view showing human ventricles and route of circulation of CSF within brain spaces

sagittal sinus, consists of arachnoid mater plus the meningeal layer of the duramater. The epithelium of this membrane shows pores. When the pressure of the CSF (within the arachnoid villi) is high, the pores open up and the fluid escapes into the venous blood. But venous blood cannot enter the villi, because:

- Pressure within these sinuses are normally very low.
- If there is any rise of venous pressure within these sinuses the pores will close down. Further, colloidal osmotic tension of venous blood plasma is high (increased conc of plasma protein) whereas that in the CSF (of the villi) is very low which also aids in the transfer of CSF to the venous blood. A part of CSF is absorbed, via the arachnoid villi, into the venous blood of cranium and spinal cord.

### Functions of CSF

1. It forms a sort of cushion round the brain. If the head receives an injury, because of the presence of the CSF, the impact of injury is distributed all over the brain and thus no single area of the brain has to bear a high degree of impact.
2. If there is an edema of the brain (as a result of brain injury/inflammation) the CSF escapes from the subarachnoid space into the venous sinuses and thus provides some room so that brain is not pressurized
3. It may carry nutrients to the brain.

## Applied Physiology

### Lumbar Puncture

In some diseases it is necessary to examine the CSF for diagnostic purposes. For this a needle is passed in between the 3rd and 4th lumbar spinous processes into the subarachnoid space within the vertebral canal (Spinal cord ends at the level of spinous process of L1 or L2 vertebra).

***Other uses of lumbar puncture***

1. *Diagnostic:* For the diagnosis of meningitis, multiple sclerosis, subarachnoid hemorrhage.
2. *Therapeutic:* To administrate antibiotics and antitumor agents.
3. *Anesthetic:* To give spinal anesthesia.

### Abnormal CSF

In cerebral/subarachnoid hemorrhage, the CSF contains blood. In purulent meningitis, the CSF is cloudy, cell count is high and consists of mainly neutrophils. Chemically sugar concentration falls, protein concentration rises. All these features are due to acute inflammation of meninges. In viral encephalitis, rise of the prote in concentration may be the only abnormality.

### Hydrocephalus

The aqueduct of Sylvius may be constricted (due to certain forms of neurosyphilis, tumor) and the CSF accumulates in the

3rd and lateral ventricle but fails to appear from 4th ventricle onwards. As a result of the accumulation, the intracranial tension rises, the brain matter is pressurized leading to considerable damage to the brain. The foramina of Luschka and Magendie may be obliterated (following inflammation to meninges) leading to similar conditions.

### Blood-Brain Barrier

The tight junctions between capillary endothelial cells in the brain and between the epithelial cells in the choroids plexus effectively prevent proteins from entering the brain in adults and slows down the penetration of smaller molecules. For example, the slow penetration of urea. This uniquely limited exchange of substances into the brain is referred to as blood-brain barrier. Through the tight junctions in the endothelial cells of the brain capillaries, particles with molecular weight more than 2000 do not pass through. However at some sites the endothelial cells are covered by foot processes of astrocytes. This covering is, however incomplete and large enough to permit the substances with a molecular weight of 40,000. If any substance has to cross this wall, it has to penetrate the cell membrane of endothelial cells. So only lipid soluble materials cross this barrier, others do not. blood-brain barrier prevents the entry of many injurious substances to the brain as brain is more delicate and vital than other tissues.

## TRIPLE RESPONSE

When skin is stroked firmly with a pointed object, it evokes a series of response classified as:

### *Red Reaction*

Reddening appears over the line of stroke. Red reaction in 10 seconds, due to capillary dilatation and release of histamines.

### *Flare*

Redness spreads out from the injury. Flare appears within 30 seconds after appearance of red line. It is due to dilatation of arterioles. Skin temperature overlying the area is raised.

The mechanism of arteriolar dilatation is due to axon reflex (Fig. 4.34; a response in which impulses initiated in sensory nerves by an injury are relayed antidromically down to other branches of sensory nerve fibers). The transmitter released at the central transmission of sensory C fiber neurons is substance P. Substance P, calcitonin gene related peptide (CGRP) dilates the arterioles. Flare is absent after a local anesthesia.

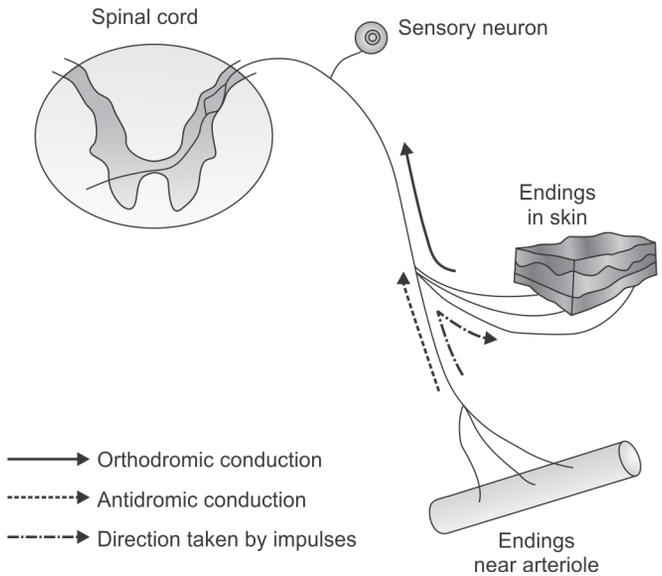



**Fig. 4.34:** Axon reflex pathway

### *Wheal*

If the stroke is strong enough, swelling is developed within the flare area. This localized edema is due to increased permeability of capillaries and postcapillary venules with consequent extravasations of fluid. Increase in permeability is produced by the release of histamine and related substances. Substance P cause extravasation of fluid. Wheal does not depend on nervous mechanism.

## CIRCULATORY SHOCK

Circulatory shock is defined as inadequate tissue perfusion with a relative or absolute inadequacy of cardiac output. It is developed by cardiovascular dysfunction.

### Types of Shock (Table 4.5)

1. Hypovolemic shock
2. Distributive shock
3. Cardiogenic shock
4. Obstructive shock.

### *Hypovolemic Shock (Decrease in Blood Volume)*

Here the amount of fluid in the vascular system is inadequate to fill it and this result in decreased circulating blood volume. Important hemodynamic changes are:

- Low cardiac output
- Low central venous pressure
- Increased systemic resistance (peripheral vasoconstriction).

**Table 4.5: Causes of different types of circulatory shock**

| *Types of shock* | *Causes* |
|---|---|
| Shock due to decreased blood volume | a. Hemorrhage-hemorrhagic shock<br>b. Trauma-traumatic shock<br>c. Surgery-surgical shock<br>d. Burns-burn shock<br>e. Dehydration-dehydration shock |
| Shock due to increased vascular capacity | a. Sudden loss of vasomotor tone-neurogenic shock<br>b. Anaphylaxis-anaphylactic shock<br>c. Sepsis-septic shock |
| Shock due to cardiac disease | a. Arrhythmia<br>b. Myocardial ischemia<br>c. Congestive heart failure |
| Shock due to obstruction of blood flow | a. Tumor in myocardium<br>b. Cardiac tamponade<br>c. Obstruction of blood vessels in lungs |

### *Clinical Features*

i. *Due to inadequate perfusion:* Cold, pale, cyanosed skin, oliguria, anuria, intense thirst.
ii. *Due to sympathetic stimulation:* Rapid thready pulse, increased sweating, hypotension.
iii. *Due to metabolic acidosis:* Rapid respiration, lactic acid accumulation (due to anaerobic glycolysis), alertness and restlessness.

Hypovolemic shock is subdivided on the basis of cause into hemorrhagic, traumatic, surgical and dehydration shock.

#### *a. Hemorrhagic shock/cold shock*

Most important cause for hypovolemic shock. The decline in blood volume produced by bleeding results in reduced venous return and thus cardiac output falls. The heart rate is increased and with severe hemorrhage, a fall in BP occurs always. With moderate hemorrhage, pulse pressure is reduced but mean arterial pressure may be normal. BP changes vary from individual to individual even when exactly the same amount of blood is lost. The skin is cold and pale with a grayish tinge because of stasis in the capillaries and a small amount of cyanosis. Here, the inadequate tissue perfusion leads to increased anaerobic glycolysis resulting in lactic acidosis.

#### *b. Traumatic shock*

It occurs due to injury causing severe damage to muscle and bone. Profuse bleeding into injured area results in shock. Breakdown of skeletal muscle (rhabdomyolysis) is a serious additional problem where there is extensive skeletal muscle crushing (crush syndrome). In crush syndrome, myoglobin leaks into circulation, gets precipitated into renal tubules and clogs them, resulting in renal damage leading to anuria.

#### *c. Surgical shock*

This occurs as a result of external or internal blood loss caused by ruptured blood vessels (during surgical procedures).

#### *d. Dehydration shock*

It occurs as a result of fluid loss from GIT (prolonged vomiting, diarrhea), kidney (diabetes mellitus, diabetes insipidus). Fluid loss also occurs from the skin due to burns (burn shock) which is characterized by hemoconcentration. In burn shock, the most important abnormality is loss of plasma as exudate from the burned surfaces. Here the plasma is lost rather than the whole blood. So hematocrit rises and results in hemoconcentration.

## *Distributive (Vasogenic/Low Resistance Shock/ Warm Shock)*

Here the blood supply to tissues is inadequate due to increased vascular capacity by extensive vasodilatation of blood vessels even though the blood volume is normal. The skin is not cold and clammy, hence called warm shock. The causes for vasodilation are:

- *Sudden loss of vasomotor tone:* Neurogenic shock
- *Anaphylaxis:* Anaphylactic shock
- *Sepsis:* Septic shock

#### *a. Neurogenic shock*

Neurogenic shock is characterized by sudden depression of nervous system due to loss of vasomotor tone which leads to vasodilatation. It is common in ischemia of brain, general anesthesia, spinal anesthesia and emotional conditions.

*Fainting (Syncope)*

Fainting or syncope is the sudden and transient loss of consciousness and postural tone with spontaneous recovery. It occurs due to temporary inadequate cerebral blood flow. It is of different types:

i. *Vasovagal syncope/emotional fainting:* It is also called neurocardiogenic syncope. It is due to extreme activation of parasympathetic system which leads to suppression of myocardium and severe vasodilatation. The cerebral blood flow also decreases.
ii. *Postural syncope:* It is due to pooling of blood in lower limbs because of prolonged standing.
iii. *Micturition syncope:* Fainting during micturition is common in patients suffering from orthostatic hypotension. Significant decrease in BP while standing is called orthostatic hypotension.
iv. *Effort syncope:* It is the common symptom in patients with stenosis of semilunar valves. These patients faint during

exercise or any strain. It is due to the failure of heart to increase the CO when the tissues need more blood flow.

v. *Cough syncope:* Sometimes, severe cough increases intrathoracic pressure, which reduces the CO leading to fainting.

vi *Carotid sinus syncope:* It is common in patients wearing tight collar. The tight collar of the dress exerts pressure over the region of carotid sinus. This leads to reduction in heart rate, vasodilatation and fainting.

***b. Anaphylactic shock***

During anaphylaxis (exaggerated allergic reaction to antigen) shock occurs due to release of histamine or histamine like substances. These substances increased the capacity of vascular system by vasodilatation and by increasing the permeability of capillaries.

When capillary permeability increases, there is loss of proteins and water from the blood into the interstitial space resulting in shock.

***c. Septic shock***

Sepsis is the pathological condition caused by bacteria or toxic substances released by bacteria. It has both distributive and hypovolemic features. Endotoxins produced by some bacteria cause vasodilatation and increase the capillary permeability, with loss of plasma in tissues.

### *Cardiogenic shock/Congested Shock*

When the pumping function of the heart is impaired, blood flow to the tissues is no longer adequate to meet resting metabolic demands, the condition that results is called cardiogenic shock. It is most commonly due to extensive infarction of the left ventricle, but it can also be caused by other diseases that severely compromise ventricular function.

Certain chemicals released by ischemic tissues stimulates ventricular receptors and cause reflex inhibition of vasomotor center producing bradycardia and hypotension (Bezold-Jarish reflex), making the shock worse. The symptoms are those of shock plus congestion of the lungs and viscera, because the heart fails to put out all the venous blood returned to it. This occurs mainly in MI, congestive heart failures, arrhythmias.

### *Obstructive Shock*

Obstructive shock is due to obstruction of blood flow.

The conditions where obstructive shock occurs are pulmonary embolism, cardiac tumor, cardiac tamponade (bleeding into the pericardium with external pressure on the heart), tension, pneumothorax.

## Stages of Shock

Shock is divided into the following three major stages:

### *Nonprogressive Stage/Compensated Stage*

It is the stage from which the normal circulatory compensatory mechanism will eventually cause full recovery without help from outside therapy.

### *Progressive Stage*

In this stage the shock becomes steadily worse until death. It is reversible with outside therapy.

### *Irreversible Stage (Refractory Shock)*

Here the shock has progressed to such an extent that all forms of known therapy are inadequate to save the person's life. If not properly treated during 2nd stage, the person goes into this stage. If it becomes severe, cardiovascular tissues deteriorate. Refractory shock is the manifestation of late effects of sympathetic vasoconstriction, long sustained decrease of regional circulation and operation of 'positive' feedback mechanisms.

The main causes which precipitate refractory shock and leading to death are:

***a. Cardiac failure***

Fall in BP and tachycardia → decreased coronary flow → myocardial depression → decreased cardiac output → decreased HR → decrease in coronary flow and myocardial depression.

***b. Vasomotor failure***

During initial stages of shock, vasomotor center is activated. If the abnormality is not corrected during 2nd stage; it will cause depression of vasomotor center.

Depression of vasomotor center → decrease in vasomotor center activity → fall in BP (both systolic and diastolic) → blood flow to vasomotor center decrease → progressive reduction in BP → finally vasomotor center fails.

***c. Sluggish circulation***

It causes blockage of minute vessels.

Blood supply to tissues affected → accumulation of lactic acid, carbonic acid, etc. → Severe acidosis → Depress the activities of myocardium, vasomotor and other tissues.

***Note***

*Acute respiratory distress syndrome*

Seen in septic and severe hypovolemic shock. It is due to hypoxia and accumulation of $H^+$ ions. There is damage to alveolar epithelium and endothelium and exudation of fluid into interstitial space.

## Compensatory Mechanisms

It is divided into two groups.

### *Short-term Mechanisms*

1. Baroreceptor reflex
2. *Chemoreceptor reflex:*
   Loss of blood causes anemia and stagnant hypoxia. It stimulates chemoreceptor reflex activities and activates vasomotor center.
3. CNS ischemic reflex.
4. Activation of renin-angiotensin system and formation of angiotensin II is increased. Angiotensin II acts on subfornical organ, which contain an osmoreceptor that increases the thirst.
5. *Increased sympathetic activity:* It leads to generalized vasoconstriction except in brain and heart. In brain and heart, vasodilatation (by $\beta_2$ receptors.)
6. *Venoconstriction:* Increased venous return, SV increases, CO increases.
7. Intense constriction of splenic vessels lead to redistribution of blood to vital organs.
8. Increases activity of reticular activating system, this increases muscle and thoracic pumping → increases venous return → increases cardiac output → increases BP.
9. Increased ACTH and aldosterone secretion causes salt and water retention and cause increase in blood volume.
10. In kidneys, there is constriction of afferent and efferent arterioles, GFR is decreased and prevents renal failure.

### *Long-term Mechanisms*

It continues for hours to days to weeks.

1. Increased thirst.
2. Increased thirst for salt.
3. Increased water absorption from renal tubules and water absorption from GIT.
4. Conservation of salt and water by kidneys mediated by hormones.
5. After moderate hemorrhage, circulating plasma volume is restored within 12–17 hours.
6. Preformed albumin enters circulation from extravascular stores.
7. Increased hepatic synthesis of albumin and other plasma proteins occurs in a period of 3–4 days.
8. Increased formation of RBC. Formation of RBCs increases, reaches a peak in 10 days and RBC content restored to normal level within 4–48 weeks.
9. Increased 2, 3 DPG content shifts $O_2$ dissociation curve to right side. It decreases the affinity of Hb for $O_2$. So more $O_2$ is released to tissues.

### Treatment

Immediate objective is to maintain and restore adequate tissue perfusion (blood flow). In anaphylactic shock, drug of choice is epinephrine (causes vasoconstriction). In septic shock, drug is antibiotics. In hemorrhagic shock, blood transfusion is done. In burn shock, infusion of isotonic normal saline (0.9% NaCl) to compensate plasma loss.

## CARDIAC ARRHYTHMIAS

The heart normally beats at a regular rhythm set by SA node. Any deviation from this normal rhythm is called cardiac arrhythmia. When any irritable focus is capable of discharging repetitively at a rate more rapid than that of SAN, it can initiate and maintain heart beat for several seconds to few hours. This is called as ectopic cardiac beat. If an irritable ectopic focus discharges once, the result is a beat that occurs before the expected next normal beat and transiently interrupts the cardiac rhythm. This results in atrial, nodal or ventricular extrasystole or premature beat. If the focus discharges repetitively at a rate higher than that of the SA node, it produces rapid, regular tachycardia resulting in atrial, ventricular, or nodal paroxysmal tachycardia or atrial flutter. Cardiac arrhythmias are generally classified into:

1. Atrial arrhythmias
2. Ventricular arrhythmias

### Atrial Arrhythmias

If the excitation spreads from an independently discharging focus in the atria, it is called atrial arrhythmia. The impulses stimulate the AV node prematurely and is conducted to ventricles. Atrial arrhythmias are further classified into (Table 4.6):

### *Atrial Tachycardia*

This occurs when an atrial site (outside the SA node) become the dominant pacemaker. It is characterized by very regular rates ranging from 140–220 beats /min. Atrial tachycardia may be caused by overindulgence in caffeine, nicotine or alcohol and may also occur during anxiety attack. It is not associated with block.

### *Atrial Flutter*

If abnormal focus is in atria, it will lead to atrial flutter. Here the rate of impulse production is 200–350 beats/min. During atrial flutter AV node is unable to transmit all of the atrial impulses to the ventricles (max capacity to transmit impulse is 230 beats/min) and therefore the ventricular rate may be half, one-third or one-fourth of the atrial rates. This is associated with 2:1/3:1 heart block. In atrial flutter, QRS complex is normal.

### *Atrial Fibrillation*

Atrial fibrillation is characterized by a totally irregular, rapid rate (300 to 500 beats/min). In it, ventricular rate is completely irregular because only a fraction of the atrial impulses that reach the AV node are transmitted to the ventricles.

**Table 4.6: Atrial arrhythmias compared**

| | *Atrial tachycardia* | *Atrial flutter* | *Atrial fibrillation* |
|---|---|---|---|
| Atrial rate | Up to 220 bpm | Between 200–350 bpm | 300–500 bpm |
| Atrial contractions | Normal, uniform | Alternate large and small contractions due to a partial refractory state in the atria | Irregular oscillations of the surface called fibrillations as length of refractory period further increases |
| Atrial (A) to ventricular (V) rate | A:V::1:1 | A:V::2:1(as AVN cannot transmit > 230 impulses/min) | A:V::2 or 3:1(due to irregular discharge from AVN) |
| ECG findings | All time intervals shorten | 2° type of Hb | a. Absence of 'P'wave<br>b. Appearance of fibrillation (f) wave<br>c. Irregular QRS complexes; no 'T'wave |

**Table 4.7: Ventricular arrhythmias compared**

| | *Ventricular tachycardia* | *Ventricular flutter* | *Ventricular fibrillation* |
|---|---|---|---|
| Ventricular rate | Up to 220 bpm | Between 500–350 bpm | 300–500 bpm |
| ECG findings | QRS complexes: polymorphic | Hairpin curves where main and terminal deflection can no longer be differentiated | Irregular, fast, small potential fluctuations. Fibrillating ventricles cannot pump blood effectively. This can lead to sudden death |

## Ventricular Arrhythmias

Ventricular arrhythmias are more serious (particularly tachycardia) because, here cardiac output is affected. Ventricular arrhythmias are further classified into (Table 4.7):

### *Ventricular Tachycardia*

It is caused by abnormal automaticity or by re-entry within diseased ventricular tissue. This most often occurs in patients with coronary artery disease or cardiomyopathy. Here QRS complex is abnormal. It is broad and bizarre shaped.

### *Ventricular Flutter*

If abnormal focus is in ventricle, it will lead to ventricular flutter. In ventricular flutter, the rate of ventricular contractions is between 200–350 beats/min. ECG shows large oscillations (Hair pin curve) where main and terminal deflections can no longer be detected.

### *Ventricular Fibrillation*

Here the rate of ventricular contractions is about 300–500 beats/min. It is a fatal condition, because fibrillating ventricles cannot pump blood effectively and circulation of blood stops causing sudden death.

### *Causes of Flutter and Fibrillations*

Flutters and fibrillations occur due to a defect in conduction that permits a wave of excitation to propagate continuously within a closed circuit (circus movement). This is referred to as circus or re-entry phenomenon, i.e. formation of circuit around a ring of myocardial fibers by the excitation process. The common sites of occurrence of this phenomenon are :

i. Tissues joining the opening of inferior and superior vena cavae.
ii. Around the AV valves.

There are two mechanisms of development of circus movements:

1. Depolarization of a ring of cardiac muscle.
2. Retrograde conduction due to transient block in bundle of His.

### *Depolarization of a Ring of Cardiac Muscle*

Normally the excitation impulse spreads in both directions in the ring and the two impulses cancel when they meet on opposite side. If there is a transient block on one side due to slowed conduction, the impulse reaching here earlier via a shorter route will find this area refractory and die off. However, the impulse which goes around the ring and reaches here late, finds this area no longer refractory. It will pass this area and continue to circle indefinitely producing circus movement (Fig. 4.35).

### *Retrograde Conduction Due to Transient Block in Bundle of His*

Transient block due to slowed conduction in parts of conduction pathway prevents 'anterograde' conduction in a portion of bundle of His and then this area is invaded from below. The area above the block has had time to recover and

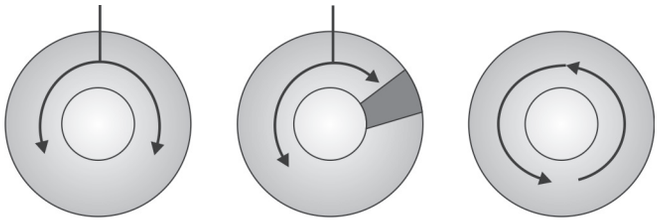


**Fig. 4.35:** Mechanism of development of circus movement; depolarization of a ring of cardiac tissue

is no longer refractory producing re-entry, i.e. retrograde conduction causing atrial depolarization resulting in atrial beat called as Atrial Echo Beat.

***Note***

1. Arrhythmias can be also be broadly classified into:
   a. *Bradyarrhythmias:* Here the heart rate is reduced. It occurs in the following conditions:
      - Sick-sinus syndrome (failure of SA node)
      - Heart block.
   b. *Tachyarrhythmias:* When heart rate is increased along with abnormal rhythm it is reffered to as tachyarrhythmias. The various tachyarrhythmias are:
      - Atrial and ventricular ectopic beat
      - Atrial and ventricular tachycardia
      - Atrial and ventricular flutter
      - Atrial and ventricular fibrillation
2. *Paroxysmal tachycardia:* If tachycardia appears and declines abruptly it is called as paroxysmal tachycardia. The attack may last from seconds or minutes to many days. It may be having focus either in the atria, i.e. paroxysmal atrial tachycardia (PAT) or in ventricles, i.e. paroxysmal ventricular tachycardia (PVT).

## CARDIAC FAILURE

It can be defined as the inability of heart to pump blood in sufficient amount to meet the requirements of body.

### *Causes*

- Decreased coronary blood flow leading to decreased contractility (MI)
- Valvular dysfunction
- Pericardial effusion
- Cardiomyopathies
- Obstruction to outflow (in hypertension, coarctation of aorta)
- Thiamine deficiency, beriberi.

### Types

1. *Systolic/forward failure:* Due to weak pumping action of ventricle.
2. *Diastolic/backward failure:* Due to decreased filling of ventricles.
3. *High output failure:* This is the type in which, although the absolute value of cardiac output is more than normal, it cannot meet the requirements of body.

### Compensatory Mechanisms

#### *Baroreceptor Mechanism*

Cardiac failure leads to decreased pumping action of heart. So cardiac output decreases and thus BP is decreased. This leads to the activation of baroreceptors. The activation of baroreceptor leads to the following changes.

a. *Stimulation of the heart:* This results in increased contractility → stroke volume increases → heart rate increases → increase in CO → results in increase in BP.
b. *Peripheral vasoconstriction:* This leads to increase in diastolic BP.
c. *Peripheral venoconstriction:* This leads to increased VR → diastolic volume increases → stroke volume increases → CO increases.

***Note:*** Adrenal medulla is a modified sympathetic ganglion, when stimulated leads to increased secretion of epinephrine and nonepinephrine in the circulation. Epinephrine acts on heart and blood vessels.

#### *Decreased Cardiac Output Leads to Renal Hypoxia*

Renin-angiotensin mechanism is activated. This will lead to vasoconstriction. There will be increased retention of salt and water by the action of aldosterone. This leads to increase in blood volume and there by CO increases.

#### *Effect of Frank-Starling Law*

In early stages of cardiac failure operation of Frank-Starling law helps in increasing CO.

(Decreased cardiac output → increased EDV → stretching of myocardium → increased force of contraction (Frank-Starling law) → increased stroke volume → increased CO).

#### *Effect of Laplace Law*

According to Laplace law

Where, $P = \frac{2T}{R}$

P = Transmural pressure; Pressure across myocardium.
T = Tension of wall.
R = Radius.

**Table 4.8: CVS changes during exercise**

| | *Changes* | *Cause for the change* |
|---|---|---|
| 1. Heart rate (HR) | Increases proportional to severity of exercise. But in trained athletes, the increase is less than that in untrained individuals. In healthy individuals, HR will not exceed 180 beats/min. In advanced age there is less HR rise even with same weightage of work done | 1. Fall in vagal tone<br>2. Rise in sympathetic activity<br>3. Adrenaline secreted in early phases of exercise<br>4. Rise in body temperature in later phases (causing tachycardia) |
| 2. Cardiac output | CO increases tremendously during exercise. The normal untrained persons can increase CO a little over 4-fold, and the well trained athlete can increase output about 6-fold | Increase in heart rate (mostly) with increase in stroke volume (mildly) together cause increase in CO (refer Frank-Starling law)<br>As the HR increases, there is shortening of diastole (less time for cardiac inflow) but the venous return increases impressively compensating the decrease in diastole period<br>In an untrained person in moderate exercise, stroke volume rises only mildly (10–30%), during severe exercise, in this person, stroke volume will rise further<br>But in a trained athlete, the stroke volume rises sharply even in moderate exercise and in severe exercise it may be doubled |
| 3. Coronary circulation | Coronary circulation increases with heaviness of exercise | This is primarily due to local hypoxia of myocardium<br>Sympathetic activity also has some role in this |
| 4. Systolic BP | SBP rises usually in moderate isotonic exercise | SBP depends more on CO and as the CO increases, SBP increases |
| 5. Vessels of skeletal muscles | Severe vasodilatation of blood vessels occurs | This may be due to vasodilator cholinergic sympathetic activity or due to local metabolites and local hypoxia |
| 6. A-V $O_2$ difference | Increases due to increased $O_2$ extraction as there will be raised coefficient of $O_2$ utilization. (from a resting value of 4 ml/100 ml to a max. of 16 ml/100 ml) | 2,3 DPG rise causes this difference. According to Bohr effect, this has to occur |

Transmural pressure is responsible for pumping action.

When radius decreases, P increases → pumping activity is increased → stroke volume increases → CO increases.

### Decompensated Heart Failure

In spite of compensatory mechanisms, if heart fails to pump adequately the blood after venous return, it is called decompensated heart failure. It can be a right sided or left sided or both sided heart failure.

## CARDIOVASCULAR CHANGES IN EXERCISE

CVS changes (Table 4.8) can be divided into:

1. Changes in heart
2. Changes in peripheral circulatory system.

### *Changes in Heart*

This includes changes in heart rate, cardiac output and coronary blood flow.

### *Peripheral Circulatory Changes*

This includes changes in systolic and diastolic blood pressure, blood vessels in skeletal muscles and capillary A-V $O_2$ difference.

#### *Benefits of Circulatory Readjustments*

Working muscles and the heart are better fed and drained well. The better draining helps them to remove their extra heat. Increased quantity as well as velocity of blood to tissues helps in better exchange of gases. Increased venous return happens because of increased physical work by muscles.

Chapter

# 5 Gastrointestinal System

To sustain life, the body needs a continual supply of water, electrolytes and nutrients. This function is served by the gastrointestinal system.

## PHYSIOLOGICAL ANATOMY OF GIT

The wall of gastrointestinal system (GIT) from posterior pharynx to anus in general consists of three layers of smooth muscle, two longitudinal and one circular. Histologically four layers are identified, they are (Fig. 5.1):

### *Mucosa*

Consists of surface epithelium. Inner to that is the connective tissue layer called lamina propria containing glands, blood vessels, nerve fibers, lymphatics. External to the lamina propria is muscularis mucosa, a very thin layer of smooth muscle.

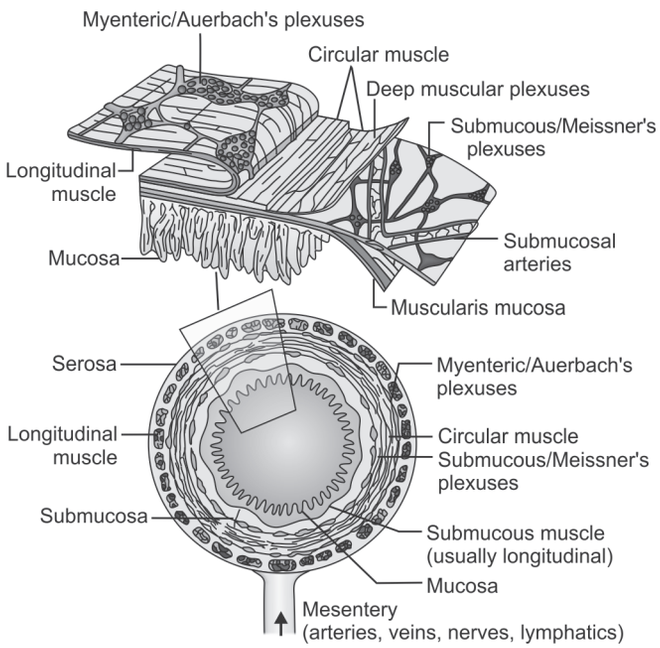



**Fig. 5.1:** Cross-section of GIT, showing the different layers of its wall

### *Submucosa*

Luminal surface is highly folded to increase the total surface area available for digestion and absorption. It contains Meissner's plexus (submucosal plexus), between the submucosa and middle circular layer.

### *Muscle Coat (Muscularis externa)*

There are two layers of muscle, inner circular and outer longitudinal. In between the two layers Auerbach's (Myenteric) plexus is present. The contraction and relaxation of smooth muscle enables peristalsis.

### *Serosa*

Outermost layer.

### Nerve Supply of GIT

Two types of innervation—they are enteric/intrinsic and extrinsic.

### *Extrinsic Innervation*

Consists of parasympathetic and sympathetic components of ANS. Parasympathetic fibers are through vagus (cranial out flow). Neurotransmitter is ACh. Fibers also originate from sacrum of spinal cord (sacral outflow). Stimulations increases the activity of intestinal smooth muscles, increases secretion and increases motility. It inhibits the sphincters. Sympathetic fibers arise from T8 to L2. Neurotransmitter is norepinephrine. They decreases motility and secretion.

### *Enteric Nervous System*

It consists of the Auerbach/myenteric plexus and the submucous/Meissner's plexus. These two plexus are interconnected. It innervates the glandular epithelium, intestinal endocrine cells and submucosal blood vessels. It is involved in control of intestinal secretion. Neurotransmitter in the system include ACh, the amines norepinephrine and serotonin, the amino acid: glutamate, aspartate, D-serine, γ-aminobutyric acid

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(GABA), the purine ATP, the gases NO and CO and many peptides like enkephalin, gastrin releasing peptide (GRP), gelatin, neuropeptide-Y, neurotensin, substance P, vasoactive intestinal peptide (VIP), somatostatin. System contains about 100 million sensory neurons. Though enteric system is controlled by extrinsic nervous system, it can function autonomously. Sensory nerve fibers elicit local reflexes within the gut or other reflexes. They send afferents to (Fig. 5.2):

a. Both plexus of enteric nervous system.
b. Prevertebral ganglia of sympathetic nervous system.
c. Spinal cord.

***Note***

Long loop reflex—center is at CNS.
Short loop reflex—center is at gut wall.

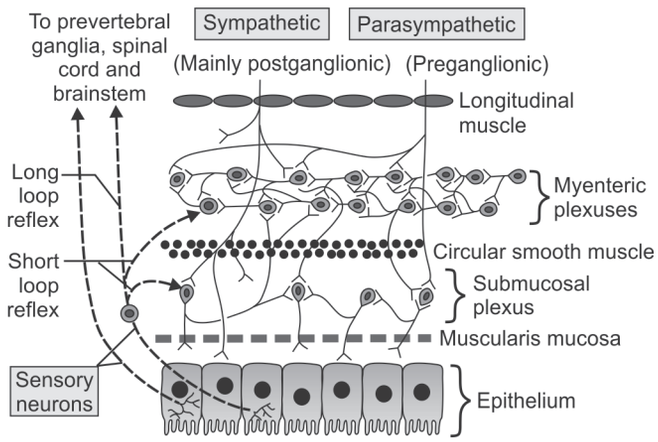


**Fig. 5.2:** Innervation of GIT

## SALIVA

About 1500 ml of saliva is secreted per day. Specific gravity is 1.002–1.009. pH is less than 7 in resting gland and it becomes 8 during active secretion.

### *Composition*

It includes 99.5% water, 0.5% solids—both organic and inorganic. Organic constituents are salivary amylase, mucous, lingual lipase, lysozymes, IgA, IgM, lactoferrin, epidermal growth factor, nerve growth factor, blood group substances, kallikrein, other substances like urea, uric acid, creatinine, thiocyanate, organisms like viruses (rabies) and bacteria. Inorganic constituents are $Na^+$, $Cl^-$, $K^+$ and $HCO_3$.

### *Salivary Glands*

It inlcudes three pairs: Parotid, submandibular, sublingual (Table 5.1).

**Table 5.1: Salivary glands—main features**

| *Gland* | *Type* | *Secretion* | *% of total saliva* |
|---|---|---|---|
| Parotid | Serous | Watery | 20 |
| Submandibular | Mixed | Moderatively | 70 |
| Sublingual | Mucous | Viscous | 5 |

The remaining 5% is contributed by minor glands in the oral cavity.

### *Functions of Saliva*

#### *Digestive Function*

First digestive juice to which food is exposed. Enzymes present are lingual lipase and salivary amylase. Salivary amylase acts on cooked food. It is the 1st enzyme acting on carbohydrates. Starch is broken down into maltose plus maltotriose plus dextrin. Site of action is 1, 4 α-glycosidic linkage. Action is for short period in mouth and its action is continued in the stomach in the interior of bolus of food, stops when pH is less than 4. Lingual lipase, secreted by Ebner's gland is 1st enzyme acting on lipids. Action starts at acidic pH of stomach.

#### *Lubricating Function*

Mucin helps in lubrication of food. It assists mastication and swallowing. It protects oral mucosa. It aids in speech by facilitating movements of tongue and lips.

#### *Protective Function*

Flow of saliva washes away pathogenic bacteria, prevents accumulation of food and thus preventing oral caries. Thiocyanate and IgA are bactericidal. Lactoferrin is bacteriostatic. Saliva contains protein antibodies that can destroy oral bacteria including some that cause dental caries. Kallikrein by enzymatic action form bradykinin and it is a vasodilator and increases salivary secretion. Buffers in saliva helps to neutralize gastric juice and protect esophageal mucosa. Saliva acts as a solvent for molecules to reach taste receptors.

#### *Excretory Function*

Excretes heavy metals like Hg, penicillin, Pb drugs.

#### *Temperature Regulation*

#### *Role in Taste Sensation*

Saliva acts as a solvent for various food stuffs. As taste is a chemical sense, the taste receptors respond only to dissolved substances.



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### Mechanism of Formation of Saliva

#### Primary Secretion of Saliva

The acinar cells of salivary glands secrete the initial saliva into the salivary ducts. The initial saliva is isotonic. The concentration of $Na^+$, $Cl^-$, $K^+$ and $HCO_3^-$ is same as that of plasma.

#### Modification of Saliva

Reabsorbtion of $Na^+$ and $Cl^-$ occurs in the ductal cells that line the tubular portions of salivary glands. $K^+$ and $HCO_3^-$ are secreted into the duct. The ducts are relatively impermeable to water and saliva becomes hypotonic and alkaline. Aldosterone acts on the ductal cells to increase the reabsorbtion of $Na^+$ and $Cl^-$ from salivary ducts.

***Note:*** $K^+$ content is highest in saliva.

### Regulation of Salivary Secretion

It is under neural and vascular control. Neural consists of sympathetic and parasympathetic system.

#### Neural

Usual stimuli are taste, smell, tactile sensation from mouth, pharynx and reflexes from stomach and intestine. Parasympathetic stimulation increases water content and decreases organic constituents (associated with local release of VIP). Food in mouth control the secretion of saliva via following reflexes:

#### Conditioned

Conditioned reflex occurs only in previous experience. Sight, smell or even thought of palatable food increase the salivary secretion. Here, the parasympathetic supplying the salivary glands are stimulated by impulses coming from higher centers of brain.

#### Unconditioned

They are initiated by stimulation of receptors in the buccal cavity. Impulses are carried through vagus to medullary center. Efferent fibers are secretomotor fibers of 7th and 8th CN. Center is at superior (for submandibular and sublingual) and inferior (parotid) salivary nucleus.

Stimulation of sympathetic nerve supply causes vasoconstriction and secretion of small amounts of saliva rich in organic constituents.

#### Vascular

Increased blood supply increases nutrition which increases secretion.

#### Frey's/Chorda Tympani Syndrome

In cases of trauma or surgery, chorda tympani nerve will be affected. During regeneration, this nerve may join with nerve fibers innervating sweat gland in the submental region. This will result in increased sweating during salivation.

## STOMACH AND ITS SECRETION

The muscle coat of stomach has three layers, an outer longitudinal, middle circular, and an inner oblique. The gastric epithelium surface shows a number of small openings called gastric pits. About 3–7 gastric glands open into a single gastric pit. Gastric glands are simple tubular glands located in mucosa. There are three types of glands: Fundic, pyloric and cardiac.

#### Fundic

Found in the fundus and over greater part of body of stomach. They contain four types of cells:

1. **Chief cells (peptic):** Secrete pepsinogen and other proteolytic proenzyme.
2. **Parietal cells (oxyntic):** Secrete HCl and intrinsic factor.
3. **Enterochromaffin like (ECL) cells:** Histamine.
4. **Neck mucous cells:** Secrete thin mucus.

#### Pyloric

Found in the antrum and pyloric region of the stomach. They contain two types of cells:

1. **Neck mucous cells:** Secrete thin mucus
2. **G-cells:** Responsible for the release of gastrin.

#### Cardiac

Found around the cardiac orifice and secrete thin mucus.

#### Functions of Stomach

1. Reception of food
2. Temporary storage of food
3. Mechanical and chemical digestion
4. Absorption of alcohol and drugs
5. Intrinsic factor helps in absorption of vitamin $B_{12}$, thus helps in maturation of RBC
6. Stomach empties its contents at a controlled rate to duodenum.

#### Composition of Gastric Juice

It is secreted 2.5 liter of gastric juice per day. pH~1. Composition is 99.5% water and 0.5% solids. Solids include both organic and inorganic.

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***Organic***

### *Enzymes*

Pepsinogen, gastric lipase, gelatinase.

### *Mucus*

Two types: thick (insoluble) and thin (soluble).
Thick: Secreted by surface epithelial cells.
Thin: Secreted by neck mucous cells of pyloric and cardiac glands.

### *Intrinsic Factor*

***Inorganic***

HCl, $SO_4^{2-}$, $HCO_3^-$, $Na^+$, $K^+$.

*Some further details about individual components:*

1. **HCl**: HCl is necessary for:
   a. The conversion of pepsinogen to pepsin.
   b. *Bacteriostatic action:* Food contains many bacteria, but they are killed by the gastric HCl, so that contents of the upper part of the small intestine are bacteriologically sterile.
   c. It stimulates the secretion of some GI hormones.
   d. HCl has a preventive role against gastric cancer. Persons who suffer from achlorhydria are thus more susceptible to gastric cancer.
2. **Pepsinogen:** In the presence of HCl, pepsin is very active and digests food protein. Thus, the combination of acid and the pepsin, called acid pepsin mixture (APM) powerfully digests food protein.
3. **Mucus:** Mucus has the following functions:
   a. It specially the thick mucus, protects the gastric mucosa mechanically from being injured by the corrosive effects of food.
   b. Together with the $HCO_3^-$ of the gastric juice, it constitutes the mucosal barrier, which prevents the autodigestion of the gastric mucosa itself by APM.
   c. Soluble mucus makes the food lubricated.
4. **Bicarbonates** act together with the gastric mucus to prevent the autodigestion of the stomach.
5. **Intrinsic factor** is needed for the absorption of orally ingested vitamin $B_{12}$.
6. **Gastric lipase** converts triglycerides into fatty acids and glycerols.
7. **Gelatinase** liquefies gelatin (protein contained in connective tissue).

## HCl Secretion

The acid is formed in the intracellular canaliculus of parietal cell (not within the cytoplasm so that the cell is not damaged due to high acidity). The intracellular canaliculi extend from apical surface of parietal cell into interior and contain $H^+$- $K^+$ ATPase and $Cl^-$ channels on the walls. The basolateral membrane on parietal cell in contact with interstitial fluid contain $Cl^-$-$HCO_3^-$ exchangers and $Na^+$-$K^+$ ATPase (Fig. 5.3).

When parietal cells are stimulated $CO_2$ and $H_2O$ combine to form $H_2CO_3$ which splits to $H^+$ and $HCO_3^-$ in presence of enzyme CA. $H^+$ is pumped into the lumen of canaliculus with the help of $H^+$-$K^+$ ATPase or proton pump (active transport). $HCO_3^-$ leaves the parietal cell by an antiport in the basolateral membrane of parietal cells that exchange $Cl^-$ for $HCO_3^-$. $HCO_3^-$ binds with $Na^+$ to form $NaHCO_3$ in capillary blood. $Cl^-$ in the cytoplasm diffuse into lumen of canaliculus. In the lumen of canaliculus, $H^+$ combines with this $Cl^-$ to form HCl. This HCl reaches gastric lumen.

For each molecule of HCl formed in gastric lumen, one molecule of $NaHCO_3$ is formed in the blood. Hence, when HCl secretion is increased after a meal, pH of blood increases and this is called ***postprandial alkaline tide***.

### *Inhibitors of HCl Secretion*

1. Somatostatin
2. Acid chyme
   a. Direct action—inhibits parietal cell directly.
   b. Indirect action—increases secretin secretion.
3. Fatty food
   a. Release GIP—inhibit G cells and parietal cell.
   b. Enterogastrone—inhibit HCl.
4. Hyperosmotic chyme-inhibit secretion and motility reflexly.
5. Prostaglandins (particularly PGE).

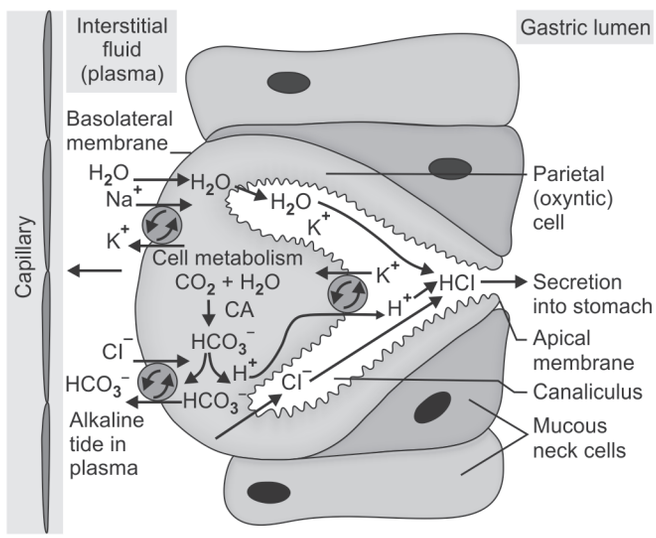


**Fig. 5.3:** HCl secretion by parietal cells in stomach



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## Pepsinogen Secretion

Pepsinogen is an inactive precursor of pepsin. It is secreted by the chief cells. Pepsinogen has no digestive activity. However, as soon as it comes in contact with HCl, it is activated to form active pepsin. Pepsin functions as an active proteolytic enzyme in a high acid medium (optimum pH 1.8 – 3.5), but above a pH of about 5 it has no proteolytic activity and becomes completely inactivated in a short time.

## Secretion of Intrinsic Factor

Intrinsic factor is secreted by parietal cells of gastric mucosa along with the secretion of HCl. The intrinsic factor is essential for absorption of vitamin $B_{12}$. It forms a complex with $B_{12}$ which is carried to the terminal ileum where the vitamin is absorbed. When the acid-producing parietal cells of the stomach are destroyed (which frequently occurs in chronic gastritis), the person develops not only achlorhydria (lack of stomach acid secretion) but often also pernicious anemia because of failure of maturation of the red blood cells in the absence of vitamin $B_{12}$ stimulation of the bone marrow.

## Regulation of Secretion of Gastric Juice

Gastric secretion is accurately synchronized with the need for gastric juice. Mechanisms regulating the gastric secretion include neural control and chemical control.

### *Neural Control*

Neural control over the gastric glands is exerted by local enteric plexus involving cholinergic neurons and impulses from CNS via vagal (extrinsic) innervations. Vagal stimulation increases the secretion of HCl by parietal cells and pepsin by chief cells. Vagal stimulation increases $H^+$ secretion by a direct and an indirect path.

In the direct path, the vagus nerve fibers innervating parietal cells stimulate $H^+$ secretion by releasing ACh which acts on through $M_3$ muscarinic receptors (to increase intracellular $Ca^{2+}$) on parietal cells it causes direct stimulation of secretion of gastric juice. In addition, ACh also potentiates the effects of histamine on $H_2$ receptors of parietal cells.

In the indirect pathway, the vagus innervates G cells and stimulates the release of gastrin into circulation through gastrin releasing peptide (GRP). The gastrin in turn stimulates $H^+$ secretion. ACh released on vagal stimulation also acts on enterochromaffin like (ECL) cells which release histamine. Histamine increases $H^+$ secretion by acting on $H_2$ receptors on the parietal cells, but the relative importance of ACh in stimulating their secretion is unsettled.

Peptic cells are stimulated by ACh released from vagus nerves or from gastric enteric nervous plexus.

### *Chemical Control*

1. *Role of gastrin:* It is a GI hormone produced by G cells located in the pyloric glands. Most known powerful stimulant of HCl secretion. Presence of products of protein digestion in the stomach acts on G cells to release gastrin. It stimulates secretory activity of parietal cell and chief cells.

#### *Actions*

   a. Gastrin stimulates the secretion of histamine from ECL cells. Histamine stimulates HCl secretion and this is the principal way by which gastrin stimulates acid secretion.
   b. Gastrin also stimulate HCl secretion by acting on the gastrin receptors in the parietal cell. This increases intracellular $Ca^{2+}$.
   c. To a lesser extent it stimulates chief cells to secrete pepsin.

2. *Role of histamine:* Histamine is released from ECL cells. Enterochromaffin like cells bear both gastrin receptors and ACh receptors. They release histamine in response to both circulating gastrin as well as ACh released by vagal fibers. The histamine released stimulates HCl secretion from parietal cells by acting on $H_2$ receptors. Histamine bind to $H_2$ receptors and via $G_s$, this increases adenyl cyclase activity and intracellular cAMP (Fig. 5.4).

   Increase in intracellular cAMP and $Ca^{2+}$ act via protein kinases to increase the transport of $H^+$ into the gastric lumen by $H^+$ - $K^+$ ATPase.
3. *Role of somatostatin:* Somatostatin is secreted by D cells in the gastric glands. They inhibits gastric acid secretion.
4. *$PGE_2$* acts via GI to decrease adenylyl cyclase activity and intracellular cAMP. This inhibits acid secretion.
5. *Low pH* (< 3) in the stomach inhibits the secretion of $H^+$ by parietal cells by negative feedback mechanism.

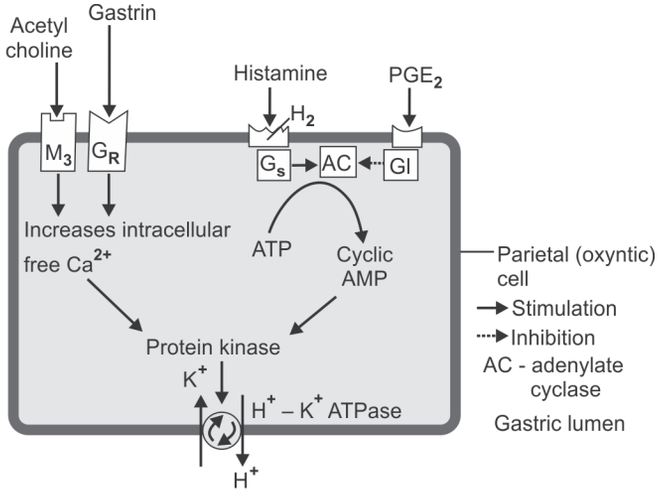


**Fig. 5.4:** Regulation of gastric acid secretion by the parietal cell

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6. *Intestinal influences:* Fats, carbohydrates and acid in the duodenum inhibit gastric acid and pepsin secretion via neural and hormonal mechanisms.
7. The rate of secretion of pepsinogen is strongly influenced by the *amount of acid* in the stomach. Acids elicits additional enteric nervous signals to the peptic cells.
8. *Emotional responses:* Psychic states have effects on gastric secretion and motility that are principally mediated via the vagi. Anger and motility are associated with hypersecretion of the gastric mucosa. Fear and depression decrease gastric secretion and blood flow and inhibits gastric motility.

## Phases of Gastric Secretion and their Regulation (Flow chart 5.1)

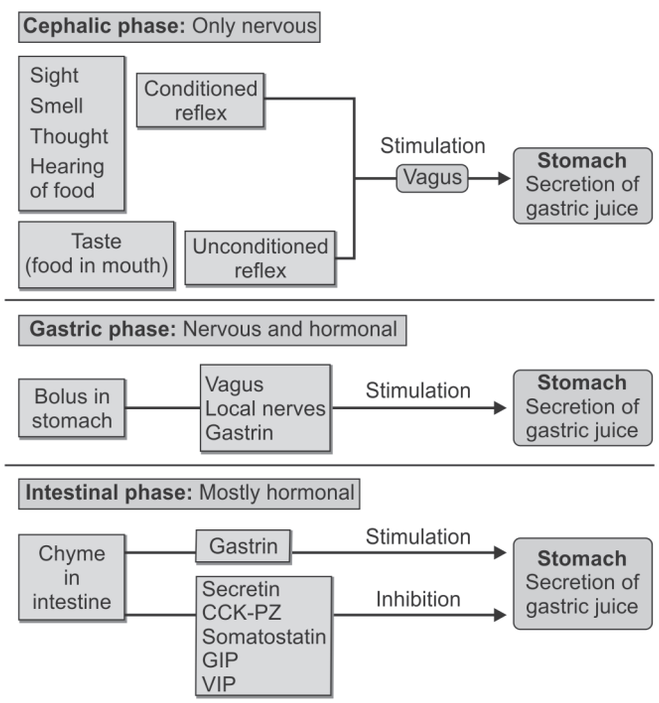
### *Cephalic Phase*

Cephalic phase of gastric secretion occurs before the entry of food into the stomach. The secretion is initiated by sight, smell, thought or taste of food. Cephalic phase is under neural control and is mediated through vagus. Twenty percent of total secretion is in this phase.

### *Gastric Phase*

Gastric phase of gastric secretion occurs when food enters stomach. Seventy percent of total secretion occurs in this phase. It is mediated by neural and hormonal mechanism.

**Flow chart 5.1:** Phases of gastric acid secretion and their regulation




a. *Neural:* Distension of stomach by food stimulates gastric juice secretion (through local myentric and vagovagal reflex).
b. *Chemical/Hormonal:* Products of partial digestion stimulate the secretion of gastrin. Gastrin enters the circulation and stimulates gastric glands.

### *Intestinal Phase*

Intestinal phase of gastric secretion begins as the chyme begins to empty from the stomach into duodenum. Accounts for 10% of gastric juice secretion. Initiatly (during the early intestinal phase) the secretion is increased and later it is inhibited. This inhibition results from the following influences.

a. *Enterogastric reflex:* It is a reflex mechanism mediated through myentric nervous system as well as through extrinsic sympathetic system and vagus nerve. It is initiated by distension of small intestine in the presence of acids or protein breakdown products in the upper intestine and irritation of mucosa.
b. *Hormonal mechanism:* Presence of acid, fat, protein break down products, hypo-osmotic or hyperosmotic fluids and any irritating factors in the upper small intestine causes release of hormones like CCK, GIP, VIP and somatostatin which inhibit gastric secretion.

## Sham Feeding

It is an experimental procedure devised by Pavlov to demonstrate the regulation of gastric secretion.

### *Procedure*

a. A hole is made in the neck of an anesthetized dog.
b. The cut ends are drawn out through the hole in the neck.
c. When the dog eats food, it comes out through the cut end of the esophagus.
d. But the dog has the satisfaction of eating the food.

This experimental procedure is supported by the preparation of Pavlov's pouch with a fistula from the stomach. The fistula opens to the exterior and it is used to observe the gastric secretion. It is useful to demonstrate the secretion of gastric juice during cephalic phase. In the same animal after vagotomy, sham feeding does not induce gastric secretion. It proves the role of vagus nerve during cephalic phase.

## Peptic Ulcer

It is an excoriated area of stomach or intestinal mucosa caused principally by the digestive action of gastric juice or upper small intestinal secretion. It frequently occurs along the lesser curvature of the antral end, of the stomach. If peptic ulcer is found in stomach, it is called gastric ulcer and if found in duodenum it is called duodenal ulcer.



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### Mucosal Protective Mechanism

The autodigestion of mucosa is prevented by:

1. *Mucosal barrier:* Gastric mucosal epithelium is covered by mucus. The mucus is primarily of the thick insoluble variety and does not flow or move easily. This is called 'unstirred layer'. But soluble mucus is also present. The acid and pepsin, after being secreted by the gastric glands reach the lumen to come in contact with the food. But it cannot return to come in contact with the mucosal epithelium, because mucus of the unstirred layer acts as a barrier (Fig. 5.5).
2. *Bicarbonate secretion:* Between the mucus and the epithelium some bicarbonate rich fluid is present. Within the lumen, the pH is low (about 2.5), hence pepsin is very active (i.e. it can digest protein easily). But near the epithelium, because of the presence of $HCO^{3-}$ ions, the pH is high, so that pepsin becomes inactive. This $HCO^{3-}$ cannot move towards the lumen because of the presence of unstirred layer.
3. *Epithelial barrier:* Intercellular tight junctions provide a barrier to back diffusion of $H^+$.
4. *Trifoil peptides:* Trifoil peptides in the mucosa of stomach are acid resistant and protect stomach.
5. *$PGE_2$:* Can help in the synthesis of mucus and formation of new mucosal cells. If there is injury in the gastric mucosa, the dead cells can be speedily replaced.

### Causes of Peptic Ulcer

1. The usual cause of peptic ulceration is an imbalance between the rate of secretion of gastric juice and the degree of protection offered by:
   a. Gastroduodenal mucosal barrier
   b. The neutralization of the gastric acid by bicarbonate.
2. Bacterial infection by *Helicobacter pylori* breaks down the mucous barrier.
3. Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin (they decrease mucus and $HCO_3^-$ secretion since they inhibit the production of prostaglandin).
4. Smoking, alcohol, etc. can also disrupt the mucosal barrier.
5. Reflux of gastric content into esophagus and duodenal content into stomach.
6. Excess secretion of gastric juices, which may be due to:
   a. Increased parietal cell mass.
   b. Increased sensitivity for secretory stimuli.
   c. *Zollinger-Ellison syndrome*: This is seen in patients with gastrinomas (tumors secreting gastrin). These tumors can occur in stomach, duodenum and mostly in pancreas. Gastrin causes prolonged hypersecretion of acid and severe ulcers are produced.
7. Poor blood supply.

The difference between duodenal and gastric ulcers is illustrated in Table 5.2

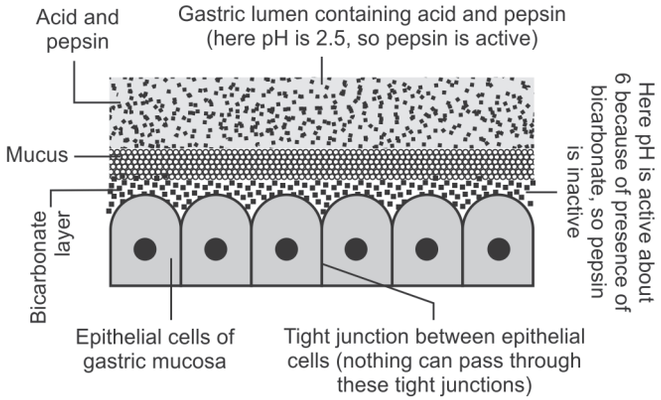


**Fig. 5.5:** Mucosal barrier

**Table 5.2: Differences between duodenal and gastric ulcer**

| *Duodenal ulcer* | *Gastric ulcer* |
|---|---|
| It is seen in 2nd part of duodenum | More common curvature of stomach; esp at incisura angularis |
| More common | Less common |
| Incidence more in younger age group | More in older age group |
| More common in males | Equal in both sexes |
| Chronic duodenal ulcers are not associated with malignancy | Chronic gastric ulcers are associated with malignancy |
| Have higher gastric acid secretion because of back diffusion of $H^+$ | Normal levels of gastric acid secretion |
| Pain relieved by food and antacids | No relief, food aggravate pain |
| Complication less | More severe |
| Superficial and smaller in size | Deep seated and larger in size |

### Complications of Ulcer

1. Perforations—ulcer burrows through all the coats of the stomach → gastric or duodenal lumen now communicates through this perforations with peritoneal cavity.
2. Hemorrhage from the ulcer.

### Physiology of Treatment

1. Antacids (Gelusil) neutralize the acid.
2. Use of antibiotics along with other agents to kill infectious bacteria.
3. Administration of an acid-suppressant drug such as ***cimetidine, ranitidine*** (both block $H_2$ histamine receptors on parietal cell), ***omeprazole*** (inhibits $H^+$- $K^+$ ATPase).
4. NSAIDs induced ulcers can be treated by stopping the use of NSAIDs or by treatment with prostaglandin agonist ***misoprostol***.
5. Gastrinomas can be removed surgically.

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6. Vagectomy, partial gastrectomy.
7. Coating agents—sucralfate.
8. Atropine—anticholinergic.

## PANCREATIC JUICE

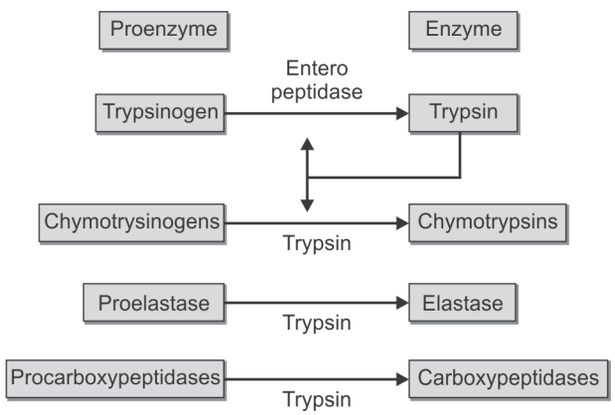
About 1500 ml is secreted per day. It is alkaline and has high $HCO_3^-$ content.

### Composition

1. *Cations:* $Na^+$, $K^+$, $Ca^{2+}$, $Mg^{2+}$
2. *Anions:* $HCO_3^-$, $Cl^-$, $SO_4^-$, $HPO_4^{2-}$
3. *Digestive enzymes*
   a. Amylolytic enzymes
      Pancreatic amylase
   b. Lipolytic enzymes
      - Pancreatic lipase
      - Cholesteryl ester hydrolase
      - Phospholipase $A_2$
      - Bile salt-acid lipase
      - Colipase
   c. Proteolytic enzymes
      - Trypsin.
      - Chymotrypsin
      - Carboxypeptidase A and B
      - Elastase
      - Collagenase
      - Ribonuclease
      - Deoxyribonuclease

### Activation of Pancreatic Proteases (Flow chart 5.2)

**Flow chart 5.2:** Activation of pancreatic proteases in the duodenal lumen




#### *Functions*

1. It contains large amount of bicarbonate ions,which helps in neutralizing the acidity of the chyme emptied from stomach.
2. Trypsin and chymotrypsin splits digested proteins into peptides of various sizes.
3. Carboxypeptidase split some peptides into individual amino acids.
4. Amylase splits polysaccharides into disaccharides and trisaccharides
5. Lipase is capable of hydrolyzing neutral fat into fatty acids and monoglycerides.
6. Cholesterol esterase hydrolyzes cholesterol esters.
7. Phospholipase splits fatty acids from phospholipids.

### Regulation of Secretion

Secretion of pancreatic juice is regulated by both nervous and hormonal factors, with the later playing the predominant role. Neural regulation is through vagal efferents supplying the exocrine gland of pancreas and hormonal regulation is through secretin, CCK-PZ, gastrin and somatostatin.

#### *Regulation of Cephalic Phase*

Cephalic phase of pancreatic secretion like that of gastric secretion, occurs before the entry of food into the stomach. Regulation of this phase is mainly through the reflex vagal stimulation which occurs:

a. By conditioned reflexes, initiated by sight, smell and thought of food.
b. Unconditioned reflexes initiated by stimulation of taste buds by food in the oral cavity, the act of chewing and swallowing.

#### *Regulation of Gastric Phase*

Gastric phase of pancreatic secretion occurs when stomach is distended by the food. This phase is regulated by neural control exerted through vagus and hormonal control executed through the hormone gastrin.

#### *Regulation of Intestinal Secretion*

The intestinal phase of pancreatic secretion begins when the chyme enters the duodenum and jejunum. It is characterized by marked increase in the secretion of both enzymes and aqueous component of pancreatic juice. This phase is regulated by hormones secretin and CCK-PZ.

***Role of secretin***

Secretin enters the blood circulation and after reaching the pancreas it acts on the duct cells and produces large amount of watery juice with high concentration of $HCO_3^-$ and poor in enzymes. The effect is due to increase in intracellular cAMP.

***Role of CCK-PZ***

CCK-PZ acts on the acinar cells to cause the release of zymogen granules and production of pancreatic juice rich in enzymes but low in volume. Effect is mediated by phospholipase C.



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### *Steatorrhea*

Pancreatectomized animals and patients with diseases that destroy the exocrine portion of pancreas have fatty, bulky, clay colored stools, because of the impaired digestion and absorption of fat. It is due mostly to lipase deficiency. Lack of alkaline secretion from pancreas also contributes by lowering the pH of intesine contents as acid inhibits lipase. Hyper secretion of gastric acid and defective reabsortion of bile salts in the distal ileum can also cause this.

## LIVER

Basic structural unit of liver is lobule. Each hepatic lobule is made of ramifying columns of hepatic cells. It is polyhedral in shape with central vein at the center. Liver cells are arranged in radial manner from the central vein in rows of 2 to 3 layers thickness. These hepatic cell are tunneled by a communicating system of lacunae called blood sinusoids. Sinusoids are lined by fenestrated endothelial cells. Endothelium contains Kupffer cells. Portal vein and hepatic artery both empties into the sinusoids. Sinusoids open into central vein. Bile canaliculi are formed or they are spaced between hepatocytes. No separate lining cells for canaliculi. Canaliculi start from central vein region. Along the periphery of each lobule are present portal triads consisting of one branch each of hepatic artery, portal vein and an interlobular bile duct. This concept of liver lobule is classic lobule (Fig. 5.6).

Another concept is acinus. Acinus is considered as basic functional unit of liver. According to this concept, individual acinus is diamond shaped, central vein occupies two corners and portal triad occupies other two corners. The region of cells near the equatorial zone is called zone-1. The cells in this zone are provided with more $O_2$ and nutrients. The zone near central vein region is called zone-3 and is least supplied by $O_2$ and nutrients. Zone between 1 and 3 is called zone-Z (Fig. 5.7).

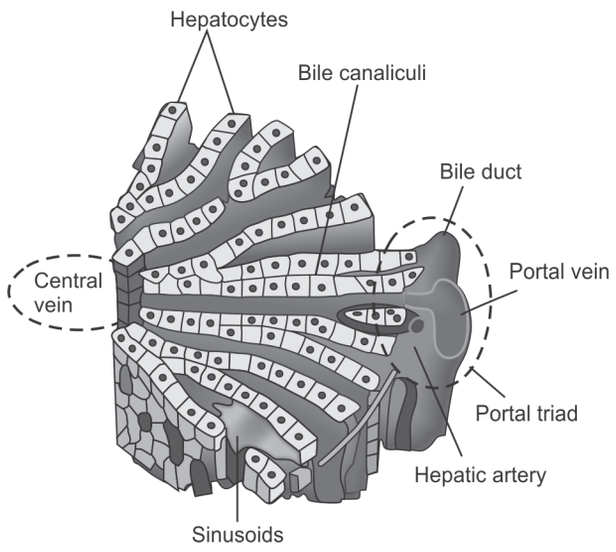


**Fig. 5.6:** Cross-section of a liver lobule

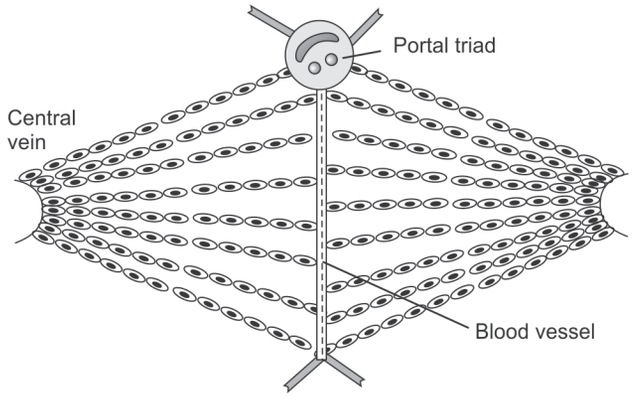


**Fig. 5.7:** Radial arrangement of liver cells from the central vein

### *Blood Supply*

From two sources—Portal vien and hepatic artery. Venous drainage is by hepatic vien. Portal vein carries blood from small intestine, large intestine, spleen and pancreas. It is rich in nutrients and poor in $O_2$. Inside the liver, portal vein divides, redivides and ultimately give rise to sinusoids. Sinusoids run with hepatic cells in liver lobules. Hepatic artery also divides and redivides and finally empties into sinusoids. It is rich in $O_2$. In the sinusoids, hepatic arterial and portal venous blood mixes. Sinusoids → central vein → unite to form large vein → hepatic vein → inferior venacava. Large gaps in endothelial cells helps in easy transport of nutrients to hepatocytes for nutriton. Kupffer cells provide immunity, they are macrophages.

### *Functions*

#### *Synthetic functions*

*Liver synthesize*

a. Most of plasma proteins especially, albumin.
b. Synthesis of clotting factors 5, 7, 9, 10, fibrinogen, prothrombin.
c. Enzymes like alkaline phosphatase, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), serum isocitrate dehydrogenase (SICD).
d. Urea.

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***Metabolic functions***

a. *Carbohydrates:* Helps in synthesis, storage and release of glucose, i.e. glycogenolysis, glucogenesis, gluconeogenesis.
b. *Proteins:* Synthesis enzymes, glycoproteins, clotting factor, plasma proteins.
c. *Lipids:* Both degradation and synthesis of fat takes place in liver. Oxidation in mitochondria to form fatty acids. (Non esterified fatty acids → esterified fatty acids → triglycerides).
   Synthesize lipoproteins, i.e. HDL, LDL, VLDL, chylomicrons.
   Synthesis of saturated fatty acids, cholesterol, phospholipids for cell membrane.

***Bile secretion***

Components of bile (bile salts, bile acids) are formed by hepatocytes. Conjugation of bilirubin occurs in hepatocytes.

***Detoxification and protective functions***

Many drugs and toxins are detoxified by liver and excreted.

***Miscellaneous***

a. *Storage function:* Glycogen, protein, fat, vitamin $B_{12}$ and vitamin A.
b. *Hormonal inactivation:* Cortisol, aldosterone, insulin, glucagon, testosterone.
c. Liver is the site of erythropoiesis in intrauterine life.
d. Reservoir of blood.

## Biliary System

Bile is formed in tiny vacuoles in hepatocytes. It is discharged into bile canaliculus. Canaliculi → bile duct at portal triad (interlobular duct) → interlobar duct → right and left hepatic duct → common hepatic duct → joins cystic duct from gallbladder → joins pancreatic duct → opens at 2nd part of duodenum at ampulla of Vater or opening of sphincter of Oddi.

## GALLBLADDER

It is a sac like structure where bile is stored in between meals. Bile ducts can hold certain amount of bile and when pressure of common bile duct is about 70 mm of $H_2O$ bile begins to pass to gallbladder. After meals, the pressure again increases and it is released to duodenum by contraction of gallbladder and relaxation of spincter of Oddi. Gallbladder has capacity to absorb $H_2O$ and $HCO_3^-$, i.e. it has concentrating function and alkalinity is slightly decreased. Gallbladder can concentrate bile up to 50 times.

***Functions***

1. Storage of bile
2. Concentration of bile by absorbing water and bicarbonate.
3. Secrete mucus.
4. Releases bile to duodenum at a controlled rate or according to the need, thus equalizing pressure in biliary system.

### *Formation and Composition of Bile*

Bile is made up of bile salts, bile pigments and other substances dissolved in alkaline electrolyte solution. The bile salts are synthesized and secreted by hepatocytes. Bile pigments are picked up from blood sinusoids. Secretion is about 500 ml/day.

Color—yellow

Taste—bitter.

So bile is an alkaline juice comprised of water and solids.

*Organic:* Bile salts, bile acids, bile pigments, lecithin, fatty acids, mucous, proteins, (lysosomal enzymes, Ig, glycoproteins, bacteria, virus.

*Inorganic:* $Na^+$, $K^+$, $HCO_3^-$

Bile secreted by hepatocytes (called hepatic bile) is concentrated in the gallbladder (called gallbladder bile).

**Comparison of hepatic duct bile and gallbladder bile (see Table 5.3**

**Composition of bile (see Table 5.4)**

**Table 5.3: Comparison of liver bile and gallbladder bile**

| | *Hepatic bile* | *Gallbladder bile* |
|---|---|---|
| Percentage of solids | 2–4 | 10–12 |
| Bile salts (mmol/L) | 10–20 | 50–200 |
| pH | 7.8–8.6 | 7.0–7.4 |

**Table 5.4: Composition of bile**

| | *Liver bile* | *Gallbladder bile* |
|---|---|---|
| Water | 97.5 g/dl | 92 g/d |
| Bile salts | 1.1 g/dl | 6 g/dl |
| Bilirubin | 0.04 g/dl | 0.3 g/dl |
| Cholesterol | 0.1 g/dl | 0.3 to 0.9 g/dl |
| Fatty acids | 0.12 g/dl | 0.3 to 1.2 g/dl |
| Lecithin | 0.04 g/dl | 0.3 g/dl |
| $Na^+$ | 145.04 mEq/L | 130 mEq/L |
| $K^+$ | 5 mEq/L | 12 mEq/L |
| $Ca^{2+}$ | 5 mEq/L | 23 mEq/L |
| $Cl^-$ | 100 mEq/L | 25 mEq/L |

### *Bile Acids*

Primary bile acids are produced by hepatocytes from cholesterol. They includes cholic acid and chenodeoxy-cholic acids. Primary bile acids contains steroid nucleus with cyclopentano perhydro phananthrene ring. They reach duodenum



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through bile. In the small intestine and colon, it is converted into secondary bile acids by bacterial action. Secondary bile acids include deoxycholic acid and lithocholic acid.

## Bile Salts

It is the sodium and potassium salts of conjugated bile acids. They are derived from primary bile acids. It is synthesized in hepatocytes. Bile acids are 1st conjugated with taurine and glycine, then they form bile salts in combination with sodium or potassium.

### *Functions*

1. Emulsification and digestion of fat
2. Absorption of fat
3. Stimulate formation of bile by hepatocyte called choleretic action
4. Stimulate release of bile from gallbladder called cholagogue action
5. Laxative action helps in easily bowel movements, stimulate peristalsis
6. Form route for removal of cholesterol as they are formed from cholesterol.

### *Bile Pigments*

These are the excretory products in bile.They are formed by breakdown of hemoglobin in RES. Bilirubin is transported to liver along with plasma proteins (this is called unconjugated bilirubin).This bilirubin is broken down by hepatocytes. Proteins separates and bilirubin conjugate with glucuronic acid and form conjugated bilirubin. In intestine, bacteria act upon bilirubin and 50% of bilirubin is converted to bilinogen. Most of bilinogen enters liver through enterohepatic circulation and is re-excreted through bile. About 5% of urobilinogen is excreted by kidney through urine. Some unabsorbed part is excreted through feces as stercobilinogen. This gives yellow color to urine and feces.

### *Functions of Bile*

1. Required for digestion and absorption of fat by two mechanisms:
   a. Active pancreatic lipase helps in digestion.
   b. Emulsification of fat and formation of micelle helps in absorption.
2. Absorption of fat soluble vitamins.
3. Choleretic and cholagogue action.
4. Endogenous synthesis of bile salts.
5. Bacteriostatic action.
6. Major route for loss of cholesterol from body.
7. Lubricating function due to mucous.
8. Alkaline helps in neutralizing acidic chyme.

### *Enterohepatic Circulation*

About 94% of the bile salts are reabsorbed into the blood from the small intestine, (about one-half of this by diffusion through the mucosa in the early portions of the small intestine and the remainder by an active transport process through the intestinal mucosa in the distal ileum) (Fig. 5.8). They then enter the portal blood and pass back to the liver. On reaching the liver these salts are absorbed almost entirely back into the hepatic cells and are resecreted into the bile.

In this way, about 94% of all the bile salts are recirculated into the bile, so that on the average these salts make the entire circuit some 17 times before being carried out in the feces. The small quantities of bile salts lost into the feces are replaced by new amounts formed continually by the liver cells. This recirculation of the bile salts is called the enterohepatic circulation of bile. This circulation is necessary because of limited pool of bile salts.

## Jaundice

Jaundice or icterus refers to the yellowish discoloration of skin, sclera, mucous membrane due to increased amount of bilirubin in body fluids. Nervous and collagen tissues have higher affinity towards bile pigments. The yellowish discoloration will be 1st detected in sclera. Different types of jaundice and their causes are mentioned in Table 5.5.

Total bilirubin is 1 mg%. When it exceeds 2-3 mg%, it is clinically detected. When it is between 1-2 mg%, it is subclinical jaundice. Other causes of yellow discoloration are: (1) Hypercarotenemia, (2) Hypothyroidism, (3) Drug mepacrine.

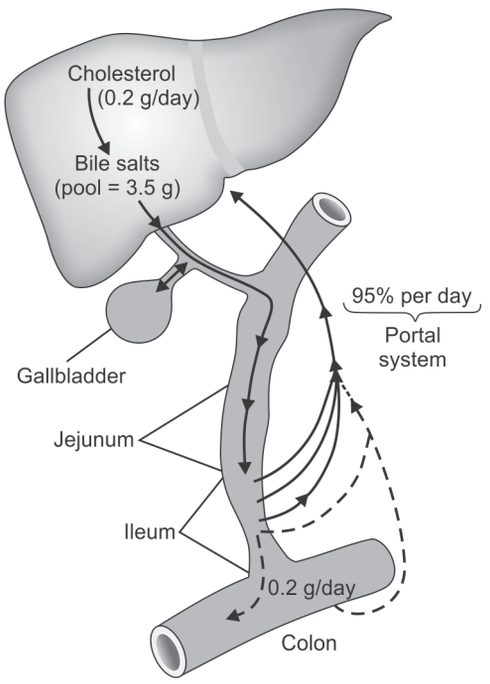


**Fig. 5.8:** Enterohepatic circulation of bile salts

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**Table 5.5: Different types of jaundice and their causes**

| *Type* | *Hemolytic/Prehepatic* | *Hepatocellular/Hepatic* | *Hepatocellular/Hepatic* |
|---|---|---|---|
| Reason | Due to hemolysis resulting in increased destruction of RBC | Due to liver disease, there is impaired uptake and release of bilirubin | Obstruction of flow of bile |
| Causes | **Intracorpuscular defect**<br>• Defect in RBC, e.g. hereditary spherocytosis (due to deficiency of protein spectrin).<br>• Hemoglobinopathies, e.g. sickle cell anemia, thalassemia<br>**Extracorpuscular defect**<br>• Infection—malarial parasite<br>• Radiation—treatment for malignancy<br>• Immunological anti-Ab | • Viral infection—hepatitis, Wiel's disease, malaria<br>• Septicemia<br>• Drugs—anesthesia and anti-TB<br>• Liver cirrhosis | **Intrahepatic**<br>• Drugs causing edema<br>• Alcohol<br>**Extrahepatic**<br>• Stones<br>• Strictures—narrowing of opening due to infection or congenital<br>• Parasites (worm infection<br>• Malignant growth (benign and malignant) |
| Bilirubin in blood | Unconjugated bilirubin | Conjugated and unconjugated bilirubin | Conjugated bilirubin |
| Bile pigments in urine | Nil | Present | Present |
| Urobilinogen in blood and urine | Present | Present | Absent |
| Stercobilinogen in feces | Present | Present | Absent (gray-colored stools) |
| van den Bergh reaction | Indirect +ve | Biphasic | Direct +ve |

## SMALL INTESTINE

Small intestine is the major site of digestion and absorbtion of carbohydrates, proteins and fats. The intestinal juice also called succus entericus comprises of:

1. Aqueous component (water and electrolytes)
2. Intestinal enzymes
3. Mucus

   Daily secretion: Three liters. It is isotonic with plasma. pH = 7.6

Electrolytes includes $Na^+$, $K^+$, $Ca^{2+}$, $Mg^{2+}$, $Cl^-$, $HCO_3^-$, $PO_4^{3-}$

### *Intestinal Enzymes*

They are located in the brush border of epithelial cells.

1. Peptidases
2. Disaccharidases—sucrase, maltase, lactase and limiting α-dextrinase.
3. Intestinal lipase
4. Enterokinase (enteropeptidase)—it activates trypsinogen.

### *Mucus*

It is secreted by Brunner's gland (in duodenum) and goblet cells. They protect the intestinal wall from acid chyme. The mucus lubricates the food and hold immunoglobulins in place. Its secretion is accelerated by cholinergic stimulation and by chemical and physical irritation.

## LARGE INTESTINE

There is no villi in large intestine. Large intestine plays an important role in the absorbtion of water, electrolytes, drugs, etc. Large intestine secretions mainly comprise mucus secreted by globlet cell. It also contains some amount of $HCO_3^-$. The mucus has got lubricating activity and movement of bowel is facilitated. Alkaline nature of large intestine juice neutralize the acids formed by bacterial action on the fecal matter.

## MOVEMENTS OF GIT

### Mastication

Process of grinding of food into smaller particles with the help of teeth and jaw muscles. It helps in mixing with secretions of salivary glands. This wetting and homogenizing action aids swallowing and subsequent digestion. It is a voluntary reflex with center in medulla oblongata. Nerve involved is 5th cranial nerve. Hypothalamus, cerebral cortex and amygdala are also involved.

Presence of bolus in the mouth → sensory areas stimulated → reflex inhibition of muscles of mastication → lower jaw drops → initiation of stretch reflex → rebound contraction of jaw muscles → raises the jaw to cause the closure of teeth → compression of bolus against sensory areas in mouth.

### *Functions*

1. Food is made fit for swallowing.
2. Breaks undigestable cellulose in fruits and raw vegetables.
3. Increases surface area and rate of digestion.
4. Damage caused by the mucosal lining can be prevented.
5. Facilitates lubrication and initiates digestion of starch by enzymes.
6. Chewing brings food in contact with taste receptors.
7. Olfactory receptors are able to detect odor of food particles.

## Deglutition

Deglutition refers to the passage of food from oral cavity into the stomach. It is a reflex response that is triggered by afferent impulses in the 5th, 9th, and 10th cranial nerve. These impulses are integrated in the nucleus of tractus solitarius and nucleus ambiguous. The efferent fibers pass to pharyngeal musculature and the tongue via 5th, 7th and 12th cranial nerve. It has three stages (Fig. 5.9):

1. Oral/buccal phase
2. Pharyngeal phase
3. Esophageal phase.

### *Oral Phase*

It is a voluntary stage. Food passes from mouth to pharynx. Includes voluntary placing of food and rolling of tongue. This backward and upward movement of tongue presses food against palate and bolus moves from mouth to pharynx.

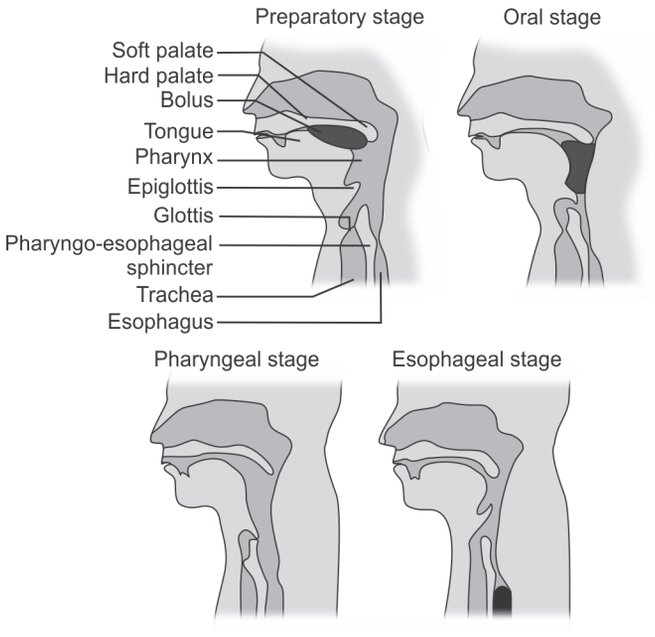



**Fig. 5.9:** Stages of deglutition

### *Pharyngeal Phase*

It constitutes passage of food through pharynx into esophagus. It is an involuntary phase. As the bolus of food enters the posterior part of the mouth and pharynx, it stimulates sensory receptors located in these areas. This will initiates reflex contraction of pharyngeal muscles. Once the food is in oropharynx, there are four possible outlets for food:

(i) Back to mouth, (ii) To nasal cavity, (iii) Into respiratory tract, (iv) Into esophagus.

Entry of food into mouth is prevented by approximation of tongue against roof of mouth. Soft palate is pulled upward to close the posterior nares, to prevent reflux of food into nasal cavities. Palatopharyngeal folds are pulled medially to make a slit like opening, through which food must pass into posterior pharynx. This slit performs selective action, allowing only properly masticated food to pass through. Vocal cords are strongly approximated (stopping the breathing temporarily called *deglutition apnea*) and the larynx is pulled upward and anteriorly by the neck muscles. Epiglottis swings backwards to close the laryngeal opening.

All these guides the food towards the esophagus and prevent its entry into trachea. The upward movement of the larynx also pulls up and enlarges the opening to the esophagus and upper esophageal sphincter relaxes, thus allowing the food to move easily from the posterior pharynx into the upper esophagus. This spintcher remains strongly contracted in between swallows to prevent entry of air into esophagus during respiration. Entire muscular wall of pharynx contracts (beginning in the superior part, then spreading downward over the middle and inferior pharyngeal areas) which propels the food by *peristalsis* (*It is a reflex response that is initiated when the gut wall is stretched by the contents of the lumen and it occurs in all parts of GIT from esophagus to the rectum*) into the esophagus. The entire process of this stage occurs in less than 2 seconds.

### *Esophageal Phase*

During this phase food bolus is propelled from upper part of esophagus to stomach. It is an involuntary stage and exhibits two types of peristalsis: Primary and secondary peristalsis.

***Primary peristalsis***

It is the continuation of peristaltic wave that begins in the pharynx and spreads to esophagus during pharyngeal stage. This wave passes from pharynx to stomach in 8-10 seconds.

***Secondary peristalsis***

When primary peristalsis fails to empty the bolus into the stomach, the retained food initiates secondary peristaltic waves due to the distention of esophagus. The 2nd waves are initiated partly by intrinsic neural circuits (in the myentric plexus) and partly by reflexes that begin in the pharynx. They

are transmitted upward through afferent fibers of vagus to medulla and back again to esophagus through IX and X cranial nerve.

When the peristaltic wave reaches lower esophageal sphincter it relaxes and allows the food to enter the stomach. This relaxation is mediated via neurons that release NO and VIP.

## Disorders of Swallowing

### *Dysphagia*

Difficulty in swallowing.

### *Achalasia*

It is a condition in which food accumulates in the esophagus. Esophagus is massively dilated.

It is due to increased resting lower esophageal sphincter (LES) tone and incomplete relaxation upon swallowing. The myenteric plexus of the esophagus is deficient at the LES in this condition, and the release of NO and VIP is defective. It can be treated by pneumatic dilation of the sphincter or incision of the esophageal muscle (myotomy). Inhibition of acetylcholine release by injection of botulinum toxin into the LES is also effective and produces relief that lasts for several months.

### *Gastroesophageal Reflux Disease*

It refers to a condition in which, there is a reflux of gastric contents into the esophagus.

It is due to the incompetence of LES.

This reflux causes heart burn and esophagitis and can lead to ulceration of esophagus.

### *Aerophagia*

Some people (especially in nervous people) swallow large amounts of air. Some air is regurgitated by bleaching, some of it is absorbed and the rest reaches colon and is expelled as flatus. In some individuals, gas in intestine causes cramps, *borborygmi* (rumbling noises) and abdominal discomfort.

# GASTRIC MOVEMENTS

## Initiation of Gastric Motility

### *Basic Electrical Rhythm*

Basic electrical rhythm (BER)/Gastric slow waves are initiated due to spontaneous rhythmic fluctuation in membrane potential (between –65 and –45 mV) of smooth muscle of GIT (except in esophagus and proximal portion of stomach). The function of BER is to cordinate peristalitic and other motor activities in GIT. They originate from interstitial cells of Cajal, which has stellate mesenchymal pacemaker cells. (These are situated in the outer circular muscle layer near the myenteric plexus in the stomach and small intestine. In the colon, they are at the submucosal border of circular muscle layer). These cells send long multiple branched processes into the smooth muscles. Slow waves include waves of depolarization and repolarization

Spike potentials occur superimposed on most of the depolarized portion of BER waves, which will increase the tension of smooth muscle (Fig. 5.10). The depolarization portion of the spike is due to $Ca^{2+}$ influx and repolarization is due to $K^+$ efflux. The rate of BER varies in different parts of GIT.

- Stomach – 4/min
- Duodenum – 12/min
- Distal ileum – 8/min
- Cecum – 9/min
- Sigmoid colon – 16/min

The degree of spike potential and tension of smooth muscle is increased by ACh released by vagal ending, gastric distension, gastrin. They are inhibited by release of epinephrine when sympathetic nervous system is stimulated, duodenal distension, presence of fat, acidic chyme and hypertonicity.

### *Motility of Empty Stomach/During Interdigestive Period*

#### *Migrating Motor Complex*

During the interdigestive period, the pattern of electrical and motor activity in the gastrointestinal smooth muscles are modified. The cycles of motor activity will be conducted from the stomach to the distal ileum. Each cycle or MMC starts with quiescent period called phase-1. Phase-1 is continuous with period of irregular pattern of electrical and motor activity called phase-2. Then motor activity drives towards aboral end at the rate of 5 cm/sec and they occur at an interval of approx 90 minutes. Migrating motor complex (MMC) clear contents from stomach and small intestine in preparation for next meal. MMC stops with intake of food and with return of other movements like BER and peristalsis.

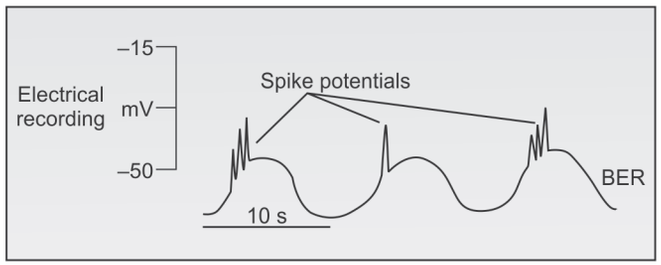



**Fig. 5.10:** Basic electrical rhythm or gastric slow waves

### Hunger Contractions

When stomach is empty for several hours, rhythmic persistant contraction occur in the body of stomach. These are associated with hunger and considered to regulate the appetite. Sometimes, when these contractions occur successively and becomes stronger, fusion of these contractions occur to cause tetanic contraction of smooth muscle which will last for 2 to 3 minutes. These are intense in healthy normal young people but also seen in people whose blood sugar is lower than normal.

The hunger contractions which cause mild pain in the width of stomach is called hunger pangs.

These hunger pangs don't occur unless 12–24 hours of starvation is present. The intensity of hunger pangs increases in 3 to 4 days and then subsides.

## *Gastric Motility Related to Meals/During Digestive Period*

### Receptive Relaxation

When food enters the stomach, the fundus and the greater curvature relaxes to accommodate the food. Receptive relaxation is a vagovagal reflex initiated by distention of stomach. Its significance is to accommodate the food easily without much increase in pressure (until a capacity of 1.5 L).

### Peristalsis

It is a reflex response that is initiated when the stomach wall is stretched by contents of the lumen. Initiated from pacemaker zone in greater curvature of stomach. It is a propulsive wave that propels food in stomach into the duodenum through the pylorus. As the food is being mixed with gastric juice and converted into semifluid called chyme. From the incisura angularis, intense waves carry the chyme through the pylorus in small squirts. Fluids easily pass through but partially digested solid food substances are propelled by the contraction of pyloric sphincter. This action is called retropulsion so that chyme is further mixed with gastric juice. Peristalsis is controlled by BER. Peristalsis in stomach occurs at 3–4 times/min. Peristalsis is due to the integrated activity of the enteric nervous system and it is independent of extrinsic innervation. Local stretch releases serotonin, which activates myenteric plexus.

### Gastric Emptying

Duration the chyme remains in the stomach and empties itself into the small intestine is called gastric emptying time.

It takes 3–4 hours for emptying of chyme from stomach into small intestine.

**Factors influencing are:**

a. **Consistency of the food:** Liquid food empties faster than solids because solids depends on mixing movements to convert it to semisolid chyme.
b. **Gastric factors (promotes emptying)**
   i. *Volume of gastric content:* Greater the vol of food in the stomach, greater is the stretching of stomach wall leading to strong peristaltic waves and increased rate of gastric emptying.
   ii. *Gastrin hormone:* It promote gastric emptying.
   iii. *Type of food ingested:* Rate of emptying - carbohydrates > proteins >fats.
c. **Duodenal factors (inhibit gastrc emptying)**
   *Enterogastric reflex* (reflex initiated in duodenum).
   Stimulated by:
   i. Acidity of chyme.
   ii. Osmolarity of food
   iii. Partially digested proteins
   iv. Distention of duodenum with partially digested food.

   *Hormones*
   i. CCK-PZ
   ii. Secretin
   iii. Gastroinhibitory peptide (GIP).

### Vomiting

It refers to the force full expulsion of contents from stomach and intestine. It is a visceral reflex action integrated in the medulla oblongata. Vomiting can be activated by two ways:

## *Activation of Vomiting Center*

Vomiting center is situated in the reticular formation of medulla. It may be activated directly or through afferents.

i. Direct activation of vomiting center in medulla oblongata, e.g. increased intracranial pressure, cerebral tumor, etc. causing projectile vomiting without nausea.
ii. Afferent impulses activating vomiting center includes:
   a. Impulses from GIT due to the irritation of mucosa.
   b. Impulses from the vestibular nuclei mediate nausea and vomiting of motion sickness.
   c. Afferents from higher centers due to emotional stimuli like nauseating smell, sickening sight, noise, etc.
   d. *Pregnancy:* Due to distention of uterus, it is also associated with nausea.

### *Due to Activation of Chemoreceptor Trigger Zone*

Chemoreceptor trigger zone (CTZ) in medulla contains chemoreceptor cells that initiate vomiting when they are stimulated. These cells are located in the area prostema. This area can be stimulated by:

i. Circulating emetic substances in patients with uremia and radiation sickness.
ii. Circulating emetic agents like morphine, apomorphine, etc.

***Vomiting reflex***

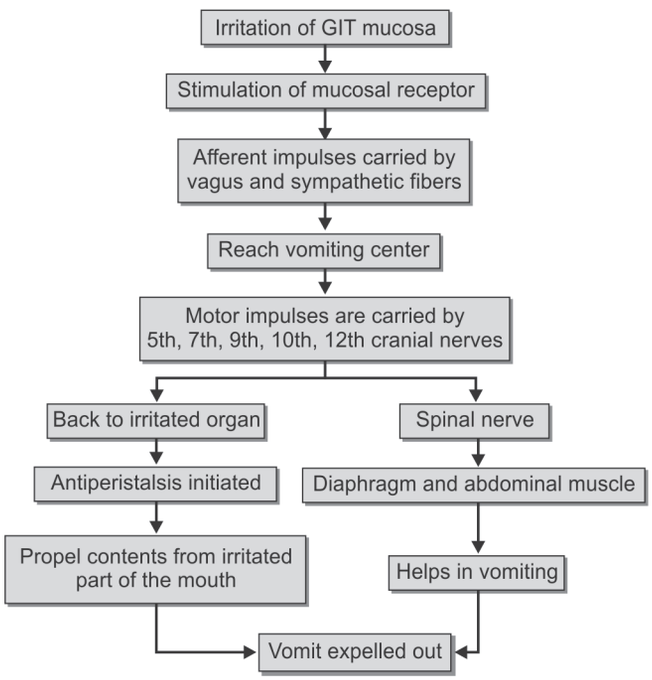
Vomiting is a reflex act. The sensory impulses for vomiting arise from the irritated or distended part of GI tract or other organs and are transmitted to the vomiting center through vagus and sympathetic afferent fibers. Pathway of vomiting reflex in case of irritation of GI tract is given below (Flow chart 5.3).

***Vomiting act***

Vomiting starts with salivation and sensation of nausea. Reverse peristalsis empties material from upper part of SI into the stomach. The glottis closes (to prevent the entry of vomitus into trachea). The breath is held in mid inspiration. The muscles of abdominal wall contracts and thus intra-abdominal pressure is increased. The LES and esophagus relax and the gastric contents are ejected.

***Note:*** Strong involuntary movements in the GI tract start even before actual vomiting and intensify the feeling of vomiting. This condition is called retching. Vomiting occurs few minutes after this.

**Flow chart 5.3:** Vomiting reflex




## MOVEMENTS OF SMALL INTESTINE

In the SI there are an avg of 12 BER /min in the proximal jejunum, declining to 8/min in the distal ileum.

### Motility of SI During Interdigestive Period

#### *Migrating Motor Complexes (MMC)*

The MMC pass along the small intestine at regular intervals during inter digestive period. The MMC sweep out the chyme remaining in the SI.

### *Motility of SI During Digestive Period*

They are mixing movements and include:

### *Pendular Movement*

When there is distention of a portion of small intestine with chyme, then there will be lengthening and shortening of smooth muscles of that portion, particularly longitudinal muscles. This will result in contraction and relaxation of those muscles and because of this, chyme move to and fro or side to side movements in pendular fashion. Purpose is to mix chyme with intestinal juice.

### *Rhythmic Segmentation Contraction*

They are ring like contraction that appear at regular intervals along the segments of small intestine when they are loaded with chyme. These ring like contractions then disappear and are replaced by another set of ring like contractions in the segments between the previous contractions (i.e. areas of relaxation become areas of constriction and vice versa) (Fig. 5.11). They move to and fro and increases its exposure to the mucosal surface. They are initiated by focal increase in $Ca^{2+}$ influx with waves of increased $Ca^{2+}$ concentration spread from each focus. It is purely myogenic than neurogenic.

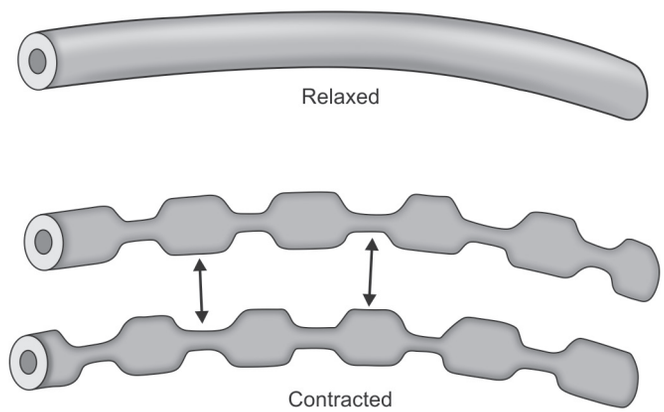



**Fig. 5.11:** Rhythmic segmental contractions

## Propulsive Movements

### *Peristalsis*

It is a propulsive wave which propels intestinal contents towards large intestine. Peristaltic contraction involves contraction of a segment behind the bolus and simultaneous relaxation of the segment in front of the bolus (Fig. 5.12). The stimulus for peristalsis is distension. Each contraction travels for a short distance and then dies out. A new contraction is then initiated from a site little distal to the site of origin of the previous contraction. In this way, a continous peristaltic wave is set in the intestine.

The peristaltic waves always travel from oral end towards the aboral end of intestine. This is called Starlings law of gut.

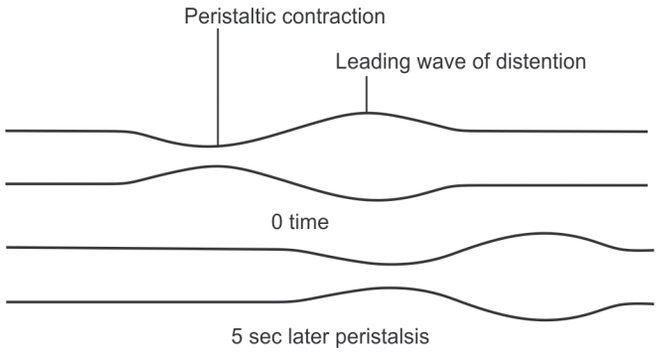



**Fig. 5.12:** Peristalsis

### *Peristaltic Rush*

Peristaltic rush refers to a very powerful peristaltic waves. It is not seen normally, but they occur when the intestine is obstructed.

### *Movements of Villi*

Movements of villi consists of alternate shortening and elongation of villi. Movements of villi helps in emptying lymph from central lacteal into the lymphatic system. The surface area of villi is increased during elongation. This helps in absorption of digested food particles from the lumen of intestine.

## MOVEMENTS OF LARGE INTESTINE/COLON

The movements of the colon are co-ordinated by BER of the colon. The frequency of this wave increases along the colon from about 2/min at ileocecal valve to 6/min at the sigmoid. The movements include:

### ***Haustrations***

Large circular constrictions occurs along the colon. At each constriction, about 2.5 cm of circular muscle contracts and this contraction can cause obliteration of lumen in the colon. When circular muscles are contracting, simultaneously the longitudinal muscles called *taenia coli* contracts. Because of the combined action, the portion of the colon wall bulges outward like a sac where fecal matter is present. Each hostile movement reaches peak intensity in 30 seconds and disappears during next 60 seconds and then appears again. This movement helps the fecal matter to be dugged and rolled over so that it is exposed to mucosal surface of colon. Because of this, fluid and electrolytes can be absorbed and it is converted into semisolid form.

### ***Mass Peristalsis***

Mass peristalsis are forceful peristaltic contractions that can propel the fecal matter into the rectum from the splenic flexure of colon. It is a propulsive type of movement.

### ***Mass Action Contractions***

This is observed only in the colon. There is a simultaneous contraction of the smooth muscles over large confluent areas. These contractions move fecal material from one portion of the colon to another. They also move material into the rectum and rectal distension initiates they defecation reflex.

## Defecation

Distention of the rectum with feces initiates reflex contractions of its musculature and the desire to defecate. Defecation involves both voluntary and reflex activity. The urge to defecate 1st occurs when the rectal pressure increases to about 18 mm Hg. When this pressure reaches 55 mm Hg, the external as well as the internal anal sphincter relaxes and there is reflex expulsion of contents of the rectum. Continual dribbling of fecal matter through the anus is prevented by tonic constriction of:

### *Internal Anal Sphincter (Involuntary)*

This sphincter relaxes reflexly in response to strech receptors when the rectum is distended. Sympathetic supply is excitatory and parasympathetic is inhibitory.

**Sympathetic:** Presacral nerve fibers from T12, L1, L2

**Parasympathetic:** Through pelvic splanchnic nerve

### *External Anal Sphincter (Voluntary)*

The nerve supply is through pudendal nerve. It is maintained in a state of tonic contraction. Mild-to-moderate distention of the rectum increases its force of contraction whereas moderately severe distension of rectum relaxes it.

### *Defecation Reflexes (Fig. 5.13)*

#### *Intrinsic Reflex*

It is mediated by intrinsic nerve plexus. Distension of rectum initiates afferent signals that spreads through myenteric plexus and initiates mass peristaltic waves in the descending colon, sigmoid colon and rectum that propel fecal matter towards the anus. The intrinsic defecation reflex functioning by itself is relatively weak. To be effective this reflex is fortified by parasympathetic defecaton reflex.

#### *Parasympathetic Defecation Reflex*

Distension of rectum by feces causes transmission of afferent impulses through pelvic nerve to sacral segments of spinal cord. This induces reflex parasympathetic discharge (mainly from S2) over the pelvic splanchnic nerve to cause:

a. Inhibition of internal anal sphincter.
b. When the rectal pressure reaches 55 mm Hg, discharge in the pudendal nerve is inhibited.

This relaxes external anal sphincter and fecal matter is expelled out.

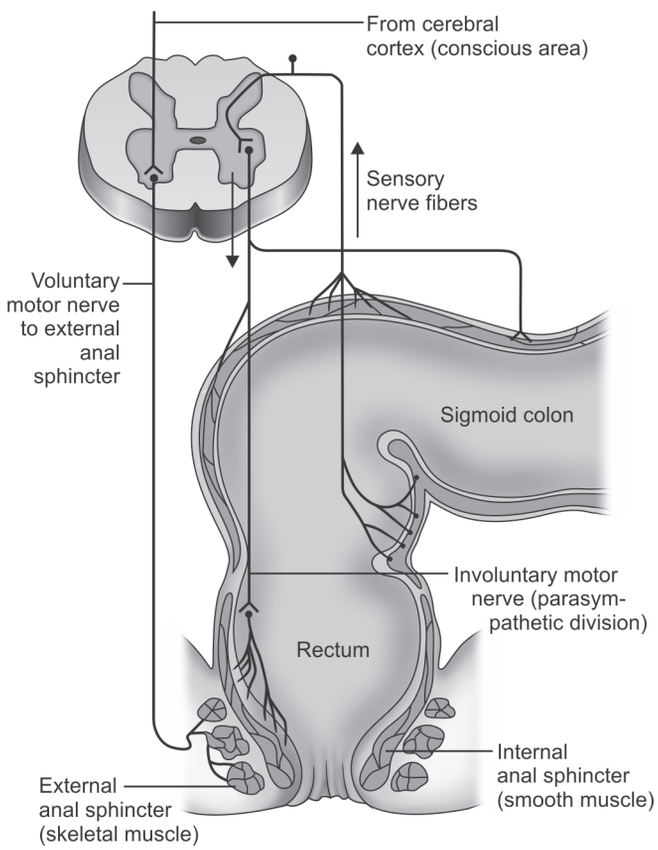



**Fig. 5.13:** Defecation reflex

***Note:*** Gastrocolic and duodenocolic reflexes also aid in defecation.

*Voluntary defecation*

Before the pressure that relaxes the external anal sphincter is reached (55 mm Hg), voluntary defecation can be initiated by straining. Defecation can be voluntarly facilitated by relaxing the external anal sphincter and contracting the abdominal muscles or inhibited by keeping the external anal sphincter contracted.

#### *Hirschsprung's Disease*

Hirschsprung's disease or aganglionic megacolon refers to the congenital absence of ganglion cells in both the myenteric and submucosal plexus. The site of involvement is distal colon. This leads to the blockage of both peristalsis and mass contractions at the aganglionic segment. Therefore, the feces pass the aganglionic region with difficulty and accumulate in large intestine. The disease can be treated by cutting the aganglionic portion of the colon and anastomosing the cut ends.

## DIGESTION AND ABSORPTION

### Carbohydrates

#### *Digestion*

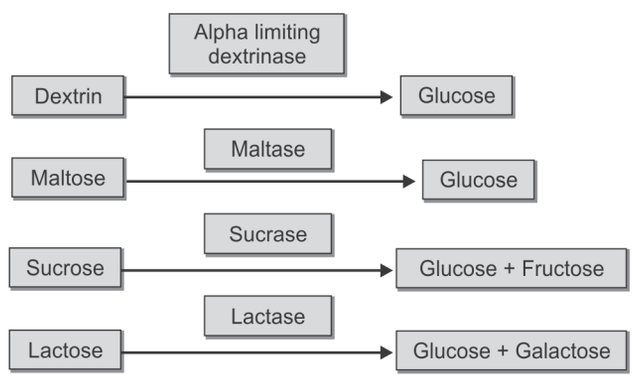
***In mouth***

Ptyalin (salivary amylase) acts on cooked food. The products of digestion are maltose, maltotriose and α-dextrins.

***In stomach***

No amylytic enzyme is secreted by stomach. Salivary amylase action continues in the stomach till the highly acidic gastric juice mixes with the food and makes it inactive. The products of digestion are maltose, maltotriose and α-dextrins (Flow chart 5.4).

**Flow chart 5.4:** Carbohydrate digestion in the stomach



***In upper SI (duodenum)***

Pancreatic amylase acts both on cooked and uncooked food at α 1,4 glycosidic. The products of digestion are maltose, maltotriose and α dextrins.

***Lower part of small intestine***

Final digestion of carbohydrates takes place here. Enzymes used are brush border enzymes. It includes disaccharidases.

### *Absorption*

Carbohydrates are absorbed in the form of monosaccharides.

- Glucose and galactose—Common $Na^+$ dependent active transport system.
- Fructose—Facilitated diffusion.
- Pentoses—Simple diffusion.

Glucose and galactose are absorbed by sodium co-transport mechanism. The carrier protein is called SGLT-1 (sodium dependant glucose transporter). Glucose and $Na^+$ combines with SGLT-1 and is released inside the intestinal cell. The $Na^+$ is transported into the lateral intercellular spaces and the glucose is transported by glucose transporter 2 (GLUT-2) into the interstitial space and thence to blood capillaries (Fig. 5.14).

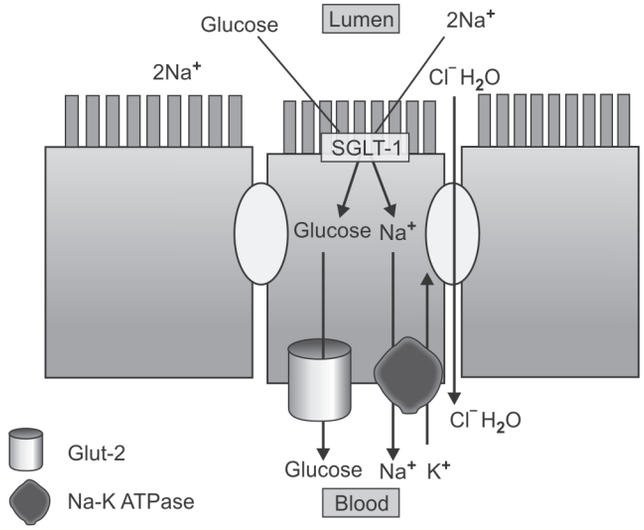



**Fig. 5.14:** Mechanism of glucose absorption across intestinal epithelium

## Proteins

### *Digestion*

***In mouth***

Digestion of proteins does not occur in the mouth, as there are no proteolytic enzymes in the saliva.

***In stomach***

Pepsin, the important peptic enzyme of the stomach, is secreted by chief cells of gastric glands in an inactive form. Pepsinogen is converted into pepsin by HCl. Pepsin is most active at a pH of 2.0 to 3.0 and is inactive at a pH above 5, therefore HCl secretion by stomach is essential for the digestion of proteins.

- Pepsin acts on proteins and splits it into proteoses, peptones and polypeptides. This splitting of proteins occurs as a result of hydrolysis at the peptide linkages between amino acids.
- Gelatinase liquefies gelatin.
- Rennin is absent in adult human.
- Optimum pH in stomach is 1.6–3.2.

***In small intestine***

Most protein digestion occurs in the upper small intestine, in the duodenum and jejunum, under the influence of proteolytic enzymes from pancreatic secretion. Immediately on entering the small intestine from the stomach, the partial breakdown products of the protein foods are attacked by major proteolytic pancreatic enzymes: trypsin, chymotrypsin, carboxypolypeptidase and proelastase.

- Trypsin, chymotrypsin and elastase ***(endopeptidases)*** act on interior of peptide chain and form small peptides. Elastase digests elastin fibers.
- Carboxy peptidases ***(exopeptidases)*** act on terminal amino acids and produce small peptides and amino acids.
- Only a small percentage of the proteins are digested all the way to their constituent amino acids by the pancreatic juices. Most remain as dipeptides and tripeptides.

The last digestive stage of the proteins in the intestinal lumen is achieved by the enterocytes that line the villi of the small intestine, mainly in the duodenum and jejunum. These cells have a brush border that consists of hundreds of microvilli projecting from the surface of each cell. In the membrane of each of these microvilli, there are multiple peptidases that protrude through the membranes to the exterior, where they come in contact with the intestinal fluids.

Two types of peptidase enzymes are especially important, aminopolypeptidase and several dipeptidases. They succeed in splitting the remaining larger polypeptides into tripeptides and dipeptides and a few into amino acids. Both the amino acids plus the dipeptides and tripeptides are easily transported through the microvillar membrane to the interior of the enterocyte.

Finally, inside the cytosol of the enterocyte there are intracellular peptidases that are specific for the remaining types of linkages between amino acids. Within minutes, virtually all the last dipeptides and tripeptides are digested to the final stage to form single amino acids. Thus, the final digestion into amino acids occurs in three locations: (1) Intestinal lumen, (2) Brush border (3) Cytoplasm of enterocyte.

### Digestion of Nucleic Acids

Nucleic acids are split into nucleotides in the intestine by the pancreatic nucleases and the nucleotides are split into the nucleosides and phosphoric acid by enzymes that appear to be located on the luminal surfaces of the mucosal cells. The nucleosides are then split into their constituent sugar, purine and pyrimidine bases. The bases are absorbed by active transport.

### Transport and Absorption

Most proteins after digestion are absorbed through the luminal membranes of the intestinal epithelial cells in the form of dipeptides, tripeptides and a few free amino acids. At least seven different systems transport amino acids into enterocyte. This multiplicity of transport proteins is required because of the diverse binding properties of different amino acids and peptides. Five of these require $Na^+$ and co-transport amino acids and $Na^+$ in a fashion similar to the co-transport of $Na^+$ and glucose. Two of these five also require $Cl^-$. In two systems, transport is independent of $Na^+$. Dipeptides and tripeptides are transported into the enterocyte by a system that requires $H^+$ instead of $Na^+$.

In the enterocytes, amino acids released from the peptides by intracellular hydrolysis plus the amino acids absorbed from the intestinal lumen and brush border are transported out of the enterocytes along their basolateral borders by five transport systems. Two of these systems are dependent on $Na^+$, and three are not. From there via, hepatic portal blood they reach the liver and general circulation. Significant amounts of small peptides also enter the portal blood.

## Fats

### Digestion

#### In Mouth

Lingual lipase is secreted by Ebener's gland on the dorsal surface of tongue. But it has no action in the mouth.

#### In Stomach

Lingual lipase is active in stomach (action starts in acidic pH).

- Digests 30% of dietary triglyceride.
- Gastric lipase is secreted in stomach, but has little importance except in pancreatic insufficiency.

#### In Small Intestine

Most of the fat digestion begins in the duodenum, pancreatic lipase being one of the most important enzymes involved. The digestion of fat includes three steps:

1. Emulsification of fat by bile salts.
2. Hydrolysis of fat by pancreatic and enteric lipolytic enzymes.
3. Acceleration of fat digestion by micelle formation.

### Emulsification of Fat by Bile Salts

The first step in fat digestion is physically to break the fat globules into very small sizes so that the water-soluble digestive enzymes can act on the globule surfaces. This process is called emulsification of the fat (Fig. 5.15).

Emulsification of fat mostly occurs in the duodenum under the influence of bile. Bile contains large quantity of bile salts as well as the phospholipid lecithin. Both of these, but especially the lecithin, are extremely important for emulsification of the fat. The polar parts of the bile salts and lecithin molecules are highly soluble in water, whereas the lipophilic non polar portions of their molecules are highly soluble in fat. Therefore, the fat-soluble portions of these liver secretions dissolve in the surface layer of the fat globules, with the polar portions projecting. The polar projections, in turn, are soluble in the surrounding watery fluids, which greatly decreases the surface tension of the fat and makes it soluble as well.

With the lowered surface tension of fats, segmentation movements of small intestine break up large fat globules into fine droplets. The surface area available for action of lipase is increased many thousand times by the emulsification of fat.

### Hydrolysis of Fat by Pancreatic and Enteric Lipolytic Enzymes

#### Pancreatic Lipolytic Enzymes

a. Pancreatic lipase—hydrolyzes triglycerides (triglycerides → free fatty acids + 2 monoglycerides).
b. Colipase-binds with pancreatic lipase and increases its lipolytic activity.
c. Bile salt activated lipase—catalyzes the hydrolysis of cholesterol esters, esters of fat soluble vitamins, phospholipids and triglycerides.

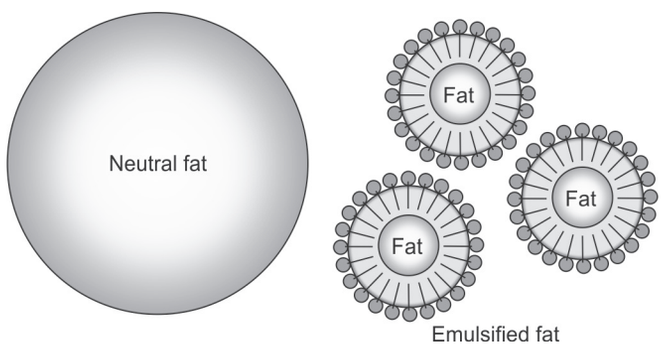



**Fig. 5.15:** Emulsification of fats by bile salts

d. Cholesteryl ester hrydrolase—hydrolyzes cholesteryl esters to cholesterol and fatty acids.
e. Phospholipase $A_2$—hydrolyze the phospholipids.

### *Enteric Lipase*

The enterocytes of the small intestine contain small amount of lipase, known as enteric lipase, but this is usually not needed.

## *Acceleration of Fat Digestion by Micelle Formation*

The hydrolysis of triglycerides is a highly reversible process; therefore, accumulation of monoglycerides and free fatty acids in the vicinity of digesting fats quickly blocks further digestion. But the bile salts play the additional important role of removing the monoglycerides and free fatty acids from the vicinity of the digesting fat globules almost as rapidly as these end products of digestion are formed.

Bile salts, when in high concentration (the concentration is called critical micellar concentration), have the tendency to form micelles. They are small spherical, cylindrical globules 3 to 6 nanometers in diameter composed of 20 to 40 molecules of bile salt in such a way that their lipid soluble non polar ends are in the central fat globule and water soluble polar ends fan out to form the outer covering of micelle. The monoglycerides and fatty acids released from the digestion of fat are quickly incorporated into the central fatty portions of micelles forming, what is known as mixed micelles (Fig. 5.16). In this way bile salts accelerate the fat digestion by allowing the lipolytic action to continue.

The bile salt micelles also act as a transport medium to carry the monoglycerides and free fatty acids, both of which would otherwise be relatively insoluble, to the brush borders of the intestinal epithelial cells. There the monoglycerides and free fatty acids are absorbed into the blood, but the bile salts themselves are released back into the chyme to be used again and again.

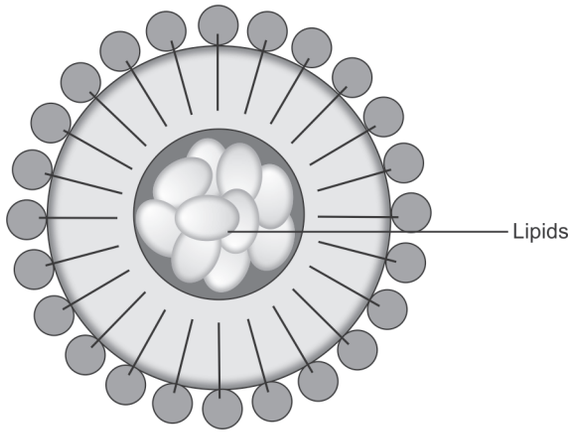



**Fig. 5.16:** Mixed micelle

## *Absorption of Fat*

Normally though lipids are thought to enter the enterocyte by passive diffusion, evidences are there regarding the involvement of carriers. In the enterocytes, the fate of fatty acids is as follows:

1. Fatty acids with less than 10 to 12 carbon atoms are water soluble and they pass through the enterocyte unmodified and are actively transported into the portal blood. They circulate as free (unesterified) fatty acids.
2. Fatty acids with more than 10 to 12 carbon atoms are re-esterified into triglycerides. The absorbed cholesterol is also esterified. Triglycerides and cholesteryl esters are then coated with a layer of proteins, cholesterol, phospholipids to form chylomicrons. They leave the cells and enter lymphatics [In mucosal cells, triglycerides are formed from 2-monoglycerides (in smooth ER). Some are formed from glycerophosphate (product of glucose catabolism). Glycerophospholipids formed from glycerophosphates (in rough ER) also participate in chylomicron formation]. (Fig. 5.17).
3. Finished chylomicrons are extruded by exocytosis from the basal or lateral aspects of the cell. The free fatty acids are diffused into portal blood while the lipids from chylomicrons are diffused into lacteal and then through the thoracic duct into circulation.

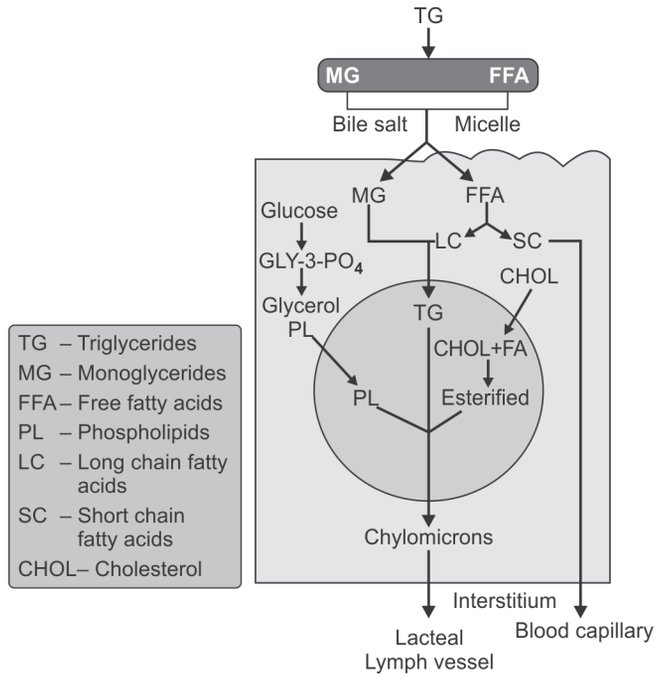



**Fig. 5.17:** Intraluminal events during fat digestion and absorption

4. Absorption of long chain fatty acids is greatest in the upper part of the small intestine, but appreciable amounts are also absorbed in the ileum.

***Note:*** Short chain fatty acids and medium chain fatty acids are directly absorbed from the intestinal lumen into the portal vein and is taken to the liver. Short chain fatty acids have 2 to 5 carbon atoms. They are formed by the action of colonic bacteria on complex carbohydrates, resistant starches and other components of the dietary fibers. Thus, short chain fatty acid is produced in the colon and absorbed from it.

### Dietary Fibers

In humans, there is no appreciable digestion of dietary fibers. For example: Cellulose, hemicellulose, lignin, etc. due to absence of certain micro-organisms in GIT which break down these substances. Therefore, ingested cellulose passes out unchanged and substances which are enclosed in cellulose wall escape digestion and absorption.

#### *Physiological Significance of Dietary Fibers*

1. Increased bulk of this undigested residue stimulates intestinal peristalsis which in turn increases passage of food through intestine.
2. Increased cellulose content of food increases the bulk of feces and thus high fiber content has role in prevention and treatment of constipation.
3. Reduces efficacy of absorption of digested food stuffs by forming mechanical barrier between nutrients and absorptive surfaces, thus reduces sudden increase in blood glucose level after a meal (postprandial hyperglycemia) This also reduces requirements of insulin during postprandial phase. This is why a high fiber diet helps in the prevention and treatment of an individual from diabetes mellitus.
4. Decreases blood cholestrol level by binding the bile salts.
   Binding of bile salt by dietary fibers → increases excretion of bile salts in feces → decreased amount of bile salt available for enterohepatic circulation → increases synthesis of fresh bile salt in the liver → increases cholesterol utilization → decreases the blood cholesterol; thus help to control metabolic disorders associated with over nutrition such as obesity, atherosclerosis, hyper-cholesterolemia and diabetes mellitus.
5. Decreases incidence of colon cancer by:
   a. Dilution of carcinogens by the water held by dietary fibers.
   b. Decreases duration of contact between carcinogen and mucous membrane of colon (as fibers increases colon mobility).
   c. Carcinogen binds to dietary fibers.

***Note***

*Dumping syndrome:* A condition characterized by development of weakness, dizziness and sweating after meals. It may be seen in patients who have undergone complete removal of stomach or gastrojejunostomy. In these cases, food enters directly and rapidly into the intestine and leads to this syndrome. It is due to the following causes:

a. *Hypoglycemia:* In these patients absorption of food is also very quick which is slow in a normal individual due to the action of stomach. Therefore, glucose, etc. are absorbed rapidly which stimulate insulin secretion. This increased insulin ultimately leads to hypoglycemia (late dumping syndrome).
b. Rapid entry of hypertonic meal into the intestine which causes rapid movement of water into the gut from plasma, thus providing hypovolemia and hypotension.

## GASTROINTESTINAL (GI) HORMONES

### Gastrin

It is a GI hormone produced by G cells located in the pyloric glands. Most known powerful stimulant of HCl secretion. It reaches the stomach through arterial circulation (it is secreted into venous blood, enters right heart, then reaches pulmonary circulation, passes to left side of heart and then to aorta and finally through gastric vessels it reaches stomach). Presence of products of protein digestion in the stomach acts on G cells to release gastrin. It stimulates secretory activity of parietal cell and chief cells.

#### *Actions*

a. Gastrin stimulates the secretion of histamine from ECL cells. Histamine stimulates HCl secretion and this is the principal way by which gastrin stimulates acid secretion.
b. Gastrin also stimulate HCl secretion by acting on the gastrin receptors in the parietal cell. This increases intracellular $Ca^{2+}$.
c. To a lesser extent it stimulates chief cells to secrete pepsin.
d. Stimulates insulin secretion after a protein meal.
e. Stimulation of the growth of the mucosa of the stomach, small and large intestine.

***Stimuli that increase gastrin secretion***

*Luminal*

1. Peptides and amino acids
2. Distention.

*Neural*

Increased vagal discharge via gastrin releasing peptide (GRP) rather than ACh

*Blood borne*

1. Calcium
2. Epinephrine

***Stimuli that inhibit gastric secretion***

*Luminal*

1. Acid
2. Somastatin

*Blood borne*

1. Secretin
2. GIP
3. VIP
4. Glucogen
5. Calcitonin

## CCK-PZ

It is a polypeptide containing 33 amino acids with 5 terminal amino acids as those of gastrin, which account for some stimulant properties that they have in common. It is produced by granular mucosal cells of upper part of small intestine, duodenum and jejunum.

### *Actions*

a. The hormone causes contraction of gallbladder to release bile and causes secretion of pancreatic juice rich in enzymes by causing discharge of zymogen granules from the pancreatic acinar cells and the effect is mediated by activation of phospholipase C.
b. It also increases the secretion of enterokinase (enteropeptidase) from the duodenum and may also increase the motility of small and large intestine.
c. It produces trophic effect (i.e. increased growth) on pancreas.
d. It is found in neurons in the brain where it helps in the regulation of food intake and is related to the production of anxiety and analgesia.

## Secretin

It was the 1st hormone discovered. It is a polypeptide and consists of 27 amino acids. It is produced by argentaffin cells in the crypts of the mucosa of upper part of small intestine, duodenum and jejunum. It is secreted as prosecetin which gets converted by gastric HCl and salts of fatty acids (soap) into secretin (active).

### *Actions*

a. It acts on the duct cells of pancreas to produce a flow of alkaline watery pancreatic juice, but poor in enzymes. The effect is mediated by increase in intracellular cAMP. As volume of pancreatic secretion increases, its $Cl^-$ concentration falls and $HCO_3^-$ concentration rises. Although, $HCO_3^-$ are secreted in small ducts, it is reabsorbed in the large ducts in exchange for $Cl^-$. The magnitude of the exchange is inversely proportional to the rate of flow.
b. It also stimulates bile secretion and potentiates the effect of CCK-PZ on the pancreas.
c. It along with CCK-PZ causes contraction of pyloric sphincter and delays gastric emptying and thus, preventing the efflux of duodenal contents into the stomach.

***Note:*** Secretin and CCK-PZ potentiates the action of other. Factors which increase secretin and CCK-PZ release:

i. Acid in the duodenum causes more of secretin liberation and feeble stimulation of CCK-PZ.
ii. Products of carbohydrates, fats and protein digestion in small intestine, cause more of CCK-PZ release.

*Other GIT Hormones*

1. Gastric inhibitory polypeptide (GIP): It is a Glucose dependent insulinotropic polypeptide
2. Vasoactive intestinal peptide (VIP)
3. Glucagon
4. Glucagon like immunoreactiviy (GLI), [Glicentin]
5. Motilin
6. Neurotensin
7. Substance P
8. Gastrin releasing peptide (GRP)
9. Somatostatin
10. Ghrelin

*Chapter*

# 6

# Renal Physiology

Renal system consists of a pair of kidneys, ureters, urinary bladder and urethra.

## INTRODUCTION

### *Functions of Kidney*

1. **Excretory:**
   Formation of urine by three mechanisms: Glomerular filtration, tubular reabsorption, tubular secretion.
   Excretion of urea, uric acid, creatinine, etc.
2. **Homeostatic:**
   It maintains constant internal environment by maintaining water and electrolyte balance and through buffering actions.
3. **Endocrine:**
   - Renin secretion during renal ischemia
   - Release of renal erythropoietic factor during hypoxia
   - Release of local hormones PG, kininogens, etc. to regulate renal blood flow.
4. Formation of vitamin $D_3$.
5. Regulation of normal arterial blood pressure.
6. Hydroxylation of 25-hydroxycholecalciferol to 1,25 dihydroxycholecalciferol (active form of vitamin D).

## NEPHRON

The functional unit of kidney are nephrons (1.3 millions/kidney). Each nephron is formed by two parts - Renal corpuscle and renal tubules (Fig. 6.1).

### *Renal Corpuscle*

*It is formed by two portions:*

i. **Glomerulus (200 µm diameter):** Glomerulus is a tuft of capillaries enclosed by Bowman's capsule. Blood enters glomerulus through afferent arteriole and leaves through an efferent arteriole.

ii. **Bowman's capsule:** Dilated portion of a nephron.

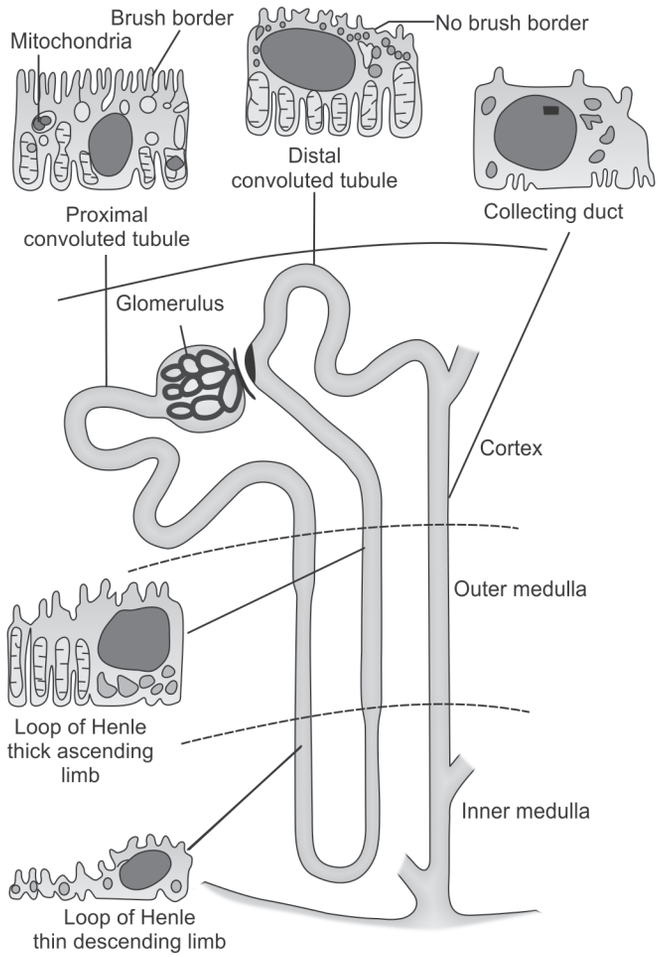



**Fig. 6.1:** Histology of a typical nephron

### *Renal Tubules*

i. **Proximal convoluted tubule (PCT):** Parts-Pars convoluta (convoluted portion) and Pars recta (straight portion). Its wall is made up of single layer of cells whose luminal edges have striate brush border due to the presence of microvilli.

Tubular cells are rich in mitochondria. The tubular cells are connected by tight junctions at their luminal edges, but there is space between the cells along the rest of their lateral borders called as lateral intercellular spaces.

ii. **Loop of Henle:** It consists of a descending and ascending limb. The descending portion of loop and proximal portion of the ascending limb is made up of thin and permeable cells, whereas the thick portion of ascending limb is made up of thick cells containing many mitochondria.

iii. **Distal convoluted tubule (DCT):** Few microvilli present; no distinct brush border.

iv. **Collecting duct:** The distal convoluted tubule opens into collecting duct. Epithelium is made up of principal cells (P cells) and intercalated cells (I cells). P cells are involved in $Na^+$ reabsorption and vasopressin stimulated water reabsorption. I cells are concerned with acid excretion and $HCO_3^-$.

Based on the situation of renal corpuscle, nephrons are classified as cortical and juxtamedullary nephrons (Table 6.1).

## Ultrastructure of Glomerular Membrane

Ultrastructure of glomerular membrane refers to the membrane that separates blood of glomerular capillaries from the glomerular filtrate in the Bowman's capsule. It consists of three layers (Fig. 6.2).

### *Capillary Endothelium*

It is perforated with thousands of small pores called fenestrae (pores have diameter of 70–90 nm). Endothelial cells have fixed negative charges that hinder the passage of plasma proteins (negatively charged).

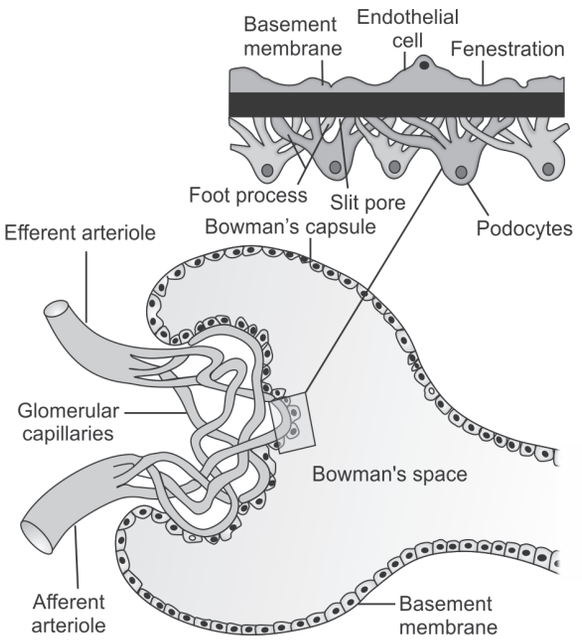



**Fig. 6.2:** Filtering membrane in renal corpuscle

### *Basement Membrane*

It consists of meshwork of collagen and proteoglycan fibrillae that have large spaces through which water and small solutes are permeable. They effectively prevent filtration of plasma proteins because of strong negative charges associated with proteoglycans.

### *Layer of Epithelial Cells*

Visceral epithelium of Bowman's capsule is constituting the epithelial layer. It is formed of special cells called podocytes. They have foot-like processes (pseudopodia) towards the basement membrane that encircle the outer surface of the capillaries. The foot processes are separated by gaps called slit pores (25 nm wide) through which the glomerular filtrate moves. The epithelial cells, which also have negative charges provide additional restriction to movement of plasma proteins.

Net diameter of a pore in glomerular membrane is 8 nm. The pore allows passage of neutral substances up to 4 nm. Around 4 to 8 nm particles can pass based on charge and size. For example, albumin (6 nm) due to its negative charge is not filtered through the glomerular membrane. Particles greater than 8 nm are completely withheld.

#### *Clinical*

1. The negativity is lost in some renal diseases. Then negatively charged substances like albumin is filtered. Hence proteinuria occurs.
2. In glomerular diseases like nephritic syndrome pore size increases.

## JUXTAGLOMERULAR APPARATUS

Juxtaglomerular apparatus (JGA) is a complex specialized structure found at the region where the tubule lies in contact with its own glomerulus forming specialized cells of varying functions.

The JGA plays an important role in the feedback mechanism called tubuloglomerular feedback mechanism which regulates glomerular filtration rate and blood flow through glomerular capillaries.

*Specialized cells are (Fig. 6.3):*

1. Macula densa
2. Laci's cells or extraglomerular mesangial cells
3. Juxtaglomerular (JG) cells

### *Macula Densa*

Macula densa are tightly packed specialized group of epithelial cells in the distal tubules that comes in contact with afferent

| Table 6.1: Differences between cortical and juxtamedullary nephron | |
|---|---|
| *Cortical nephron (85%)* | *Juxtamedullary nephrone (15%)* |
| Occupies 2/3rd of cortex and a very small portion of medulla | Occupies 1/3rd of cortex and most other parts in medulla |
| Loop of Henle is short | Loop of Henle is long |
| Descending limb of loop of Henle contains a thin segment where as ascending limb contain thin and thick segment | Both descending and ascending limb contains thin segment |
| Efferent arteriole continues as peritubular capillaries | Efferent arteriole continues as vasa recta |
| Associated with formation of urine | Associated with concentration of urine |
| Efferent arteriole is smaller than afferent | Efferent arteriole has same diameter as afferent |

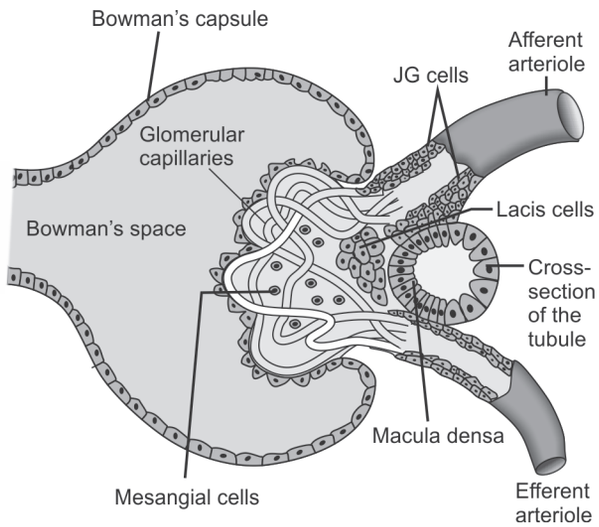



**Fig. 6.3:** Structure of juxtaglomerular apparatus

and efferent arterioles of its own glomerules. These cells can detect the $Na^+$ load in the filtrate and can regulate secretion of renin. It is likely that macula densa mediated renin secretion helps to maintain systemic arterial pressure under conditions of reduced vascular volume.

### *Lacis Cell/Extraglomerular Mesangial Cells*

Lacis cells are mesangial cells located outside the glomerulus (found in the triangular area between the afferent arterioles, efferent arterioles and macula densa). They are agranular cells. They produce renin in small amounts. These cells are contractile and play a role in the regulation of GFR by regulating blood flow through the glomerular capillaries or by altering the capillary surface area.

### *Juxtaglomerular Cells*

They are modified smooth muscles cells lining afferent arterioles near the glomeruli. They are granular and can synthesize, store and releases renin. The JG cells are innervated by sympathetic nerve fibers and release their renin content in response to sympathetic discharge. They acts as baroreceptors. They monitor renal perfusion pressure and are stimulated hypovolemia or decreased renal perfusion pressure.

## Renin-Angiotensin System

Cells in the afferent arterioles (JG cells) are the sites of synthesis, storage and release of the proteolytic enzyme renin.

*Stimulants for renin secretion are:*

1. Fall in arterial BP.
2. Reduction in ECF volume.
3. Increased sympathetic activity.
4. Decreased load of $Na^+$ and $Cl^-$ in macula densa.
5. Prostaglandins.

### *Inhibitors for Renin Secretion*

1. Increased load of $Na^+$ and $Cl^-$ in macula densa.
2. Increased afferent arteriolar pressure.
3. Angiotensin II (via negative feedback).
4. Vasopressin.

Renin alone does not have a physiological function; it functions solely as a proteolytic enzyme. Its substrate is a circulating protein angiotensinogen, which is produced by the liver. Angiotensinogen is cleaved by renin to yield a decapeptide, angiotensin I. Angiotensin I also has no physiological function, and it is further cleaved to an octapeptide, angiotensin II by a converting enzyme (ACE) secreted from the lungs. Various peptidases converts angiotensin II to angiotensin III (heptapeptide) and angiotensin IV (hexapeptide) (Fig. 6.4).

### *Actions of Angiotensin II*

1. Causes vasoconstriction leading to increase in arterial BP.
2. Increases BP indirectly by increasing release of norepinephrine from postganglionic sympathetic fibers (norepinephrine is a vasoconstrictor).
3. Acts directly on adrenal cortex to increase the secretion of aldosterone (aldosterone increases retention of Na) (Fig. 6.5).

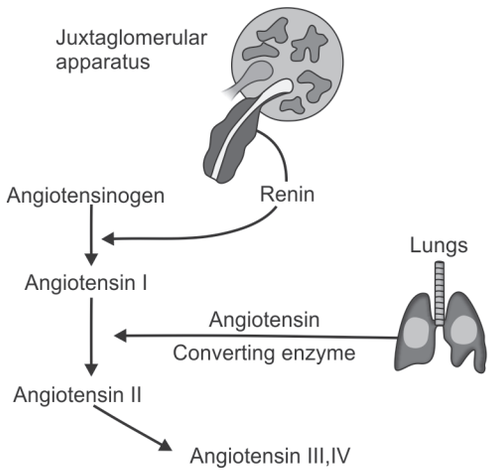



**Fig. 6.4:** Renin-Angiotensin system

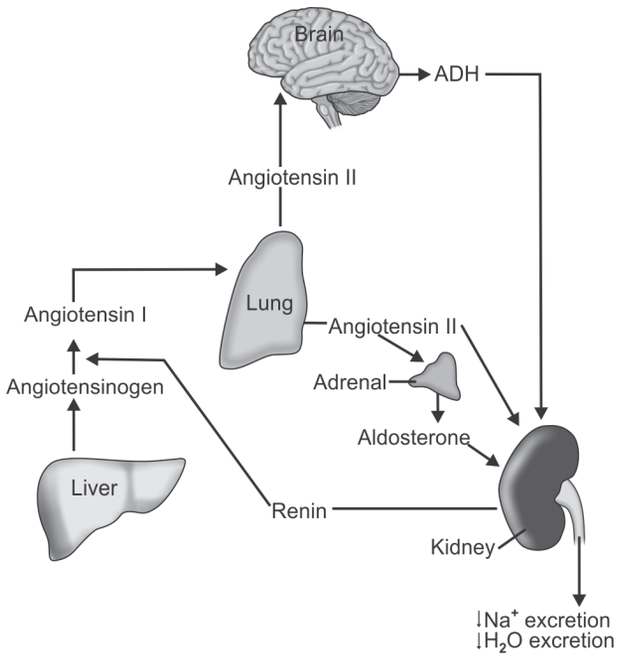



**Fig. 6.5:** Release and actions of angiotensin

4. It acts on brain to decrease response of baroreceptor reflex.
5. It increases water intake by stimulating thirst center.
6. It increase the secretion of ADH and ACTH.

Angiotensin III has pressor activity and aldosterone stimulating activity.

***Applied aspects***

Angiotensin converting enzyme inhibitors are drugs (e.g. captopril) used in the treatment of hypertension and congestive cardiac failure. They inhibits the formation of angiotensin II and thus decrease $Na^+$ and water retention.

## RENAL CIRCULATION

Normal renal blood flow: 1100 ml/min, i.e. 22% of cardiac output.

### *Special Features of Renal Circulation*

1. Renal blood flow is maximum when compared to other circulations in the body, i.e. 25% of total cardiac output.
2. *Double portal system:* Two types of blood vessels are present. They are glomerular capillaries (for filtration) and peritubular capillaries (for reabsorption).
3. *Regional blood flow:* There is a variation in the blood flow through various parts of the kidney, i.e. flow to cortex is greater than flow to medulla. Renal cortex has 4–5 ml/g/min where as medulla has only 1–2 ml/g/min (outer) and 0.3 ml/g/min (inner).
4. *$O_2$ consumption:* Kidney is the 2nd highest $O_2$ consumer next to heart, i.e. 6 ml/100g/min.
5. *Renal arterial blood pressure:* Highest as it originates directly from abdominal aorta.
6. *Vasa recta:* Presence of vasa recta, the longest capillary, for concentrating the urine.
7. Shows autoregulation.

#### *Why Blood Flow in Cortex is Greater than in Medulla?*

Cortex contains major components of the nephron. In inner medulla, long vasa recta and high interstitial osmotic pressure causes slower blood flow. This is one of the reason for production of hypertonic urine.

### *Renal Blood Vessels*

The following is the order of flow of blood in the kidney.

Renal artery → interlobar artery → arcuate artery → interlobular artery → afferent arterioles → glomerular capillaries → efferent arterioles → stellate vein → interlobular vein arcuate vein → interlobar vein → renal vein

Renal vascular resistance changes with renal perfusion. The effects of changes in renal vascular resistance with constant renal perfusion is given in Figure 6.6.

### Regulation of Renal Blood Flow

Regulatory mechanism of renal blood flow (RBF) include autoregulation, neural regulation and hormonal regulation. Autoregulation is also called as intrinsic mechanism. Extrinsic mechanism include both neural and hormonal mechanisms.

### *Autoregulation by Kidney*

The RBF and thus GFR remain constant over a wide range of renal arterial pressures (90–220 mm Hg) (Fig. 6.7). This

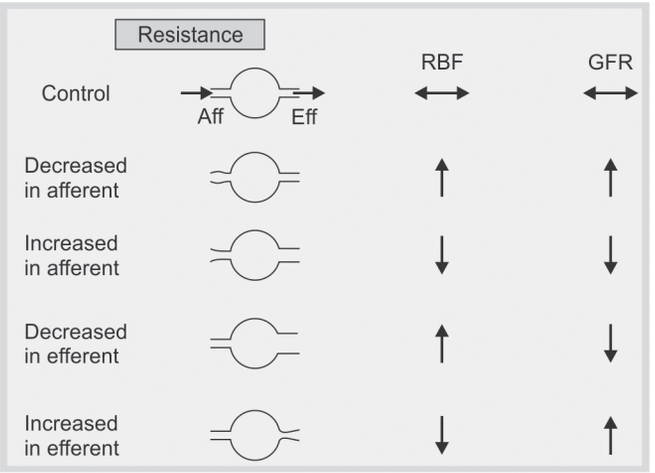



**Fig. 6.6:** Effects of changes in renal vascular resistance with constant renal perfusion

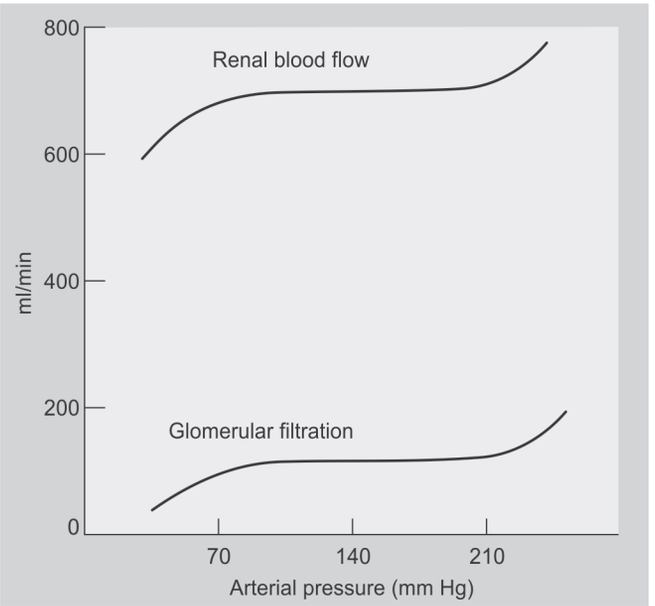



**Fig. 6.7:** Autoregulation of renal blood flow and glomerular filtration rate in kidney

occurs due to an intrarenal mechanism known as autoregulation. This is brought about by two mechanisms—myogenic theory and tubuloglomerular feedback.

### *Myogenic Theory*

It is the ability of individual blood vessels to resist stretching during increased arterial pressure. This phenomenon is referred to as myogenic mechanism of autoregulation of RBF. When the blood flow to the kidneys increases (BP increases), it stretches the elastic wall of the afferent arteriole. The stretch of the vessel wall increases the flow of calcium ions from extracellular fluid into the cells. The influx of calcium ions lead to the contraction of smooth muscles in afferent arteriole which causes constriction and increase in resistance in afferent arteriole. There by the blood flow is controlled.

### *Tubuloglomerular Feedback*

This mechanism is based on NaCl concentration of tubular fluid. Tubuloglomerular feedback mechanism maintains a constant RBF and GFR when there is a fluctuation in arterial BP between 90–220 mm Hg.

The signals from the renal tubules in each nephron feedback to affect filtration in it's glomerulus. The tubuloglomerular feedback mechanism has two components that act together to control GFR (Fig. 6.8).

- An afferent arteriolar feedback mechanism
- An efferent arteriolar feedback mechanism.

When GFR is decreased NaCl load reaching the macula densa is decreased (due to increased NaCl reabsorption at PCT). Macula densa senses NaCl concentration in the tubular fluid. Decrease in NaCl concentration initiates a signal from the macula densa that has two effects.

a. It decreases resistance to blood flow in afferent arterioles which raises glomerular hydrostatic pressure and thus GFR is brought back to normal.
b. It increases renin release from JG cells of afferent and efferent arterioles.

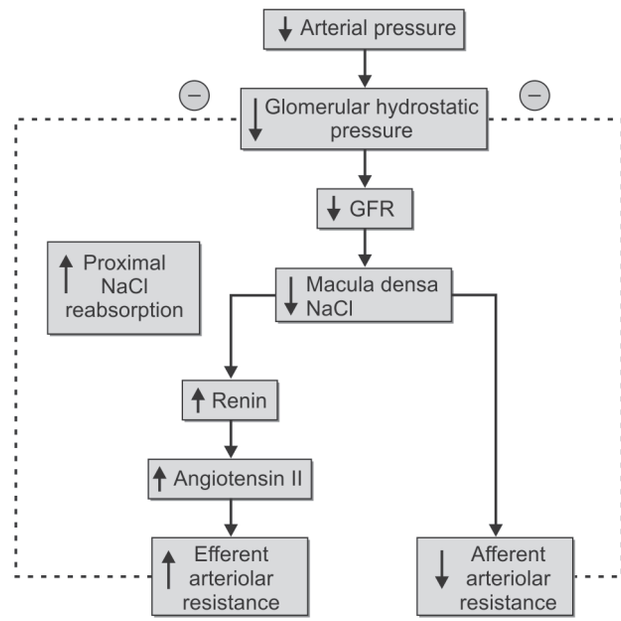



**Fig. 6.8:** Macula densa feedback mechanism for autoregulation of glomerular hydrostatic pressure and GFR during decreased renal arterial pressure

Renin increases efferent arteriolar resistance by increasing the concentration of angiotensin I, which is converted to angiotensin II. Thus GFR and RBF are brought back to normal.

### *Neural Regulation*

Afferent and efferent arteriolar lining smooth muscles are supplied by sympathetic nervous system. Here, slight to moderate sympathetic stimulation will not affect GFR and RBF much as autoregulation overrides nervous regulation. But very strong sympathetic stimulation causes constriction of renal arterioles resulting in decreased RBF and GFR.

If strong sympathetic stimulation is continued, RBF and GFR increases within 20–30 min. This may be due to decay of neurotransmitter at nerve endings. There are some nerves innervating renal tubular cells and JG cells. If they are stimulated, JG cells secrete renin. Then RBF increases.

### *Hormonal Regulation*

a. *Catecholamines*
   i. *Norepinephrine:* Renal vasoconstriction, increased resistance, decreased RBF.
   ii. *Dopamine:* Renal vasodilatation increased RBF.
b. *Angiotensin II:* Vasoconstriction, decreased RBF.
c. *Prostaglandins:* Renal vasodilatation, increased RBF.
d. *Ach:* Renal vasodilatation, increased RBF.
e. *ADH:* Vasoconstriction, decreased RBF, so decreased urine output.
f. *ANP:* Renal vasodilation, increased RBF.

### *Other Factors*

a. *Hypoxia:* When arterial $O_2$ becomes <50% normal → chemo receptor are stimulated → vasomotor center activated leading to renal vasoconstriction and decreased RBF.
b. *Hemorrhage:* When blood loss occurs, RBF decreases.
c. *Renal arterial blood pressure:* When BP increases sympathetic tone decreases reflexly → renal vasodilatation → RBF increases.
d. *High protein diet:* RBF increases as a result of increased glomerular capillary pressure.
e. *Postural changes and in muscular exercise:* A change in position from supine to standing posture causes decrease in RBF, due to increased sympathetic activity.
f. *Bacterial pyrogens:* Renal vasodilatation, increased RBF.
g. *Fever due to other reasons:* Vasoconstriction, decreased RBF.

## MECHANISM OF URINE FORMATION

The formation of urine include three processes:
1. Glomerular filtration.
2. Tubular reabsorption.
3. Tubular secretion.

The substances to be excreted are removed by glomerular filtration and renal tubular secretion and passed into the urine. The substances that the body needs are retained by tubular reabsorption, e.g. $Na^+$, $HCO_3^-$.

### Glomerular Filtration

Glomerular filtration is the initial step in urine formation. The plasma that traverses the glomerular capillaries is filtered by the highly permeable glomerular membrane and the resultant fluid, the glomerular filtrate is passed in to Bowman's capsule. Glomerular filtrate is identical with the plasma in respect of osmolality, pH, electrical conductivity, concentration of electrolytes except that it contains no proteins and no cells. Therefore glomerular filtrate is called the ultrafiltrate of plasma.

### *Glomerular Filtration Rate*

Glomerular filtration rate (GFR) refers to the volume of the glomerular filtrate formed each minute by all the nephrons in both the kidneys. Normal value -125 ml/min =180 L/day.

#### *Factors Affecting GFR*

$$GFR = K_f [(P_G - P_B) - (\pi_G - \pi_B)$$

So GFR depends on $P_G$, $P_B$, $\pi_G$, $\pi_B$ and $K_f$
Where,
$P_G$ = Hydrostatic pressure in the glomerular capillaries (60 mm Hg)
$P_B$ = Hydrostatic pressure in Bowman's capsule (18 mm Hg)
$\pi_G$ = Colloidal osmotic pressure of glomerular capillary (32 mm Hg)
$\pi_B$ = Colloidal osmotic pressure of Bowman's capsule (negligible)
$K_f$ = Filtration coefficient (permeability of capillaries × effective capillary surface area).

1. **Hydrostatic pressure in the glomerular capillaries ($P_G$)**
   - GFR is directly proportional to $P_G$.
   - Increased arterial pressure causes increase in $P_G$, so GFR increases.
   - Increase in afferent arteriolar resistance decreases $P_G$ then GFR decreases.
   - Increase in efferent arteriolar resistance increases $P_G$, but renal blood flow decreases therefore GFR increases slightly but if there is severe constriction, GFR decreases.
2. **Hydrostatic pressure in Bowman's capsule ($P_B$)**
   - GFR is inversely proportional to $P_B$.

- $P_B$ increases in case of obstruction of urinary tract. Then GFR decreases, e.g. kidney stones.

3. **Colloidal osmotic pressure in glomerular Capillary ($\pi_G$)**
   GFR is inversely proportional to $\pi_G$.
   - In hypoprotienemia $\pi_G$ decreases, so GFR increases.
   - During dehydration : $\pi_G$ increases, then GFR decreases.
   - Increase in arterial plasma COP: increases $\pi_G$; so decrease in GFR.
   - Increase in filtration fraction (fraction of plasma filtered by glomerular capillary) causes increase in $\pi_G$ and so decrease in GFR.
   - Filtration fraction = GFR/RPF
     = 125/700
     = 19% of RPF
4. **Colloidal osmotic pressure in Bowman's capsule ($\pi_B$)**
   Favors filtration.
5. **Filtration coefficient ($K_f$)**
   It is a function of the membrane permeability and capillary surface area.
   a. *Permeability of capillaries-depends on:*
      i. Size of particle
      ii. Charge of particle
      All neutral substances having diameter less than 4 nm can pass through. Around 4–8 nm particles can pass based on charge and size. Particles greater than 8 nm are completely withheld. Glomerular membrane contain proteoglycans which are negatively charged. So they repel negatively charged albumin.
   b. *Capillary surface area:*
      Contraction of mesangial cells decreases surface area available for filtration. This decreases filtration coefficient ($K_f$). Angiotensin II is an important regulator of mesangial contraction.

***Note:*** In chronic uncontrolled diabetes mellitus and hypertension, $K_f$ decreases due to thickness of glomerular capillary membrane.

6. **Renal blood flow (RBF):** GFR is directly proportional to the RBF.
7. **Age:** GFR decreases with increasing age due to decrease in the renal plasma flow (RPF), cardiac output (CO) and renal tissue mass.

### *Regulation of Glomerular Filtration Rate (Table. 6.2)*

1. Autoregulation: Refer from regulation of RBF.
2. Neural: Write from regulation of RBF.
3. Hormonal

**Table 6.2: Hormones and autocoids that influence GFR**

| *Hormone or autocoid* | *Effect on GFR* |
|---|---|
| Norepinephrine | Decrease |
| Epinephrine | Decrease |
| Endothelium | Decrease |
| Angiotensin II | Do change, but prevents decrease |
| Endothelial derived nitric oxide | Increase |
| Prostaglandins | Increase |

***Note***

***1. Net filtration pressure (NFP)***
It is the balance between the pressure favoring filtration and pressure opposing filtration.

$$NFP = (P_G - P_B) - (\pi_G - \pi_B)$$

$$GFR = K_f \times NFP$$

$K_f$ = Filtration coefficient of the glomerular membrane is 12.5 ml/min/mm Hg. It is the GFR at 1 mm Hg NFP.

***2. Filtration fraction***
The fraction of the renal plasma which becomes the filtrate.

$$\text{Filtration fraction} = \frac{GFR}{\text{Renal plasma flow}} \times 100$$

Normal value = 0.16 – 0.2

## Tubular Reabsorption

Tubular reabsorption is selective. There are two routes (Fig. 6.9) for the substances to be reabsorbed from tubular lumen into peritubular capillary called transcellular and paracellular routes.

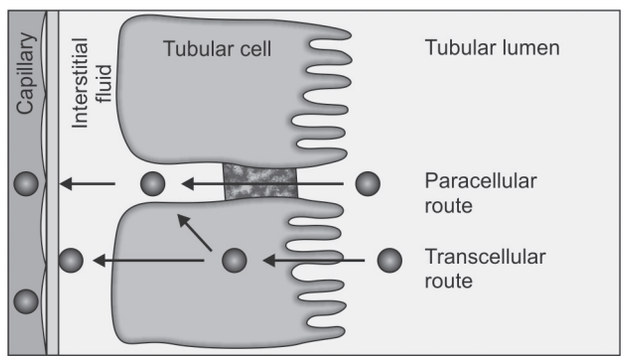



**Fig. 6.9:** Routes of reabsorption

## Reabsorption of Sodium in Proximal Convoluted Tubule

Sixty seven percent of sodium is reabsorbed in PCT. The process of $Na^+$ reabsorption in PCT is iso-osmotic, i.e. the

reabsorption of $Na^+$ and water are exactly proportional. Mechanism $Na^+$ reabsorption in the early proximal tubule and late proximal tubule is different.

## In the Early Proximal Tubule

The $Na^+$ absorption is a three step process.

1. Transport from tubular lumen into tubular cell.
   $Na^+$ is transported from tubular lumen into tubular cell by:
   a. *Unidirectional $Na^+$ transport/symport:* $Na^+$ moves out of tubular lumen along with glucose (and other solutes like aminoacids, Pi, lactate) through the apical membrane of the tubule.
   b. *$Na^+$ - $H^+$ exchange/antiport:* Here $Na^+$ is reabsorbed in exchange of $H^+$. $Na^+$-$H^+$ antiporter couples entry of $Na^+$ with extrusion of $H^+$ from the cell. $H^+$ secretion results in reabsorption of $NaHCO_3$.
2. Transport from tubular cell into interstitial fluid and lateral intercellular spaces.
   Most of the Na are actively pumped into the lateral intercellular spaces by $Na^+$ - $K^+$ ATPase. The rest of the Na are pumped into the interstitial fluid by $Na^+$ - $K^+$ pump situated at the basal part of the cell membrane (Fig. 6.10).

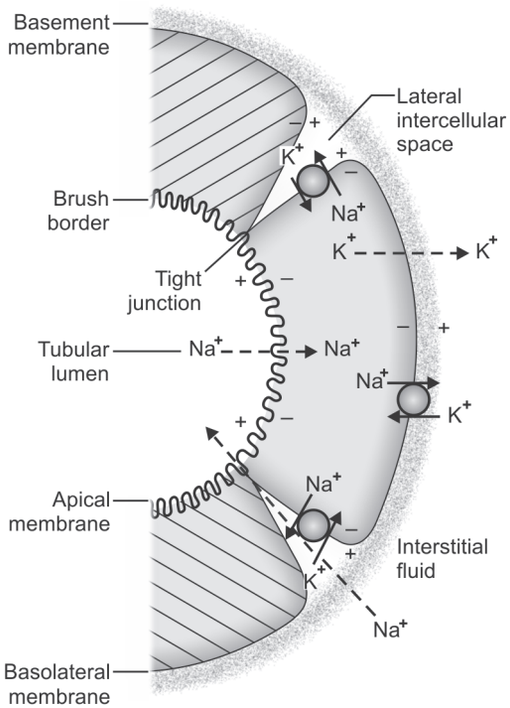



**Fig. 6.10:** Sodium reabsorption from early proximal convoluted tubule

***Note***

A small amount of $Na^+$ re-enters the tubular lumen by passive transport through the tight junctions.

3. Transport from interstitial fluid and lateral intercellular spaces to peritubular capillaries.
   From the lateral intercellular spaces and interstitial fluid, $Na^+$ enters the peritubular capillaries by concentration gradient.

## In the Late Proximal Tubule

In the 2nd half of the proximal tubule, $Na^+$ is mainly reabsorbed with $Cl^-$ across both the transcellular and paracellular pathways.

***Paracellular pathways***

$Na^+$ is primarily reabsorbed with $Cl^-$ rather than organic solutes or $HCO_3^-$ as the accompanying anion because the $Na^+$ transport mechanisms in the 2nd half of the proximal tubule differ from those in the 1st half. Further more, the tubular fluid that enters the 2nd half contains very little glucose and amino acids, but the high concentration of $Cl^-$ (140 mEq/L) in tubule fluid exceeds that in the 1st half (105 mEq/L). The high [$Cl^-$] is due to the preferential reabsorption of $Na^+$ with $HCO_3^-$ and organic solutes in the first half of the proximal tubule. This concentration gradient favors diffusion of $Cl^-$ from the tubular lumen across the tight junction into the lateral intercellular space. Movement of the negatively charged $Cl^-$ results in the tubular fluid becoming positively charged relative to blood cell.

***Transcellular pathways***

$Na^+$ and $Cl^-$ enter the cell across the apical membrane via the operation of parallel $Na^+$-$H^+$ and $Cl^-$ - anion antiporters. The secreted $H^+$ and anion combine in the tubular fluid to form an $H^+$-anion complex that can recycle across the plasma membrane.

Accumulation of the $H^+$-anion complex in tubular fluid establishes an $H^+$-anion concentration gradient that favors $H^+$-anion recycling across apical plasma membrane into the cell. Inside the cell, $H^+$ and the anion dissociate and recycle back across the apical plasma membrane. The net result is the uptake of NaCl across the apical membrane. The anion may be hydroxide ions, formate, oxalate, bicarbonate or sulfate (Fig. 6.11).

## In Loop of Henle

Twenty-five percent of Na is reabsorbed. Ascending limb is permeable to solutes and impermeable to water. Descending limb is permeable to water and impermeable to solutes. When

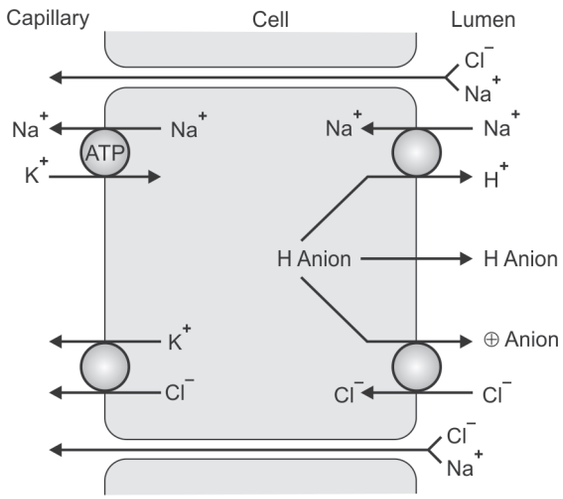



**Fig. 6.11:** Sodium reabsorption from late PCT

the filtrate enters loop, it is isotonic. But in descending limb, $H_2O$ is reabsorbed thus filtrate becomes hypertonic. In the ascending limb it becomes hypotonic. Here 1Na, 1K, $2Cl^-$ are reabsorbed into the tubular cell (by $Na^+$-$K^+$-$2Cl^-$ transporter). From the cell Na is reabsorbed into the peritubular capillaries by Na - K pump. One $K^+$ and one $Cl^-$ are co-transported out of the cell; another $Cl^-$ passes out passively by diffusion. The other $K^+$ is secreted back into the lumen (Fig. 6.12).

An $Na^+$- $H^+$ antiport in apical cell membrane also mediates $Na^+$ reabsorption, as well as $H^+$ secretion. Paracellular passive reabsorption of $Na^+$, $K^+$, $Ca^{2+}$ and $Mg^{2+}$ also occurs in the thick ascending limb.

***Note***

Because thick ascending limb does not reabsorb water, reabsorption of NaCl and other solutes reduces the osmolarity to 150 mOsm/L. Thus because the thick ascending limb produces a fluid that is dilute relative to plasma, the ascending limb of Henle's loop is called the ***"diluting segment".***

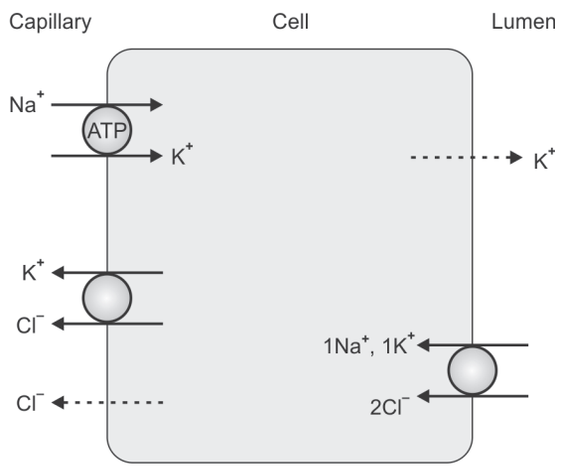



**Fig. 6.12:** Sodium reabsorption in loop of Henle

### *In DCT and Collecting Duct*

Five percent reabsorption in DCT and three percent reabsorption in collecting duct. In the early part of DCT, entry of NaCl into the cell across the apical membrane is mediated by an $Na^+$ - $Cl^-$ symporter. $Na^+$ leaves the cell via the action of $Na^+$- $K^+$ ATPase, and $Cl^-$ leaves the cell via diffusion through $Cl^-$ channels.

In the late part of DCT and collecting duct, the reabsorption is via ENaC (epithelial sodium channel) under the influence of aldosterone.

***Note***

1. **Barter's syndrome:** It is an autosomal recessive genetic disorder characterized by hypokalemia, metabolic alkalosis and hyperaldosteronism. Inactivating mutations in the gene coding for $Na^+$- $K^+$ - $2Cl^-$ symporter, the apical $K^+$ channel, or the basolateral $Cl^-$ channel decrease both NaCl and $K^+$ reabsorption by thick ascending limb, which in turn causes hypokalemia and a decrease in ECF volume. The fall in ECF volume stimulates renin and aldosterone secretion, which inturn stimulates NaCl reabsorption and $H^+$ secretion by distal tubule and collecting duct.
2. **Liddle's syndrome:** It is a genetic disorder characterized by an increase in BP secondary to increase in ECF volume. Liddle's syndrome is caused by activating mutations in either the β or γ subunit of ENaC (ENaC is composed of 3 subunits, α, β and γ). These mutations increase the number of $Na^+$ channels in the apical cell membrane of P cells and thereby the amount of $Na^+$ reabsorbed by each channel. In Liddle's syndrome, the rate of renal reabsorption is inappropriately high, which leads to an increase in ECF volume and hypertension.

**Table 6.3: NaCl transport along the nephron**

| *Segment* | *Percentage of filtrate reabsorbed* | *Mechanism of Na entry across the apical membrane* |
|---|---|---|
| Proximal tubule | 67% | $Na^+$ - $H^+$ antiporter, $Na^+$ symporter with amino acid and organic solutes, 1 $Na^+$ $1H^+$ - $2Cl^-$ anion antiporter, paracellular |
| Loop of Henle | 25% | 1 $Na^+$ - $1K^+$ -2Cl - symporter |
| Distal tubule | 5% | NaCl symporter (early) |
| | | $Na^+$ channels (late) |
| Collecting duct | 3% | $Na^+$ channels |

### *Factors Affecting Sodium Reabsorption*

1. ***Hydrostatic pressure in peritubular capillaries ($P_c$)***
   - Increased $P_c$ opposes reabsorption.
   - It is influenced by arterial pressure and the resistances of afferent and efferent arterioles.

     $\uparrow P_c \rightarrow \downarrow$ Reabsorption
     - $\downarrow R_A \rightarrow \uparrow P_c$
     - $\downarrow R_E \rightarrow \uparrow P_c$
     - $\uparrow$ Arterial Pressure $\rightarrow \uparrow P_c$

   - Normally it is 10 mm Hg (low) and favors reabsorption.
2. ***Colloid osmotic pressure in peritubular capillary ($\pi_c$)***
   - Increased favors reabsorption
   - It is influenced by arterial plasma colloidal osmotic pressure ($\pi_A$) and filtration fraction (FF).

     $\uparrow \pi_c \rightarrow \uparrow$ Reabsorption
     - $\uparrow \pi_A \rightarrow \uparrow \pi_c$
     - $\uparrow FF \rightarrow \uparrow \pi_c$

3. ***Sodium intake:*** More the Na intake less the $Na^+$ reabsorption.
4. ***Peritubular capillary filtration coefficient ($K_f$ ):*** $K_f$ is a measure of the permeability and surface area of capillaries, so increase in $K_f$ raises reabsorption.
5. ***GFR:***GFR influences $Na^+$ reabsorption by two mechanisms
   a. Tubuloglomerular feedback
   b. Glomerulotubular balance

An increase in GFR, causes an increase in the reabsorption of solutes and consequently water, primarily in the PCT. So that in general, the tubule tends to reabsorb a constant fraction of amount filtered rather than a constant amount.This process is called ***glomerulotubular balance.***

6. ***Sympathetic stimulation:*** Activation of sympathetic nervous system can increase Na reabsorption.
7. ***Hormones:***
   a. *Aldosterone:* It increases sodium reabsorption and K secretion by stimulating $Na^+$-$K^+$ ATPase pump (on the basolateral side of CT) and promoting the opening of ENaC. Site of action is CT and distal part of DCT.
   b. *Angiotensin II:* It increases sodium reabsorption by 3 main effects.
      - Stimulates aldosterone secretion
      - Constricts efferent arteriole (so that $P_c$ decreases)
      - Directly stimulates Na reabsorption in PCT, loop of Henle, DCT and collecting duct.

   c. Atrial natriuretic peptide (ANP) decreases NaCl and water reabsorption.
   d. $PGE_2$ decreases $Na^+$ reabsorption.
   e. Endothelin and Interleukin I increases the production of $PGE_2$ and decreases $Na^+$ reabsorption.
   f. Ouabain inhibits $Na^+$-$K^+$ ATPase and decrease $Na^+$ reabsorption.

## Reabsorption of Water

Normally 180 L of fliud is filtered /day. But out of this only 1–1.5 L is excreted daily. The rest is reabsorbed from renal tubules. As a result urine osmolality is 1400 mOsm/L. Reabsorption of water occurs from PCT, loop of Henle, DCT and CT.

### *In PCT*

PCT is freely peremeable to water. About 60–70% of water is reabsorbed from PCT. In PCT, passive reabsorption of water occurs along with the active transport of solute. This is called as ***obligatory reabsorption***. In PCT water channels called aquaporins are present on the apical surface of epithelial cell. Water channel involved here is aquaporin-1. In PCT fluid is isotonic.

### *In Loop of Henle*

Descending limb is freely permeable to water and not to solutes. Here 15% of water is reabsorbed. Water moves out of tubule and the filtrate becomes hypertonic. At the tip of loop of Henle, filtrate has an osmolarity of 1200 mOsm/L. Ascending limb is impermeable to water, permeable to solutes. So solutes move out, making filtrate hypotonic.

### *In DCT*

It is relatively impermeable to water. Only 5% of filtered water is reabsorbed.

### *In Collecting Tubule*

Here reabsorption is under the control of ADH, so called as ***facultative reabsorption***. Collecting tubule has cortical and medullary parts. P cells contain aquaporin-2 through which water is reabsorbed. ADH stimulates the movement of aquaporin-2 to the luminal side of cell membranes. Ten percent of the reabsorption occurs from cortical part where as 5% from medullary part of collecting duct. As a result of reabsorption of water from various segments urine becomes hypertonic (1400 mOsm/L).

***Note***

A part of osmotic flow of water occurs through tight junctions between the epithelial cells. The osmotic water flowing especially in PCT also carries with it some of the solutes, a process referred to as ***solvent drag***.

## Reabsorption of Glucose

Glucose is completely reabsorbed in the PCT along with $Na^+$. This reabsorption of glucose occurs along with the reabsorption of Na by symport/cotransport mechanism. Glucose and $Na^+$

bind to a common carrier SGLT-2 in the luminal membrane. Glucose is carried into the cell as Na moves down its electrical and chemical gradient. The $Na^+$ is then actively pumped out of the cell into lateral intercellular spaces and interstitium (Fig. 6.13). Glucose combines with another carrier protein GLUT-2 on the basal surface of same cell and moves into the peritubular capillaries by simple diffusion. Thus glucose transport across PCT is an example for secondary active transport.

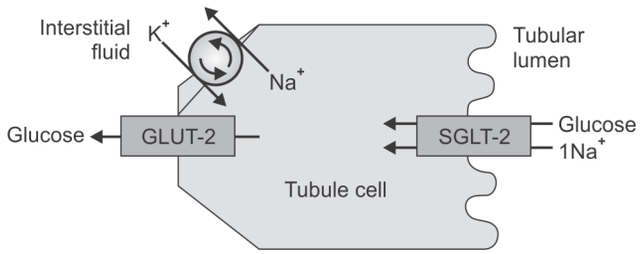



**Fig. 6.13:** Sodium reabsorption from PCT (SGLT-2: Sodium dependent glucose transporter 2, GLUT-2: Glucose transporter 2)

***Note***

1. A variety of other substances are transported by secondary active transport via symports, with the energy provided by active transport of $Na^+$ out of the renal tubular cells. These substances include some amino acids, lactate, inorganic phosphate, $H^+$, and $Cl^-$.
2. Glucose transport in kidneys is inhibited by phlorhizin, a plant glycoside, which competes with glucose for binding to the carrier.
3. Glycosuria is common during pregnancy due to decrease in renal threshold and increase in GFR.

### *Characteristic of Glucose Transport and Excretion*

Rate of filtration of glucose at glomerulus
= Resting plasma level of glucose × GFR
= 80 × (125/100) ml/min
= 100 mg/min

**Transport Maximum ($T_M$)**

The substances reabsorbed actively from the renal tubules require some specific transport system. There is a limit to the rate at which solute can be transported. This limit is due to saturation of transport systems involved, when maximum solute is delivered to the tubule. The maximum rate at which a substance is reabsorbed from renal tubule is called transport maximum for that substance. For example, the transport maximum for glucose ($T_M$G) is 375 mg/min in males and 300 mg/min in females.

**Renal threshold value for glucose**

The renal threshold for glucose is the plasma level at which the glucose first appears in the urine more than the normal minute amounts. This renal threshold is calculated by $T_M$G / GFR.

Theoretically the renal threshold would be about 300 mg/dl, i.e. 375 mg/min ($T_M$G) divided by 125 ml/min (GFR). However, the actual renal threshold is about 200 mg/dL of arterial blood or 180 mg/dL of venous blood. This anomaly between predicted value and practical value can be demonstrated by a graph. (Fig. 6.14).

The actual curve is rounded and deviates from the "ideal" curve. This deviation is called ***splay.*** It represents the excretion of glucose in urine before the $T_M$G is reached. It is due to:

a. All the nephrons does not have the same $T_M$G.
b. Below $T_M$G levels the interaction between a carrier and glucose is not completely an irreversible process , so some glucose escapes reabsorption.

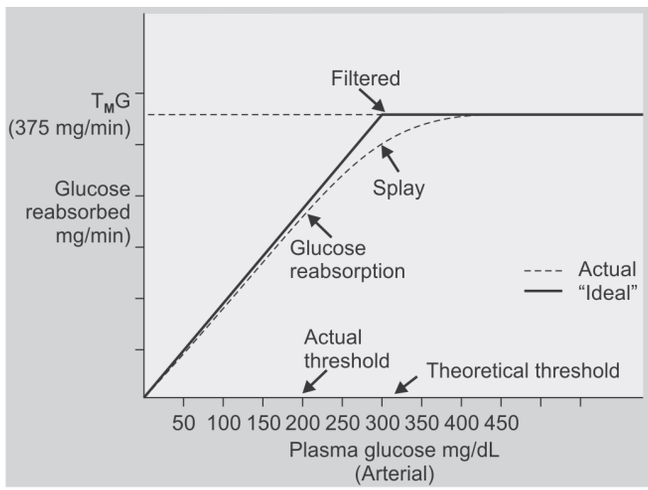



**Fig. 6.14:** Relationship between the plasma glucose concentration and glucose transport

## REABSORPTION OF BICARBONATE

Reabsorption of $HCO_3^-$ occurs throughout the nephron, except in the descending limb of LH.

### *In PCT*

About 90% of the filtered $HCO_3^-$ is reabsorbed into the PCT. $H^+$ secretion across the apical membrane of the cell occurs by both $Na^+$- $H^+$ antiporter and $H^+$-ATPase. The $Na^+$ - $H^+$ antiporter is the predominant pathway for $H^+$ secretion and uses the lumen to cell [$Na^+$] gradient to drive this process. Within the cell, $H^+$ and $HCO_3^-$ are produced in a reaction catalyzed by CA. The $H^+$ is secreted into tubular fluid, whereas $HCO_3^-$ exits the cell across the basolateral membrane and

returns to the peritubular blood. Movement of $HCO_3^-$ out of the cell across the basolateral membrane is coupled to other ions (Fig. 6.15).

a. The majority of $HCO_3^-$ exits via a symporter that couples with efflux of $1Na^+$ with $3HCO_3^-$ (sodium bicarbonate cotransporter).
b. In addition, some of the $HCO_3^-$ may exit in exchange for $Cl^-$. CA is also present in the brush border of the proximal tubule cells. This enzyme catalyzes the dehydration of $H_2CO_3$ in the luminal fluid and thereby facilitates reabsorption of $HCO_3^-$.

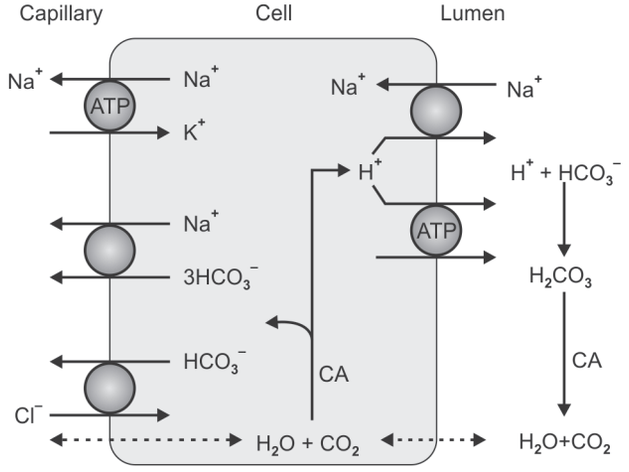



**Fig. 6.15:** Bicarbonate reabsorption in proximal convoluted tubule

### *In LH*

The cellular mechanism responsible for reabsorption of $HCO_3^-$ in thick segment of LH is very similar to that in PCT. A $K^+$ - $HCO_3^-$ symporter in the basolateral membrane may also contribute to the exit of $HCO_3^-$ from the cell.

### *In DCT and CT*

Intercalated cells secretes $H^+$ (reabsorbs $HCO_3^-$). Within this cell, $H^+$ and $HCO_3^-$ are produced by the hydration of $CO_2$, this reaction is catalyzed by CA. The $H^+$ is secreted into tubular fluid via two mechanisms (Fig. 6.16):

a. The first involves an apical membrane $H^+$-ATPase.
b. The second couples the secretion of $H^+$ with the reabsorption of $K^+$ via an $H^+$, $K^+$-ATPase similar to that found in the stomach. The $HCO_3^-$ exits the cell across the basolateral membrane in exchange for $Cl^-$ (via $Cl^-HCO_3^-$ antiporter) and enters the peritubular capillary blood.

## $K^+$ Transport

The kidneys play a major role in maintaining $K^+$ balance. It helps in maintaining a balance between urinary excretion and dietary intake of $K^+$, thereby ensuring $K^+$ homeostasis.

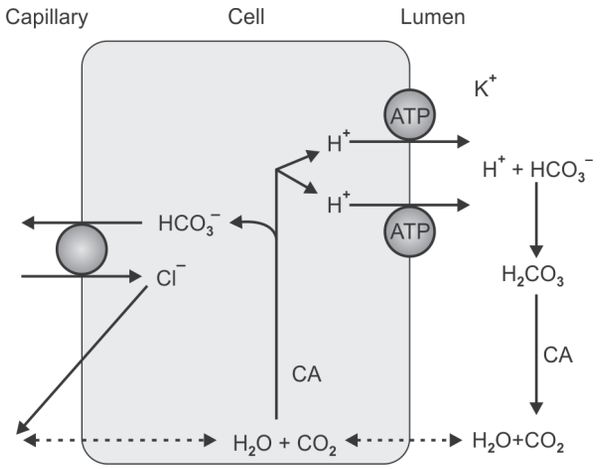



**Fig. 6.16:** Bicarbonate reabsorption in distal convoluted tubule

### *Glomerular Filtration*

Because $K^+$ is not bound to plasma proteins, it is freely filtered by glomerulus. The $K^+$ is the plasma electrolyte that is both reabsorbed and secreted into renal tubules.

### *Reabsorption of $K^+$ by Proximal Tubule*

About 67% of the filtered $K^+$ is reabsorbed by active transport in the PCT. In PCT, the amount of $K^+$ reabsorbed is a constant fraction of the amount filtered.

### *Reabsorption of $K^+$ by Loop of Henle*

About 20% of the filtered $K^+$ is reabsorbed through thick ascending limb of loop of Henle along with $Na^+$ reabsorption.

### *Reabsorption and Secretion of $K^+$ by DCT and CT*

The distal tubule and CT are able to reabsorb or secrete $K^+$. The rate of $K^+$ reabsorption or secretion by DCT and CT depends on variety of hormones and factors. Most of $K^+$ produced in the urine is due to secretion of the $K^+$ in the DCT which contributes approximately 75% of excreted $K^+$. The $K^+$ secretion from blood into the tubule lumen is a two step process and it involves an active as well as a passive process.

a. Uptake of $K^+$ from blood across the basolateral membrane into the DCT by $Na^+$-$K^+$ ATPase. This is the critical step and is associated with active $Na^+$ efflux via the $Na^+$-$K^+$ ATPase.
b. The elevated intracelular $K^+$ so achieved favors the net $K^+$ diffusion at the apical membrane down a concentration gradient into the tubular lumen.

### *Factors Affecting $K^+$ Transport*

1. Plasma [ $K^+$] is an important determinant of $K^+$ secretion by the DCT and CT. Hyperkalemia (e.g. resulting from a high $K^+$ diet or from rhabdomyolysis) stimulates secretion of $K^+$. Tubular secretion of $K^+$ is markedly decreased in $K^+$ and $Na^+$ depletion.
2. In DCT, $K^+$ and $H^+$ are both exchanged for $Na^+$ which is reabsorbed and the two ions compete for the exchange mechanism. Therefore $K^+$ excretion is decreased when $H^+$ secretion is increased.
3. Flow of tubular fluid: The rate of $K^+$ secretion is proportionate to the rate of flow of tubular fluid through the distal portion of the nephron, because with rapid flow there is less opportunity for the tubular $K^+$ concentration to rise to a value that stops further secretion.
4. Mineralocorticoids (e.g. aldosterone) increases $K^+$ secretion by:
   a. Increasing the activity of basolateral $Na^+$- $K^+$ ATPase, which increases $K^+$ entry into the DCT.
   b. Increasing the permeability of the luminal membrane to $K^+$.

### Tubular Secretion

Some substances are secreted into the lumen from peritubular capillaries through tubular epithelial cells. It is known as tubular secretion. Secreted substances are $H^+$, $K^+$, $NH_3$, weak acids, steroids, drugs (penicillin).

## CONCENTRATION OF URINE

Kidney is able to excrete very concentration urine with osmolarity of 1400 mOsm/L and very dilute urine with osmolarity of 50 mOsm/L. Process of concentration or dilution of urine requires kidney to excrete water and solutes independently. When water intake is decreased, solutes are excreted in excess of water resulting in concentrated urine of maximum osmolarity 1400 mOsm/L. When water intake is increased, water is excreted in excess of solutes resulting in the formation of dilute urine of minimum osmolarity 50 mOsm/L.

### Formation of Concentrated Urine

The basic requirement for forming a concentrated urine are:
1. Hyperosmotic renal medulla (Fig. 6.17).
2. Secretion of ADH.

### *Hyperosmotic Renal Medulla*

Increasing osmotic gradient that is present along medullary interstitium is produced by combined action of loop of Henle and vasa recta as counter current multiplier and counter current exchanger respectively.

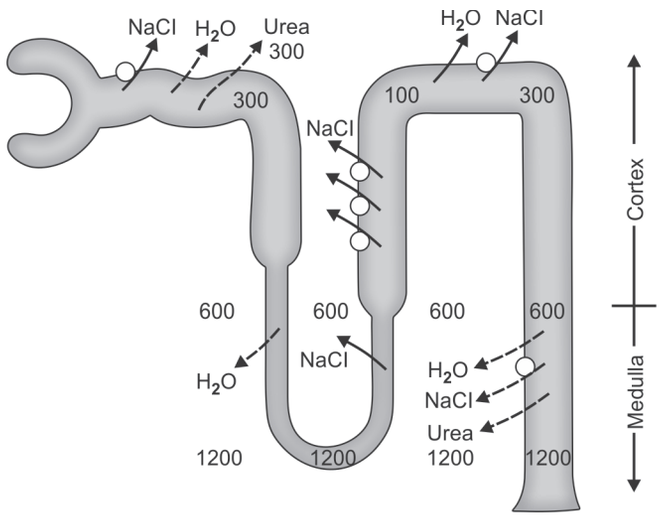



**Fig. 6.17:** Formation of a concentrated urine when ADH levels are high

Counter current system is defined as the system in which inflow runs parallel to and in close proximity to outflow in the opposite direction.

Thus counter current system has two components:
a. Countercurrent multiplier system.
b. Countercurrent exchanger system.

### *Countercurrent Multiplier System*

Loop of Henle functions as countercurrent multiplier and plays an important role in producing hypertonic medullary interstitium. Ascending limb and descending limb are parallel to each other and in close proximity.

The descending limb is highly permeable to water. So water moves from the tubular lumen into medullary interstitium (not accompanied by $Na^+$).The medullary gradient is such that the interstitium becomes more and more hyperosmolar in the deeper parts of the medulla, which is the main reason why water flows from the lumen to interstitium and not in the reverse direction. As a result the tubular fluid becomes more and more concentrated as it descends down the thin descending limb of LH. (1200–1400 mOsm/L at the apex of LH) (Fig. 6.18).

Then, the tubular fluid reaches the ascending limb. The thick segment of ascending limb vigorously reabsorbs $Na^+$ (along with $Cl^-$ and $K^+$), but this segment is impermeable to water. Therefore, the tubular fluid loses $Na^+$, $Cl^-$ and $K^+$ but no water. This means the tubular fluid begins to become diluted in the ascending limb of LH.

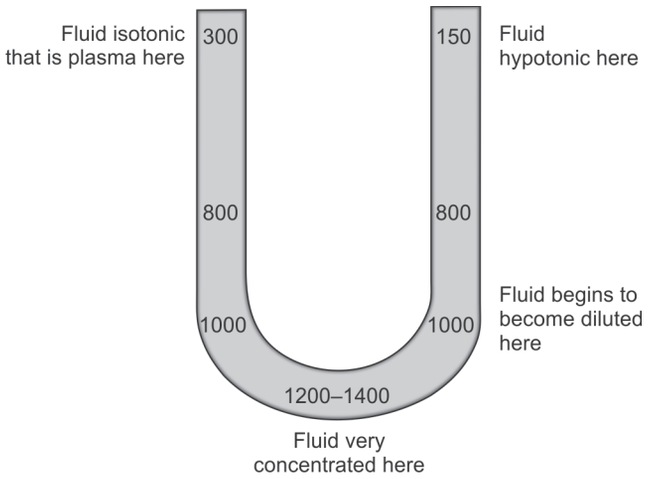



**Fig. 6.18:** Summary of changes in the osmolality (in mOsm/L) of tubular fluid

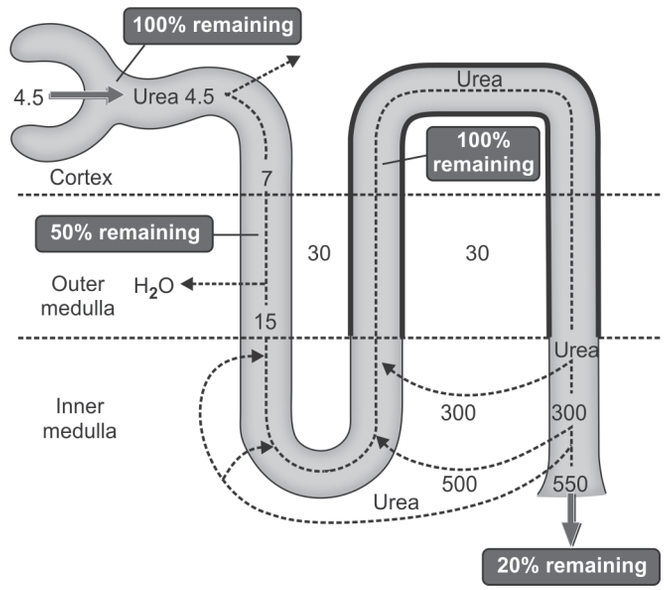



**Fig. 6.20:** Recirculation of urea absorbed from the medullary collecting duct into the interstitial fluid

Because of movement of solutes from ascending limb of LH to interstitium the osmolarity of medullary interstitium increases and becomes hypertonic (Fig. 6.19). This situation is maximum in JG nephrons because of long LH.

The hypotonic tubular fluid is then delivered to the DCT. In the early DCT, reabsorption of $Na^+$ continues which causes further dilution of luminal fluid.

Finally the fluid enters the cortical collecting tubule. When ADH acts on cortical collecting tubules, water flows massively from CD to the interstitium through aquaporins. This flow of fluid continues until the osmolality of the CD fluid attains that of interstitium. Thus the urine formed is very concentrated.

Medullary interstitial hypertonicity is also contributed by urea which moves out of inner medullary portion of the collecting tubule. This urea also plays an important role in concentration of urine. This in turn is influenced by a protein diet. So high protein diet produce a high concentration capacity for kidney.

The Figure 6.20 shows the recirculation of urea absorbed from the medullary collecting duct into the interstitial fluid, this urea diffuses into the thin loop of Henle,and then passes through the distal tubules, and finally passes back into the collecting duct. The recirculation of urea helps to trap urea in the renal medulla and contributes to the hyperosmolarity of the renal medulla. The heavy dark lines, from the thick ascending loop of Henle to the medullary collecting ducts, indicate that these segments are not permeable to urea. (Numerical values are in milliosmoles per liter of urea during antidiuresis, when large amounts of antidiuretic hormone are present. Percentage of the filtered load of urea that remain in the tubules are indicated in the boxes).

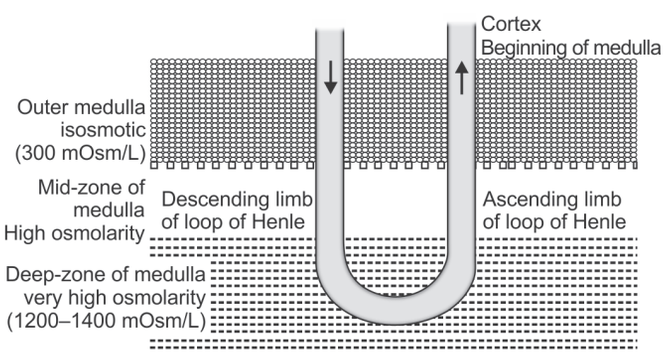



**Fig. 6.19:** Operation of countercurrent exchange system

### *Countercurrent Exchanger System*

Vasa recta functions as countercurrent exchanger. It is responsible for maintenance of the hyperosmolarity of medullary gradient developed by countercurrent multiplier system. If blood vessel was straight and the blood flow were high, the solute pumped into renal medulla by countercurrent multiplier system would rapidly dissipate.

Vasa recta also has a descending and ascending limb. It runs parallel to LH. Both limbs are permeable to water and solutes (except for plasma proteins). Blood entering DL has an osmolarity of 300 mOsm/L and osmolarity of blood leaving the AL is 325 mOsm/L. As the blood descends into the medulla it becomes progressively more concentrated, partially by solute (NaCl, urea, etc.) entry from the interstitium and partially by loss of water into the interstitium. By the time the blood reaches the tips of vasa recta, it has a concentration of about 1200 mOsm/L.

As the blood ascends back toward the cortex, it becomes progressively less concentrated as solutes diffuses back out into the medullary interstitium and as water moves into the vasa recta. The blood passing through the AL of vasa recta carry very little amount of NaCl from the medulla. Thus, NaCl and urea are exchanged for water between the AL and DL of vasa recta, hence this system is called countercurrent exchanger (Fig. 6.21).

If vasa recta was straight $Na^+$ and urea in the interstitium would have been removed by circulation. The sluggishness of blood flow ensures the retention of $Na^+$ in the medullary interstitium.

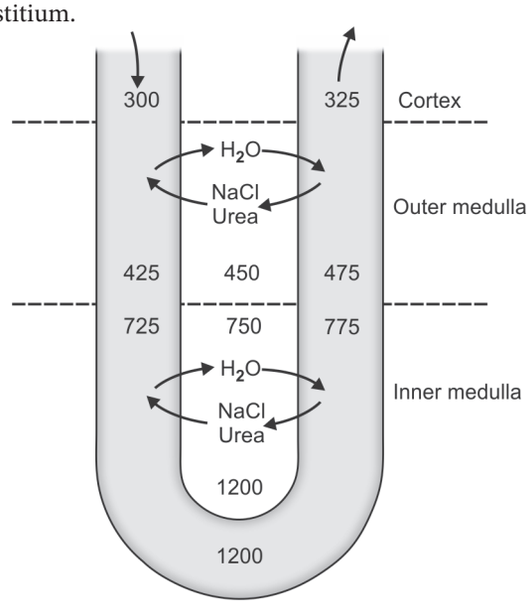



**Fig. 6.21:** Countercurrent exchange in the vasa recta

**Secretion of ADH**

In the late distal tubules and cortical collecting tubules, the osmolarity of fluid depends on the level of ADH. With high levels of ADH, these tubules are highly permeable to water.

**Formation of Dilute Urine**

When water content in the body increases, kidney excrete dilute urine. It is achieved by inhibition of ADH secretion (Fig. 6.22)

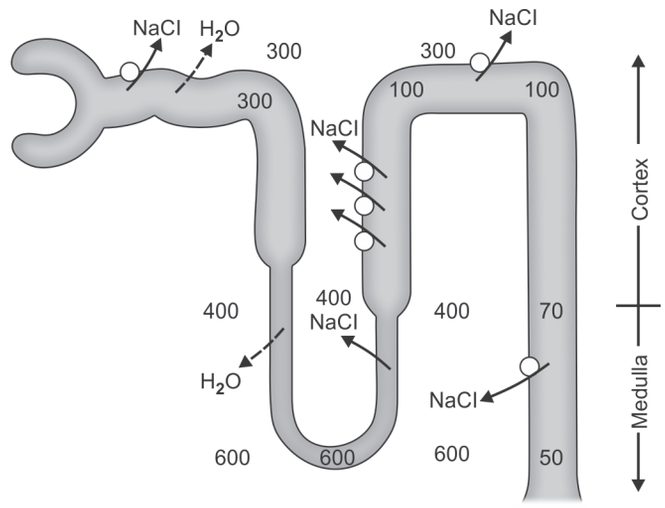



**Fig. 6.22:** Formation of dilute urine when ADH levels are very low

## ACIDIFICATION OF URINE

Kidneys plays an important role in the maintenance of acid-base balance by excreting $H^+$ and retaining $HCO_3^-$. pH of glomerular filtrate: 7.4 (same as plasma). Normally the urine is acidic in nature with a pH of 4.5–6.

### Secretion of $H^+$

1. The cells of PCT, thick segment of ascending limb of LH, DT and CT secrete $H^+$. The reaction that is responsible for $H^+$ secretion in PCT, thick segment of ascending limb of LH and early distal tubules is $Na^+$ - $H^+$ exchange. When $Na^+$ is reabsorbed from tubular fluid into tubular cell, $H^+$ is secreted from the cell into the tubular fluid in exchange for $Na^+$. The $H^+$ comes from intracellular dissociation of $H_2CO_3$ and the $HCO_3^-$ formed diffuses into the interstitial fluid. Thus for each $H^+$ secreted one $Na^+$ and one $HCO_3^-$ enter the interstitial fluid (Fig. 6.23).
2. In late distal and collecting tubules, $H^+$ is secreted by an ATP driven proton pump mechanism. Secretion of $H^+$ occurs in a special type of cell called I cells of late distal tubules and CT. It occurs in the luminal membrane of the tubular cell where, $H^+$ is transported directly by a specific protein, a hydrogen-transporting ATPase. The I cells contain an anion exchange protein called band 3 in their basolateral surface of cell which helps in exchange of $HCO_3^-$ and $Cl^-$. Some $H^+$ are also secreted by $H^+$ - $K^+$ ATPase (Fig. 6.24).

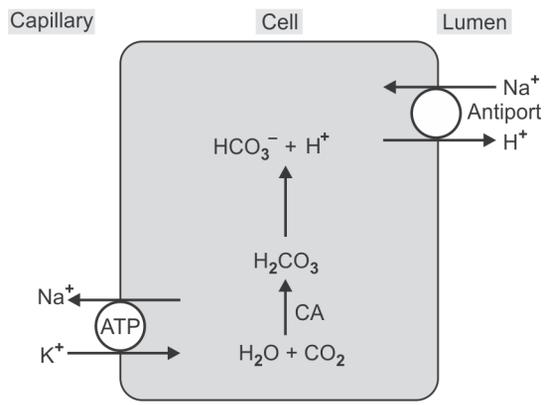



**Fig. 6.23:** Cellular mechanism for secretion of hydrogen ions into PCT, thick ascending limb of loop of Henle, DT and CT

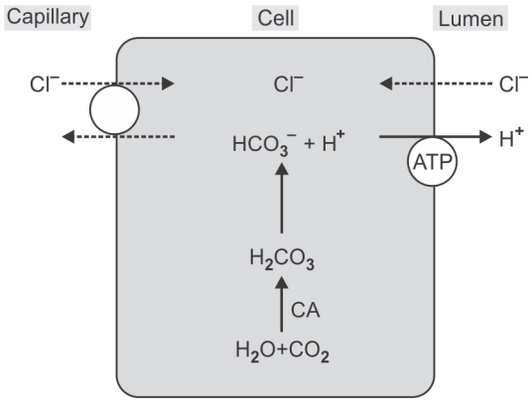



**Fig. 6.24:** Cellular mechanism for secretion of hydrogen ions into late DT and CT

## Removal of $H^+$

If $H^+$ ion secreted into the lumen were not removed in time acidity of urine increases rapidly and attains limiting pH which inhibits further secretion of $H^+$ ion by tubular cell. This removal is done by three mechanisms:

### *Bicarbonate Mechanism*

The $H^+$ secreted into the renal tubule combines with filtered $HCO_3^-$ forming $H_2CO_3$. The $H_2CO_3$ dissociates into $CO_2$ and $H_2O$. $CO_2$ diffuses into cell and it is used to form $H_2CO_3$ (Fig. 6.25).

Thus for each mole of $HCO_3^-$ removed from the tubular fluid 1 mole of $HCO_3^-$ diffuses from the tubular cells into the blood. This mechanism particularly takes place in proximal tubules since carbonic anhydrase is present in the brush border of the cells.

### *Phosphate Mechanism*

In the tubular cell $CO_2$ combines with $H_2O$ to form $H_2CO_3$. It immediately dissociates into $H^+$ and $HCO_3^-$. $HCO_3^-$ from the tubular cell enters the interstitium, simultaneously $Na^+$ is reabsorbed. The $H^+$ is secreted into the tubular lumen it reacts with sodium hydrogen phosphate ($NaHPO_4$) to form sodium dihydrogen phosphate ($NaH_2PO_4$). $NaH_2PO_4$ is excreted in urine. This happens mainly in distal tubules and collecting duct (Fig. 6.26).

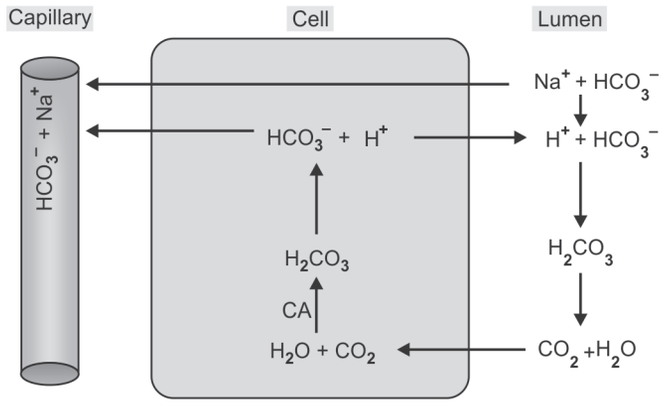



**Fig. 6.25:** Reabsorption of bicarbonate ions by secretion of hydrogen ions in renal tubule

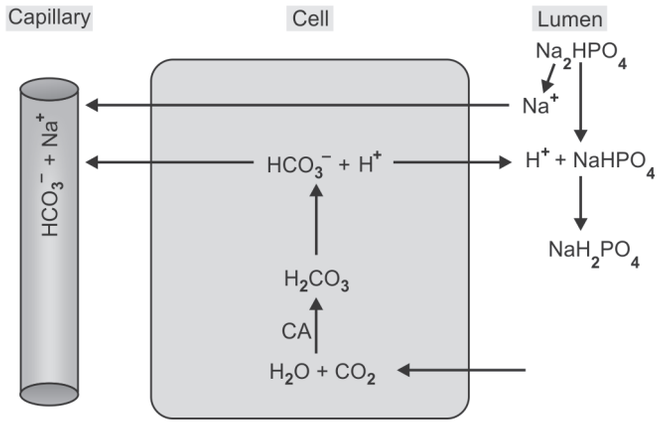



**Fig. 6.26:** Excretion of hydrogen ions in combination with phosphate ions

### *Ammonia Mechanism*

In the tubular epithelial cells, $NH_3$ is formed from glutamine. Glutamine is 1st converted to glutamate by glutaminase. Glutamic dehydrogenase then catalyzes the convertion of glutamate to α ketoglutarate, with the production of $NH_3$. The $NH_3$ formed in the tubular cells is secreted tubular lumen in exchange of $Na^+$ ion. Here it combines with $H^+$ to form ammonium. ($NH_4^+$) and is excreted (Fig. 6.27).

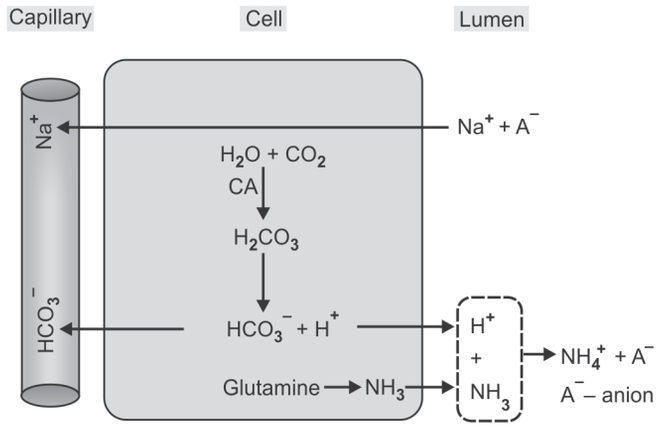



**Fig. 6.27:** Excretion of hydrogen ions in combination with ammonia

***Factors affecting $H^+$ secretion along with $HCO_3^-$ reabsorption***

**Increase in $H^+$ secretion**

1. *Increased $pCO_2$:* Increase in $pCO_2$ increases the secretion of $H^+$ and $HCO_3^-$ absorption. When there is more $pCO_2$ it results in acidosis.

2. *Hypokalemia:* When $K^+$ concentration is low, no competition with $Na^+$ for secretion.
3. *Increased aldosterone and adrenocortical steroids:* It acts on distal tubule, more $Na^+$ is reabsorbed and more $H^+$ is secreted.

**Decrease in $H^+$ secretion**

1. Decreased $pCO_2$
2. Hyperkalemia
3. Decreased aldosterone
4. By carbonic anhydrase inhibitors—this is because $H_2CO_3$ is not formed

## RENAL CLEARANCE TESTS

These tests are done to assess the functions of different parts of nephrons. Renal clearance of a substance is the volume of plasma that is completely cleared of a substance by the kidneys per unit time. It is calculated from the following formula:

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

where,

C = Clearance
U = Concentration of the substance in urine
V = Volume of urine exceted per unit time
P = Concentration of the substance in blood.

### *Measurement of Glomerular Filtration Rate*

A substance that is completely filtered but neither reabsorbed nor secreted should be used to measure GFR. Inulin is an subtance used to measure GFR.

**a. Inulin Clearance Test**

A large initial dose of inulin is injected intravenously into the body. To maintain a relatively constant arterial plasma level inulin is infused at a constant rate into the body. After sometime concentration of inulin in plasma in venous blood ($P_{in}$), urinary concentration ($U_{in}$) and volume of urine excreted per minute (V) are determined.

$$\text{Inulin clearance, } C_{in} = \frac{U_{in} \times V}{P_{in}}$$

For example the concentration of inulin in urine is 125 mg%. The plasma concentration is 1 mg%. The volume of urine output is 1 ml/min thus $C_{in}$ gives GFR.

Inulin clearance is used as an indicator of plasma clearance mechanism. A comparison of the clearance of a given substance ($C_x$) with the clearance of inulin ($C_{in}$) provides information about the renal mechanisms used to remove the substances from plasma.

- When $C_x$ equals $C_{in}$, excretion is by filtration alone.
- When $C_x < C_{in}$, excretion is by filtration and reabsorption.
- When $C_x > C_{in}$, excretion is by filtration and secretion.

**b. Creatinine Clearance**

The most common method to measure GFR in clinical practice is to determine the 24 hour endogenous creatinine clearance. Its determination does not require administration of exogenous creatinine, as creatinine is a product of muscle metabolism.

Normal range for creatinine clearance: 80–110 ml/min. However, some creatinine is reabsorbed by the tubules and some may be secreted. So, when precise measurement of GFR is required, inulin clearance is preferred.

### *Measurement of Renal Plasma Flow*

To measure renal plasma flow, a substance, which is filtered and secreted but not reabsorbed should be used. Such a substance is para-aminohippuric acid (PAH).

**a. PAH clearance**

A known amount of PAH is injected into the body. After sometime, the concentration of PAH in plasma and urine and the volume of urine excreted are estimated. Since PAH is completely cleared from the plasma, the clearance rate of that substance is equal to the total renal plasma flow.

PAH clearance,

$$C_{PAH} = U_{PAH} \times \frac{V}{P_{PAH}}$$

Thus $C_{PAH}$ gives renal plasma flow.

**b. Diodrast clearance** can be also used to measure this.

### *Measurement of Renal Blood Flow*

To determine renal blood flow value of two factors are necessary.

i. Renal plasma flow
ii. Percentage of plasma volume in the blood.

Renal blood flow = renal plasma flow/ % of plasma in blood
Formula can be also expressed as:

$$\text{Renal blood flow} = RPF \times \frac{1}{1\text{-Hct}}$$

where Hct = hematocrit.
Renal plasma flow is measured by using PAH clearance. The percentage of plasma volume is calculated indirectly by using PCV. If PCV is 45%, then the plasma volume in blood is 100 – 45 = 55%.

### *Quantifying Renal Urine Concentration and Dilution*

**Osmolar clearance**

The total clearance of solutes from blood can be expressed as the osmolar clearance. This is the volume of plasma cleared of solutes each time.

$$C_{OSM} = \frac{U_{OSM} \times V}{P_{OSM}}$$

where,
$U_{osm}$ is the urine osmolarity
V is the urine flow rate
$P_{osm}$ is the plasma osmolarity.

**Free water clearance**

It determines how much water is reabsorbed or lost while concentrating or diluting urine. It is calculated as the difference between urine flow rate and osmolar clearance.

$$C_{H_2O} = V - C_{OSM} = V - \frac{(U_{OSM} \times V)}{(P_{OSM})}$$

Thus rate of free water clearance represents the rate at which solute free water is excreted by the kidneys. When free water clearance is negative, water is conserved. When it is positive excess water is excreted by the kidney.

## MICTURITION

Process of voiding the urine is called micturition. It is a reflex process. Although the micturition reflex is a spinal cord reflex, it can also be inhibited or facilitated by centers in the cerebral cortex or brainstem. The main physiological events in the process of micturition are filling of bladder and emptying of bladder.

### Innervation of Urinary Bladder

#### *Sympathetic Innervations*

Preganglionic fibers of sympathetic nerve arise from 1st and 2nd lumbar segments of spinal cord. They pass through lateral sympathetic chain and terminate in hypogastric ganglion. The postganglionic fibers arising from this ganglion form the ***hypogastric nerve*** and supplies detrusor muscle and internal sphincter (Fig. 6.28). Stimulation of sympathetic nerve results in filling of bladder (by relaxation of detrusor muscle and contraction of internal sphincter). The sympathetic nerves to the bladder have no role in micturition, but they mediate contraction of bladder that prevents semen from entering the bladder during ejaculation.

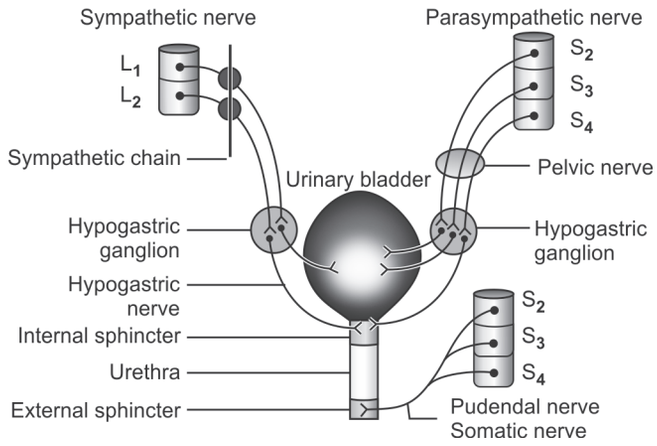



**Fig. 6.28:** Innervation of urinary bladder

#### *Parasympathetic Innervation*

Preganglionic fibres of parasympathetic nerve form the pelvic nerve ***(nervi ergentis)***. Pelvic nerve arise from 2nd, 3rd, and 4th sacral segments and terminate in hypogastric ganglion. The post ganglionic fibres arise from hypogastric ganglion and innervate detrusor muscle and internal sphincter. Stimulation of parasympathetic nerve results in emptying of bladder (by contraction of detrusor muscle and relaxation of internal sphincter). The pelvic nerve also has the sensory fibers which carry impulses from stretch receptors present on the wall of urinary bladder and urethra to sacral segments of spinal cord.

#### *Somatic Nerve Supply*

The external sphincter is innervated by the somatic nerve called the pudendal nerve. It arises 2nd, 3rd, and 4th sacral segments of spinal cord. It maintains tonic contraction of skeletal muscle fibers of external sphincter and keeps external sphincter constricted. During micturition this nerve is inhibited, leading to voiding of urine. Pudendal nerve is responsible for voluntary control of micturition.

### Filling of Urinary Bladder

Urine formed in the kidney flows through ureter to urinary bladder. The physiological capacity of the bladder varies with age; 20–50 ml at birth, 200 ml at 1 year and 600 ml in adults. The anatomical capacity of bladder is 1 L.

### *Volume and Pressure Changes in Bladder During Filling*

As bladder is filled up, it adjusts its tone and large volume of urine can be accommodated with minimal alterations in intravesical pressure. Each time urine flows, relaxation

of detrusor muscle occurs until the physiological limit is exceeded.

***Cystometrogram***

A plot of intravesicle pressure against volume of fluid in the urinary bladder is called cystometrogram. Normal cystometrogram shows three phases of filling (Fig. 6.29).

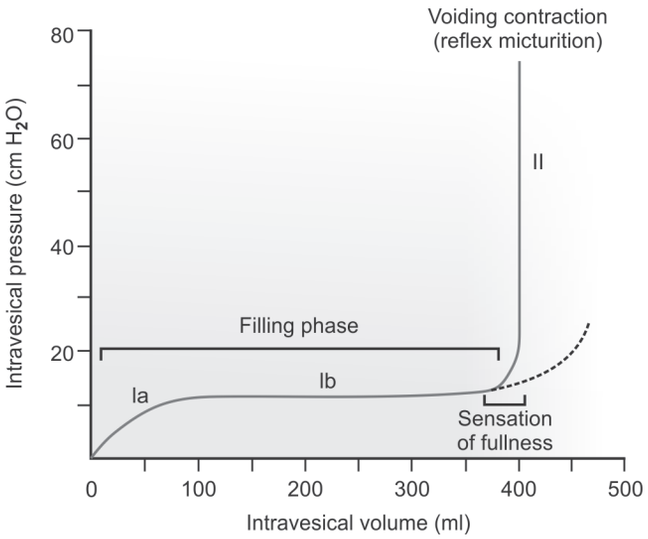



**Fig. 6.29:** Cystometrogram in a normal human

*Phase Ia*

It is the initial phase of filling in which pressure rises to 5 - 10 cm of $H_2O$, when about 50 ml of fluid is collected in the bladder.

*Phase Ib*

- This segment shows plateau, i.e. the intravesical pressure remains more or less at 10 cm of $H_2O$ for a volume up to 400 ml of fluid. The flatness of phase Ib is a manifestation of law of laplace.

  Law of Laplace - P= 2T/R .

  where P = pressure in bladder, R = radius of bladder, T= tension on walls.
- In the bladder, tension increases as the urine is filled. At the same time the radius also increases due to relaxation of detrusor muscle. Therefore the pressure increase is slight.

*Phase II*

- Once the volume reaches 400 ml, pressure suddenly rises. This is shown by phase II of the graph. This is the volume at which micturition reflex occurs.

***Note:*** The 1st urge to void is felt at about 150 ml and a marked sense of fullness at about 400 ml. When it is increased beyond 450 ml, pain and discomfort occurs.

## Emptying of Bladder

### *Micturition Reflex (Flow chart 6.1)*

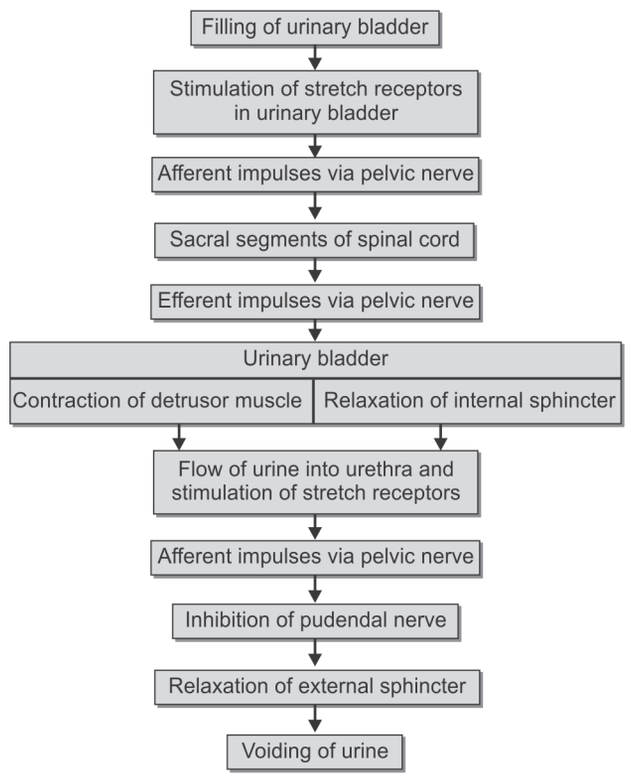
Micturition reflex is initiated by stimulation of stretch receptors located in the wall of urinary bladder. Filling of bladder by 300–400 ml of urine in adults is the normal stimulus for micturition to occur.

The sensory (afferent) impulses from the receptors reach the sacral segments of spinal cord via the sensory fibers of pelvic (parasympathetic) nerve. The motor (efferent) impulses produced in spinal cord, travel through motor fibers of pelvic nerve towards bladder and internal sphincter. The motor impulses cause contraction of detrusor muscle and relaxation of internal sphincter so that urine enters the urethra from the bladder.

Once urine enters urethra, the stretch receptors in the urethra are stimulated and send afferent impulses to spinal cord via pelvic nerve fibers. These impulses inhibit pudendal nerve. So external sphincter relaxes and micturition occurs.

Once a micturition reflex begins it is self regenerative, i.e. initial contraction of bladder further activates the receptors to cause still further increase in sensory impulses from bladder and urethra which cause further increase in reflex contraction of bladder. The cycle thus keeps on repeating itself again

**Flow chart 6.1:** Micturition reflex



and again until the bladder has reached a strong degree of contraction.

Voluntary contraction of the abdominal muscles aids the expulsion of urine by increasing the intra-abdominal muscle.

### *Higher Centers for Micturition (Voluntary Control of Micturition)*

Spinal centers for micturition are present in sacral and lumbar segments. But these centers are regulated by brain. The facilitatory area is located in the pontine region and in the posterior hypothalamus. The inhibitory area is in the midbrain. Several centers located in the cerebral cortex are mainly inhibitory, but can become excitatory.

Higher centers exert final control of micturition by following means:

a. The higher centers keep the micturition reflex partially inhibited all the time except when it is desired to micturate.
b. The higher centers can prevent micturition, even if the micturition reflex occurs, by continual tonic contraction of external urinary sphincter until a convenient time is present.
c. When convenient time to urinate is present, the higher centers can facilitate sacral micturition center to initiate a micturition reflex and at the same time inhibit external urinary sphincter so that urination can occur.

### *Voluntary Urination*

First, a person voluntarily contracts his or her abdominal muscles. This increases the pressure in the bladder and allows extra urine to enter the bladder neck and posterior urethra. This stimulates stretch receptors, which excites the micturition reflex and simultaneously relaxes external urethral sphincter.

***Note:*** In infants and young children micturition is purely a reflex action because the control from higher centers are not well established.

## *Abnormalities of Micturition*

### *Atonic Bladder*

Caused by destruction of sensory nerve fibers from urinary bladder. So micturition reflex contraction cannot occur. Instead of emptying periodically, the bladder is completely filled with urine. Later overflow occurs in drops through the urethra. This is called overflow incontinence.

Usually this occurs in injury to sacral segments of spinal cord. Certain diseases like syphilis can cause degeneration of dorsal nerve root fibers. This condition is called tabes Dorsalis, so the condition is also referred as tabetic bladder.

### *Automatic Bladder*

Caused by spinal cord damage above the sacral region. Micturition reflexes can still occur as sacral cord segments are intact. However they are no longer controlled by brain. Voluntary control of micturition is completely lost. Whenever the bladder distention reaches a critical point, micturition reflex is set up and results in urination.

Myelination of pyramidal tract will be completed by the age of two years only. So till then, there will be involuntary micturition or automatic bladder which is considered as normal in infants. In adults, automatic bladder may be seen in abnormalities like upper motor neuron lesions.

### *Uninhibited Neurogenic Bladder*

Caused by lack of inhibitory signals from the brain. There will be frequent and relatively uncontrolled micturation. Due to partial damage in the spinal cord or brainstem, most of the inhibitory signals are interrupted. Therefore facilitative impulses by higher centers keep sacral centers so excitable that even a small quantity of urine elicits an uncontrollable micturition reflex.

### *Autonomous Bladder*

This condition occurs if sacral segments of spinal cord is destroyed or if cauda equine is severed. The bladder has no reflex control or voluntary control. Bladder wall is flaccid and capacity is greatly increased. It fills to capacity and overflows, which results in continual dribbling.

## DIURESIS

Diuresis is the condition where urine output is increased.

### Water Diuresis

Increased water intake leads to decreased plasma osmolarity. This results in decreased secretion of ADH that results in decreased water reabsorption in CD, so dilute urine is excreted which is referred to as water diuresis. Effect of secretion of dilute urine starts 15 minutes after the ingestion of the water load and reaches a maximum at 40 minutes.

### *Water Intoxication*

Maximum urine flow in water diuresis is 16 ml/min. If water is ingested at a rate higher than this for any length of time, swelling of cells because of uptake of water from the hypotonic ECF becomes severe. Swelling of cells in the brain causes convulsions and coma and leads eventually to death. Water intoxication can also occur when water intake is not reduced after administration of exogenous vasopressin or secretion of

endogenous vasopressin in response to nonosmotic stimuli such as surgical trauma.

## Osmotic Diuresis

Presence of large quantities of unreabsorbed solutes in tubules can cause increased urine output which is referred to as osmotic diuresis. Medullary hypertonicity is decreased when ascending LH cannot reabsorb $Na^+$ maximally. It causes decreased water reabsorption from descending LH which causes more fluid entry into CD. So there is marked increase in urine volume and increased $Na^+$ and solute excretion. Osmotic diuresis can be induced by administration of mannitol and infusion of large amount of NaCl and urea.

### *Difference between Osmotic Diuresis and Water Diuresis*

In water diuresis, the amount of water reabsorbed in the proximal portions of nephrons is normal and the maximal urine flow that can be produced is about 16 ml/min. Inj osmotic diuresis, increased urine flow is due to decreased water reabsorption in proximal tubules and loops and very large urine flows can be produced. As the load of excreted solute is increased, the concentration of urine approaches that of plasma in spite of maximal vasopressin secretion because large fraction of excreted urine is isotonic with proximal tubular fluid.

## Diuretics

Diuretics are substances which enhance the output of urine. These substances increase the excretion of water, sodium, chloride through urine.

Most diuretics used clinically decreases rate of $Na^+$ reabsorption in renal tubules. Natriuresis occurs then, in turn increases $H_2O$ output. Tubular reabsorption of many other solutes like $K^+$, $Cl^-$, $Mg^{2+}$, $Ca^{2+}$ are influenced by $Na^+$ reabsorption secondarily. So, many diuretics increases renal output of these solutes also.

Osmotic diuretics increases osmotic pressure of tubular fluid thereby decreses $H_2O$ reabsorption and increases urine output.

## Sites of Action of Various Diuretics (Fig. 6.30)

1. Furosemide and other loop diuretics - thick ascending limb of loop of Henle.
2. Thiazides-early portion of distal convoluted tubule.
3. Aldosterone antagonist (Spironolactone triamterene) - collecting duct.
4. Antagonist to $V_2$ vasopressin receptors-on collecting duct.

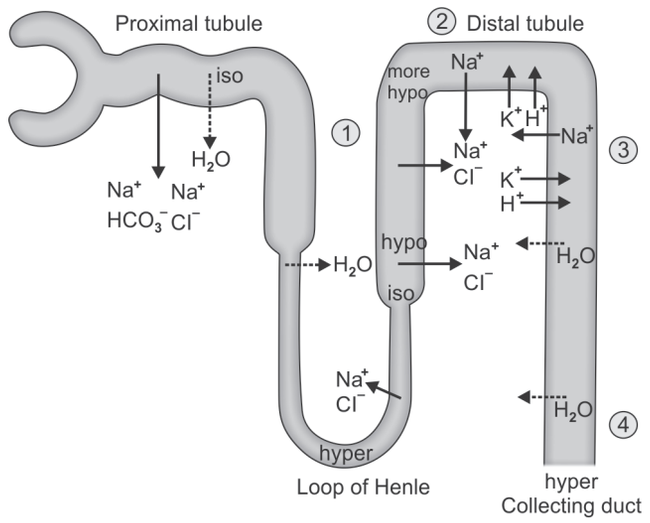



**Fig. 6.30:** Site of action of various diuretics

### *Mode of Action*

a. *Furosemide:* Inhibit $Na^+$ - $K^+$ - $2Cl^-$ Cotransport.
b. *Thiazides:* Inhibit $Na^+$ - $Cl^-$ Cotransport.
c. *Aldosterone antagonist:* Inhibit action of aldosterone on tubular receptor.
d. *Antagonist to $V_2$ vasopressin receptors:* Inhibits the action of vasopressin.
e. *Xanthines like theophylline and caffeine:* Decrease tubular reabsorption of $Na^+$ and increase GFR.
f. *Acetazolamide (carbonic anhydrase inhibitor):* Decrease $H^+$, with resultant increase in $Na^+$ and $K^+$ excretion.
g. *Water and ethanol:* Inhibits vasopressin secretion.
h. *Glucose and Mannitol:* Produce osmotic diueresis.

## DIALYSIS

The basic principle of the artificial kidney is to pass blood through minute blood channels bounded by a thin cellophane membrane. On the other side of the membrane is a dialysing fluid into which unwanted substances in the blood pass by diffusion (Fig. 6.31).

Cellophane is porous enough to allow the constituents of the plasma, except the plasma proteins to diffuse in both directions from plasma into the dialyzing fluid or from the dialyzing fluid back into the plasma.

If the concentration of a substance is greater in the plasma than in the dialyzing fluid, there will be net transfer of the substance from the plasma into the dialyzing fluid. The rate of movement of the solute across the dialyzing membrane depends upon:

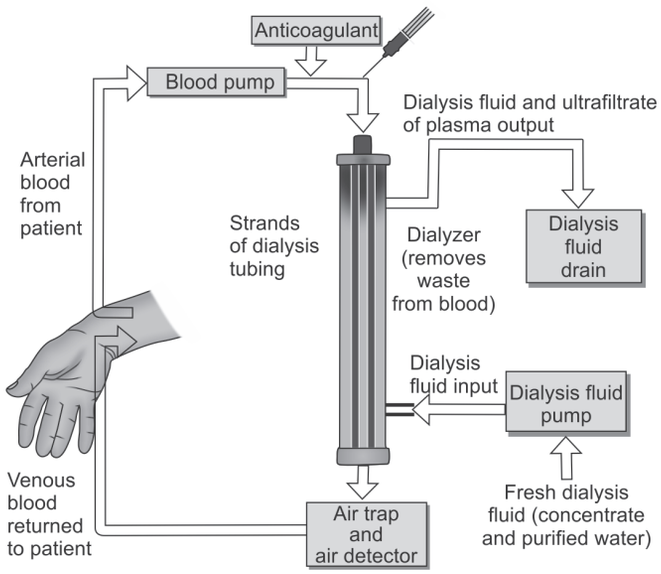



**Fig. 6.31:** Principles of dialysis

1. Concentration gradient of the solute between the two solutions.
2. Permeability of the membrane to the solute.
3. Surface area of the membrane
4. Length of time that the blood and fluid remain in contact with the membrane.

### Dialyzing Fluid

The concentration of ions and other substances in the dialyzing fluid are not the same as that in normal plasma or uremic plasma. They are adjusted to levels that are needed to cause appropriate movement of water and solutes through the membrane during dialysis. It contains no creatinine, urea, or other substances to be completely removed from plasma.

***Note***

### Renal Failure

Renal failure refers to the severe deterioration of renal function. It is of two types: acute and chronic.

*Acute renal failure:* The onset of this condition is sudden (within days or weeks). It may be due to decreased blood supply to the kidneys, obstruction of the urinary collecting system, etc.

*Chronic renal failure:* Refers to a slow (over a period of months), irreversible deterioration of renal functions. It results from diabetes is mellitus, glomerulonephritis, pyelonephritis, TB, etc.

### Nephrotic Syndrome

It is characterized by loss of large quantities of plasma proteins into the urine. The cause of protein loss in urine is increased permeability of glomerular membrane. So diseases like chronic glomerulonephritis, amyloidosis which increases permeability of membrane can cause nephrotic syndrome. As a consequence of the decreased plasma protein concentration, the plasma colloid osmotic pressure falls to low levels. This causes the capillaries all over the body to filter large amounts of fluid into the various tissues, which in turn causes edema and decreases the plasma volume.

Renal sodium retention in nephrotic syndrome occurs through multiple mechanisms activated by leakage of protein and fluid from the plasma into the interstitial fluid, activation of $Na^+$ retaining systems such as the renin-angiotensin system, aldosterone, sympathetic nervous system. However, because of the large amount of $Na^+$ and water retention, the plasma protein concentration becomes further diluted, causing still more fluid to leak into the tissues of the body.

### Fanconi's Syndrome

It is associated with increased urinary excretion of amino acids, glucose and phosphates. In severe cases other manifestations are also observed such as (a) failure to reabsorb sodium bicarbonate (b) increased excretion of $K^+$ and $Ca^{2+}$ (c) failure of kidney to respond to ADH. The causes for Fanconi's syndrome are hereditary defects in cell transport mechanisms, toxins or drugs that injure the renal tubular epithelial cells, ischemia (causes injury to tubular cell). The proximal tubular cells are especially affected due to tubular injury.

### Nocturnal Enuresis

Voiding of urine in the bed during sleep is normal in the infants and young children. Nocturnal enuresis is sometimes seen in older children and adults due to organic leisions. For example, lumbosacral vertebral defect and also due to psychological factors.

### Urinary Calculi/Renal Stones

These are mainly composed of calcium stones, i.e. calcium oxalates or calcium phosphates. It may sometimes due to uric acid. They cause obstruction to urine flow. Complications include vomiting, sweating, fever, severe pain and hematuria.

*Treatment:* Flushing, minor surgery.

Chapter

# 7 Temperature Regulation

Normal body temperature depends on balance between heat production and loss.

*Body heat is produced by:*

a. Metabolism of food (basal)
b. Food assimilation
c. Muscular activities
d. Accumulation of brown fat.

*Body heat is lost by:*

a. Radiation
b. Conduction
c. Vaporization of sweat
d. Small amount through urine and feces.

Group of reflex responses that are primarily integrated in hypothalamus, operated to maintain body temperature in a narrow range in spite of wide fluctuation in environment temperature in warm blooded (homeothermic animals) constitute the mechanisms of temperature regulation.

*Regulation of body temperature is important because:*

1. Speed of chemical reaction taking place in the body depends on body temperature.
2. Enzymes of body show optimum activity within a narrow range of temperature.

## Measurement

Using clinical thermometer,
C = (F–32) × 5/9; Unit is °C.
F = (C × 9/5) +32; Unit is °F.
Normal oral temperature: 36.3–37.1°C/98.3-98.8°F
Scrotal temperature: 32°C to facilitate spermatogenesis.
Oral temperature is 0.5°C less than rectal temperature. Oral temperature is variable but rectal/core temperature is constant.

*Hyperthermia* is when temperature increases more than 41.6°C (107°F ). *Hypothermia* is when temperature decreases less than 25°C (95°F).

### Physiological Variation

- Temperature normally increases in the morning and decreases in the evening
- In females during ovulation body temperature increases
- During exercise body temperature increases to 40°C.

### Causes

1. Inability of heat dissipating mechanism to handle increased amount of heat production.
2. Elevation of body temperature, i.e. set point of hypothalamus at which heat dissipating mechanisms are activated.

Some adults have chronically above normal temperature known as constitutional hyperthermia. Temperature regulation is less precise in young children, they may normally have a temperature that is 0.5°C or so above the established norm for adults. In females body temperature is normally 0.5°C more than in males (During ovulation and after ovulation, till menstruation, i.e. during luteal/progestational phase).

### Pathological Variation

#### *Hyperthyroidism*

In hyperthyroidism temperature increases 0.5°C more than normal.

## Central Regulation of Temperature

Hypothalamus is considered as thermostat. Temperature is set at normal level in hypothalamus and when body temperature increases or falls from set point level, various mechanisms gets activated to bring back temperature to set point level.

- Anterior hypothalamus is activated by warmth and is considered to be *heat loss center.*
- Posterior hypothalamus is activated by cold and is known as *heat gain center.*

### Various Mechanisms of Temperature Regulation

Afferent impulses reach hypothalamus from receptors in skin, deep tissue, spinal cord, extrahypothalamic region of brain and other parts of brain and activate the following mechanisms.

### Mechanisms Activated by Cold

***Increase in heat production***

a. *Shivering:* Shivering is an involuntary response of skeletal muscle to cold which increases skeletal muscle contraction which in turn increases heat production.
b. *Increased hunger:* Increased food intake, increases utilization of food which increases body temperature.
c. *Increased voluntary activity:* This leads to increase in body temperature.
d. Increased production of epinephrine and norepinephrine.

***Decrease in heat loss***

a. Vasoconstriction: Amount of heat reaching skin from deeper tissues is decreased and will store heat centrally in blood vessels. Cutaneous vessels being cool is more sensitive to catecholamines leads to further constriction of arterioles and venules.
b. *Horripilation (Goose wildeness):* Cold intended contraction of piloerector muscles, important in animals. Increased trapping of hair causes increased heat production.
c. *Concurrent flow of blood:* In animals at extremities arteries and veins are arranged parallely. Deep veins run along side arteries supplying limbs. Heat transfer from between warm arterial blood going to the limbs and cold venous blood coming from extremities cause counter current exchange of heat causing conservation of heat.
d. Behavioral changes like curling up.

## Mechanisms Activated by Heat

### Increase in Heat Loss

***Increased heat loss by conduction, convection and radiation***

When surrounding temperature is much lower, heat loss takes place mainly through conduction, convection and radiation. When surrounding temperature is close to body tempeature, evaporation becomes major route of heat loss.

***Sweating***

When body temperature increases, there is increased sweating, thus increased vaporization of water from body surface, which in turn decreases body temperature. Vaporization also occurs through mucous membrane of oral cavity and respiratory packages. Thus, there is certain amount of water loss continuously called insensible loss of water. Vaporization of 1 gm of water removes 0.6 kcal of heat.

***Cutaneous vasodilatation***

Conduction occurs from surface of one object to surface of another object. Temperature of skin determines to a great extent the degree to which heat is gained or lost. Amount of heat reaching the skin, from deeper tissues can be varied by changing the blood flow to the skin. When temperature increases, cutaneous vessels are dilated, warm blood reaches skin and is lost to the surroundings. Rate at which heat is transferred from deep tissues to the skin is called tissue conductance and it increases at high temperature.

***Panting***

Rapid shallow breathing seen in animals.

### Decrease in Heat Production

***Generalized lethargy and apathy***

Causes decreased muscular activity and thus heat production is decreased.

***Loss of appetite***

This causes decreased food intake and thus decreased heat production.

## Fever

Oldest and most universally known hallmark of diseases. The causes of fever are infection and injuries. During fever, temperature is raised, thermoregulatory mechanism act to regulate body temperature at its new higher levels, i.e. there is apparent reset of thermostat to higher level.

Infection or tissue injury → release endotoxin or pyrogens → Act on RE cells and thereby stimulate monocytes, macrophages, Kupffer cells → produce cytokinins (interleukins, interferons) → cytokinins act on (organum vasculosum of the lamina terminalis (OVLT) → Preoptic area of hypothalamus stimulated (OVLT) → release of local PGs → raise temperature set point → fever resulted.

Advantage of fever is that increased temperature decreases bacterial growth.

### Malignant Hyperthermia

This is due to mutation of gene coding for ryanodine receptors. This results in increased $Ca^{2+}$ release, thereby excessive contraction of muscle occurs which leads to increased heat production.

Chapter

# 8 Endocrinology

The biological functions of the multicellular living organism are well oriented. This coordination is achieved by two main control systems, nervous and the endocrine system. The important endocrine glands include hypothalamus, anterior, pituitary, posterior pituitary, thyroid gland, parathyroid gland, islets of Langerhans, pancreas, adrenal cortex, adrenal medulla, kidney, ovary and testes.

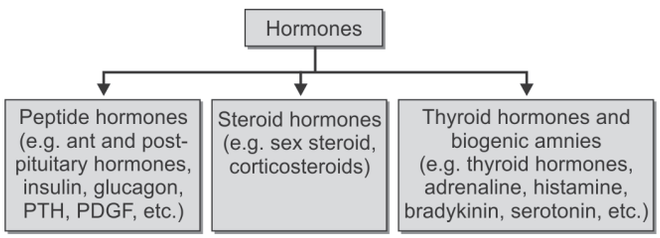
## Hormone

Hormones are secretory products of ductless (endocrine) glands released directly into circulation in small amounts in response to a specific stimulus and on delivery in circulation produce response on target cells.

### *Classification*

#### *Depending Upon the Chemical Nature (Flow chart 8.1)*

**Flow chart 8.1:** Classification of hormones based on chemical nature




#### *Depending Upon the Mechanisms of Action*

1. *Group I hormone:* These act by binding to intracellular receptors and mediate their actions via formation of a hormone receptor complex. These include steroid, thyroid hormones. These hormones have intracellular receptors.
2. *Group II hormone:* These involve second messenger to mediate their effect. These hormones have cell membrane receptors.

## Mechanism of Hormone Action

On the target cell, the hormone in combination with the receptor acts by any of the following mechanisms:

- By altering the permeability of the cell membrane.
- By activating the intracellular enzyme.
- Through effect on gene expression.
- Through tyrosine kinase activation.

### *Action Through Change in Membrane Permeability*

Hormone bind with receptors present in the cell membrane (external receptors) leading to its conformational change causing either closing or opening of the ion channels (such as $Na^+$, $K^+$ channel), e.g. adrenaline, noradrenaline act by this mechanism.

### *Action Through Secondary Messengers which Activate the Intracellular Enzyme*

The peptides and biogenic amines are two principal classes of hormones which act through second messengers. The hormone, which acts on a target cell is called first messenger. This hormone in combination with the receptor forms hormone-receptor complex. This in turn activates the enzymes of the cell and causes the formation of another substance called the second messenger (cAMP, IP3, DAG). The release of second messenger is mediated by GTP binding proteins or G proteins (Fig. 8.1).

#### *cAMP as the Second Messenger (Fig. 8.2)*

G protein stimulate the enzyme adenyl cyclase. This increases the formation of intracellular cAMP from ATP. cAMP stimulate protein kinase A. Protein kinase A phosphorylates enzyme protein, thus enzyme is stimulated or inhibited. For examples, epinephrine, norepinephrine, ACTH, LH, GnRH, hCG, TSH.

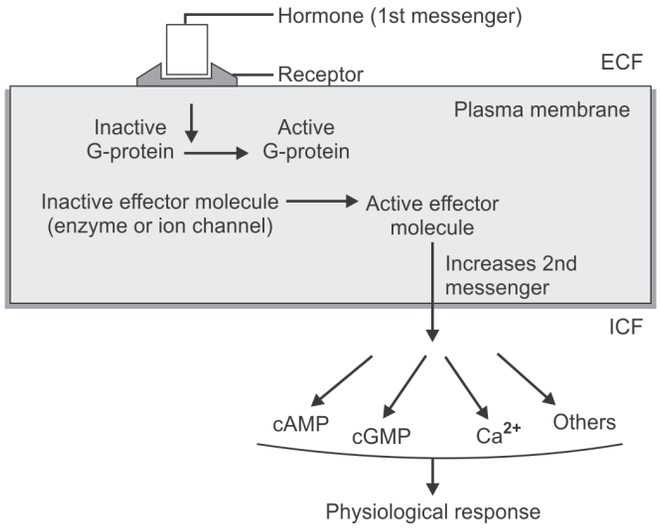
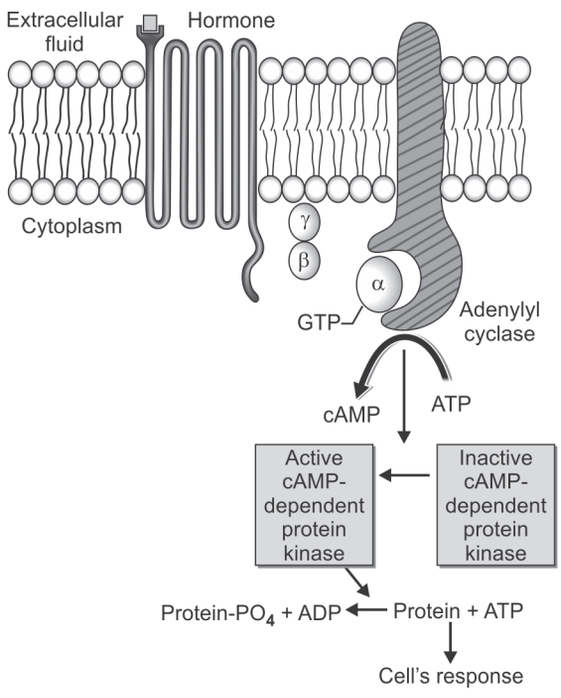



**Fig. 8.1:** Secondary messenger mediated hormone activity




**cAMP as the second messenger**

**Fig. 8.2:** cAMP mediated hormone activity

### *$IP_3$ and DAG Acts as Second Messenger (Fig. 8.3)*

Here activated G protein (present in the membrane) called Gp protein stimulate phospholipase C. Phospholipase C hydrolyses phosphotidyl inositol diphosphate ($PIP_2$) forming inositol triphosphate and diacylglycerol (DAG). $IP_3$ and DAG

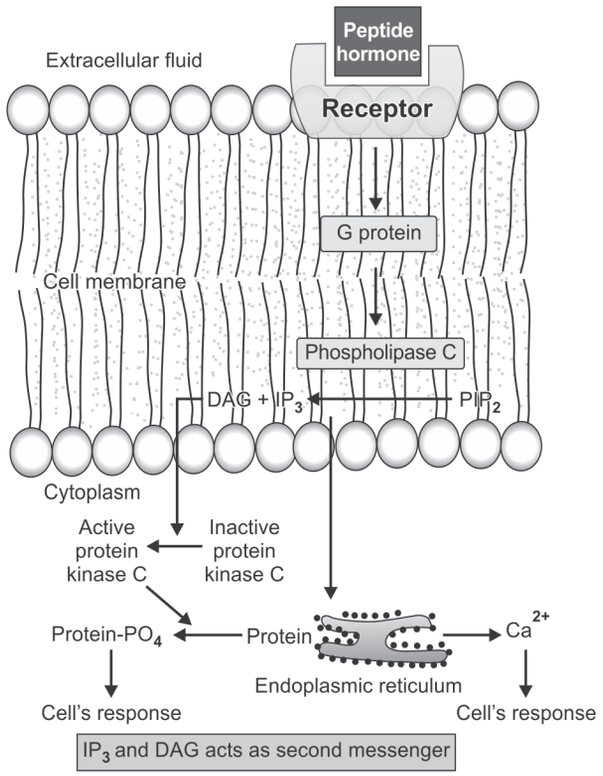



**Fig. 8.3:** $IP_3$ and DAG mediated hormone activity

are the second messenger. They brings out response via protein kinase C. For example, angiotensin-II and vasopressin.

### *Calcium Calmodulin Second Messenger System*

Many hormones act by increasing the calcium ion, which acts as second messenger along with another protein called calmodulin. System operates in response to the entry of Ca into the cells. Ca entry is initiated by:

- Changes in membrane potential that open Ca channels.
- A hormone interacting with membrane receptors that open Ca channels.

On entering a cell, calcium ions bind with the protein calmodulin. Calmodulin has four calcium sites and when three or four of these sites have bound with calcium, the calmodulin changes shape. This initiates multiple effects inside the cell, including activation or inhibition of protein kinases. Activation of calmodulin-dependent protein kinases causes activation or inhibition of proteins involved in the cell's response to the hormone (via phosphorylation).

### ***Through Effect on Gene Expression***

The mechanism of action of thyroid and hormones is by acting on the genes of the target cells (Fig. 8.4).

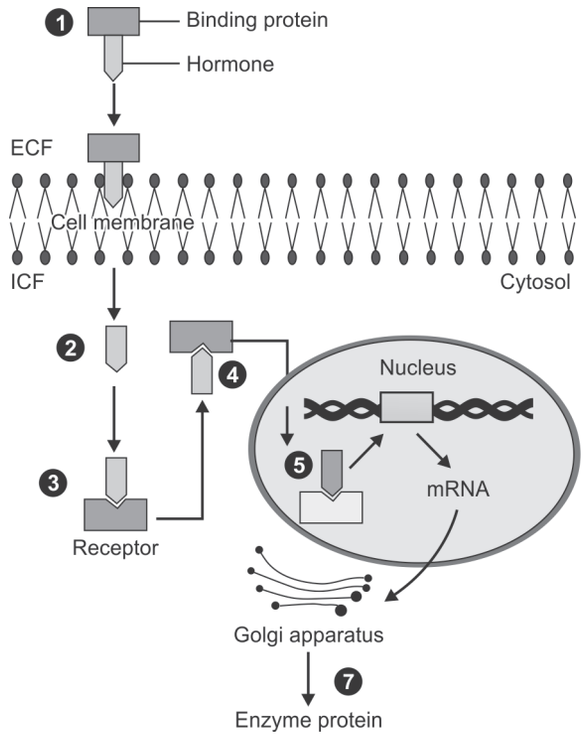



**Fig. 8.4:** Mechanisms of interaction of lipophilic hormones, such as steroids, with intracellular receptors in target cells

***Sequence of Events are:***

1. Transport-after secretion, the hormone is carried to the target tissue on serum binding protein.
2. Internalization-being lipophilic the hormone easily diffuse through the plasma membrane.
3. Receptor hormone complex (RHC) is formed by binding of hormone to the specific receptor inside the cell.
4. Conformational change occurs in receptor protein leading to activation of receptors.
5. The activated RHC then diffuse into the nucleus and binds on specific region on DNA. This initiates transcription.
6. Binding of the RHC to DNA alters the rate of transcription of mRNA.
7. The mRNA moves out of the nucleus and reaches ribosomes. Here it promotes translation process. In this way new proteins are formed which result in specific responses.

### *Action Through Tyrosine Kinase Activation*

***Enzyme-linked hormone receptors***

These receptors when activated, functions directly as enzymes or are closely associated with enzymes that they activate. These enzyme linked receptors have their hormone binding site on the outside of the cell membrane and their catabolic or enzyme binding site on the inside. When the hormone binds to the extracellular portion of the receptor, an enzyme immediately inside the cell is activated (or occasionally inactivated). This mechanism of signal generation from plasma membrane receptors does not require G protein intermediaries. For examples, leptin receptor.

The activation of tyrosine kinase occurs by two mechanism.

1. Due to the binding of hormone to the receptor, the receptor itself becomes a tyrosine kinase that phosphorylates tyrosine residue on intracellular protein substrates. This sets into motion a cascade of events leading to enzyme activation and gene expression.
2. Hormone binding to extracellular portion of the receptor can attract intracytoplasmic tyrosine kinases like janus kinase (JAK) and then activates them. This causes phosphorylation of transcription factor proteins and ultimately modulate gene expression.
   For example, insulin, IGF, EGF (epidermal growth factor), PDGF, ANF, GABA.

## PITUITARY GLAND

The pituitary gland consists of:

1. Anterior pituitary/Adenohypophysis
2. Posterior pituitary/Neurohypophysis
3. Intermediate lobe/Pars intermedia (rudimentary).

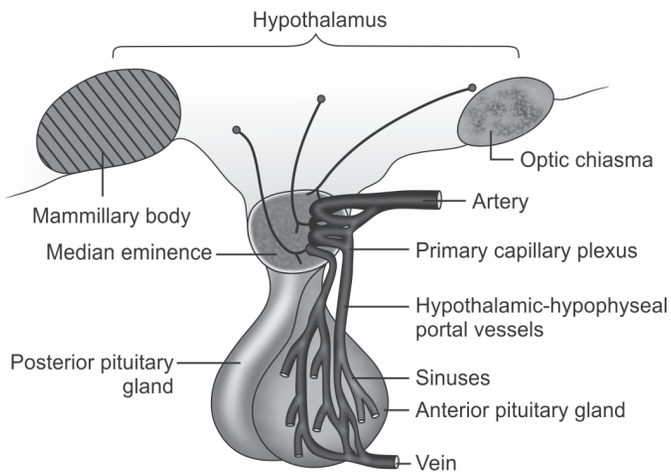



**Fig. 8.5:** Hypothalamic hypophysial portal system

### Hypothalamo-pituitary Relationship

The secretion of anterior pituitary is controlled by hormones called hypothalamic releasing/hypothalamic inhibitory factors secreted within hypothalamus itself. They are then conducted to anterior pituitary through hypothalamo-hypophyseal portal vessel (Fig. 8.5). In anterior pituitary these releasing and inhibitory hormones act on glandular cells to control their secretion. Posterior pituitary does not secrete hormones.

Postpituitary hormones are synthesized by cell bodies located in ***supraoptic and paraventricular nuclei*** of hypothalamus. The hormones are then transported in the axoplasm of nerve fibers to postpituitary. Axons that arise from supraoptic and paraventricular nuulei of hypothalamus pass to posterior pituitary via hypothalamo-hypophyseal tract (Fig. 8.6). The nerve endings contains secretory granules (Herring bodies). They secrete ADH /vasopressin and oxytocin.

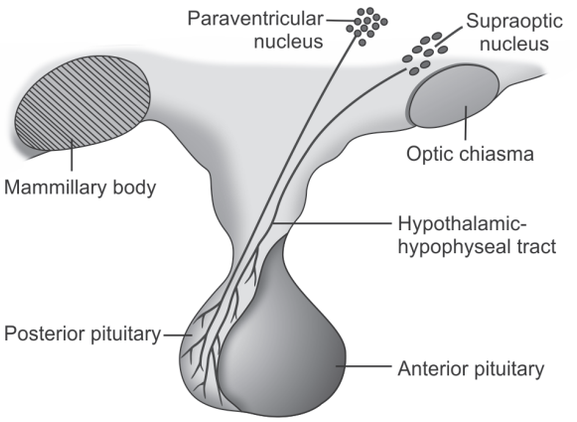



**Fig. 8.6:** Hypothalamic-hypophyseal portal system

## Pituitary Hormones

### *Anterior Lobe*

TSH, ACTH, GH, FSH, LH, prolactin and β lipotropin.

### *Posterior Lobe*

ADH and oxytocin.

### *Intermediate Lobe*

α and β melanocyte stimulating hormone.

## GROWTH HORMONE

Also called as somatotropin/somatotropic hormone. It causes growth of almost all tissues of the body that are capable of growing.

### *Somatomedins*

They are polypeptide growth factors secreted by the liver and other tissues. The effects of GH on growth, cartilage and protein metabolism depends on the interaction between GH and somatomedins. They are also called insulin like growth factors (IGFs; their effects on growth are similar to effects of insulin on growth). The principal circulating somatomedins are IGF I (somatomedin C) and IGF II.

### *Metabolic Effect of GH*

#### *On Protein Metabolism*

Growth hormone has an anabolic effect on protein metabolism. It increases amino acid uptake into the cells. It increases protein synthesis in ribosomes (enhances RNA translation). GH stimulates the transcription of DNA to form RNA. It decreases the catabolism of protein and amino acids.

#### *On Fat Metabolism*

It is increases level of circulating FFA. It mobilizes fat from adipose tissue. It enhances the conversion of fatty acids to acetyl CoA.

*Protein sparing effect:* Free fatty acid (FFA) are utilized for energy and thus decreases the breakdown of cell protein.

*Ketogenic effect:* Excessive amounts of GH mobilizes more FFA so that large quantities of acetoacetic acid are formed (in liver) and released into body fluids.

#### *On Carbohydrate Metabolism*

Growth hormone is diabetogenic. It increases the production of glucose by liver. It increases insulin production and decreases sensitivity to insulin (insulin resistance) hence it decreases glucose uptake on adipose and skeletal muscle.

#### *On Electrolyte Metabolism*

Intestinal absorption of Ca is promoted. Renal excretion of electrolytes like $Na^+$, $Ca^{2+}$, $PO_4^{3-}$ and $K^+$ is suppressed. Retention of electrolytes and diversion of those electrolyte to growing tissue.

#### *Actions on Growth*

***Before the closure of epiphysis***

Growth hormone increases the length of the bones. It stimulates the proliferation of chondrocytes and osteogenic cells. Protein deposition by chondrocytes and osteogenic cells are increased. It causes the conversion of chondrocytes into osteogenic cells (thus causing deposition of new bones). GH stimulates osteoblastic activity which converts cartilage into bone.

***After closure of epiphysis***

Linear growth not promoted. Bone thickening can occur through periosteal growth.

### *Regulation of GH Secretion (Fig. 8.7)*

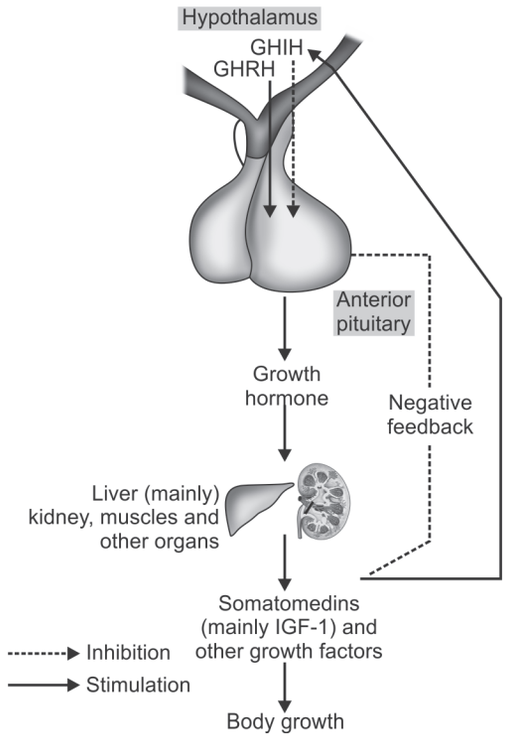



**Fig. 8.7:** Regulation of GH secretion

### *Stimuli that Affects GH Secretion*

#### *Stimulate Growth Hormone Secretion*

1. Decreased blood glucose
2. Decreased blood free fatty acids
3. Starvation or fasting, protein deficiency
4. Trauma, stress, excitement
5. Exercise
6. Testosterone, estrogen
7. Deep sleep (stages II and IV)
8. Growth hormone releasing hormone.

#### *Inhibit Growth Hormone Secretion*

1. Increased blood glucose
2. Increased blood free fatty acids
3. Aging
4. Obesity
5. Growth hormone inhibitory hormone (somatostatin)
6. Growth hormone (exogenous)
7. Somatomedins (insulin like growth factors).

## Applied Aspects

### *Gigantism*

Due to hypersecretion of GH in growing children before the closure of epiphysis. It is usually caused due to tumor of pituitary gland.

***Clinical features***

- Abnormal height (6.5–9 feet)
- Large hands and feet
- Bilateral gynecomastia
- Loss of libido/impotence
- Hyperglycemia caused by GH leads to excess insulin secretion
- Over activity of β cells of pancreas ultimately leads to degeneration of these cells and deficiency of insulin resulting in diabetes mellitus.
- The tumor of the pituitary gland itself causes headache and visual disturbances (bitemporal hemianopia).
- If untreated gigantism ends in hypopituitarism due to destruction of the gland by tumor.

***Treatment***

Irradiation of tumor.

### *Acromegaly*

Due to hypersecretion of GH in adults after the closure of epiphysis. It can be caused by extrapituitary as well intrapituitary GH secreting tumors and by hypothalamic tumors that secrete GRH. Height will not be increased, but bones become thicker and soft tissues continues to grow. Hypersecretion of growth hormone is accompanied by hypersecretion of prolactin in 20–40% of patients with acromegaly.

***Clinical features (Fig. 8.8)***

- Hands and feet are enlarged (acral parts)
- Protrussion of lower jaw due to elongation and widening of mandible ***(Prognathism)***.
- Overgrowth of the malar, frontal and facial bones combines with prognathism to produce the coarse facial features called ***acromegalic facies***.
- The changes in the vertebra causes a hunched back. ***(Kyphosis)***.
- The skeletal changes predisposes to osteoarthritis.
- Excessive growth of internal organs, i.e. cardiomegaly, hepatomegaly, splenomegaly and renomegaly.
- Excessive growth of body hair.
- Bitemporal hemianopia (optic chaisma is compressed due to pituitary tumor).

In 4% there will be gynecomastia with or without lactation.

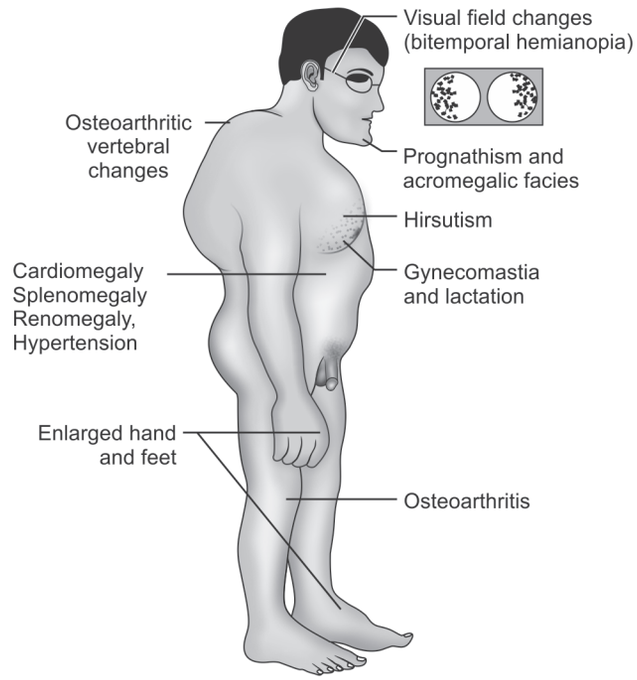



**Fig. 8.8:** Clinical features of acromegaly

### *Treatment*

Benign tumor-surgery followed by irradiation.
Malignant-irradiation, surgery usually not done.

### *Dwarfism*

***Endocrinal causes***

a. *Pituitary dwarf (GH deficiency):* It is due to the GH deficiency secondary to decrease in GHRH. Its characteristic features are plumpness (fatness), immature facies, small genitalia, delicate extemites, delayed skeletal and dental development.
b. *Hypothyroid dwarf (cretinism):* It is due to thyroid hormone deficiency.
   The difference between pituitary and hypothyroid dwarf is given in Table 8.1

***Genetic cause***

*Laron dwarfism (GH insensitivity syndrome):* The plasma GH level is normal or elevated. But the GH receptors are unresponsive (due to mutation in the gene for receptors). Also there is a marked decrease in plasma IGF-I.
*African pigmies:* They have normal plasma GH levels. Plasma concentration of GH binding protein decreases. The plasma IGF-I concentration fails to increase at the time of puberty.

**Table 8.1: Difference between pituitary and hypothyroid dwarf**

| *Pituitary dwarf* | *Hypothyroid dwarf/Cretin* |
|---|---|
| Due to GH deficiency since childhood | Due to thyroid hormone deficiency |
| Normal mental activity | Mentally retarded |
| Sexually mature | Sexually immature |
| Different parts of the body are proportionate | Different parts of the body are disproportionate |

***Nutritional cause***

Marasmus and rickets.

***Note***

*Achondroplasia:* It is an autosomal dominant condition caused by mutation in the gene that codes for fibroblast growth factor receptor. So there is faulty endochondral ossification resulting in dwarfism. Here subject is mentally sound. It features are abnormal body proportions (large head, short limbs).

## Physiology of Growth

### *General Growth Curve (Fig. 8.9)*

General growth curve applies to the skeletal growth as a whole, the muscles and the thoracic and abdominal viscera. After birth the curve shows four distinct phases.

1. A rapid increase during infancy, i.e. specially during first year, weight increases from 3.5–10.5 kg. It accounts for 30% of total growth.
2. A slow progressive growth from 3 to 12 years of age. During this period boys are taller than girls. By the end of 12 years of age, growth reaches 60% of the total growth.
3. A marked increase in growth occurs at the time of puberty also called *growth spurt*. It appears earlier in girls, hence girls mature earlier than boys. Thus, rate of increase of

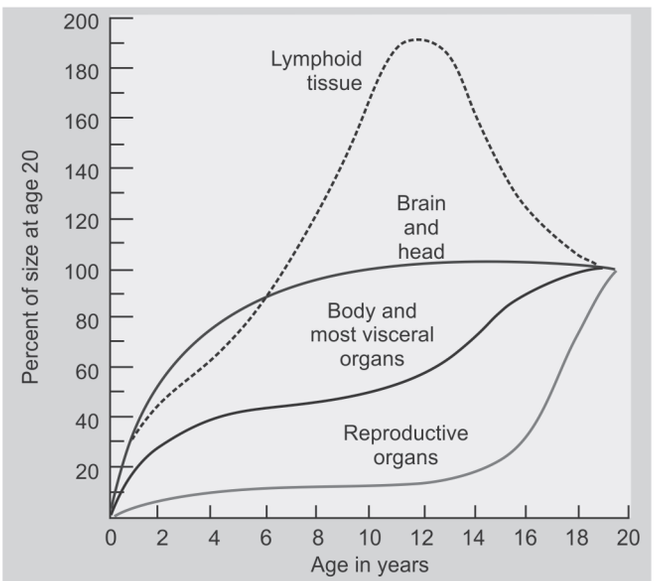



**Fig. 8.9:** Growth curve

height and weight is the greatest in girls at 12–14 years and in boys at 14–16 years. In girls, the increase in weight is mainly due to increased fat formation and in boys it is due to increased muscular growth.

4. Even though pubertal growth has finished at 18 years in girls and 20 years in boys, a small growth occurs until 30 years.

Thus in humans there are two periods of rapid growth:

- First in infancy (partly a continuation of fetal growth period).
- Second at the time of late puberty just before growth stops.

Certain parts of the body have distinctive growth curves. In both sexes, the rate of growth of individual tissue varies. These are mainly of three types:

***Neural type***

Here there is a rapid initial increase in size of the brain, spinal cord and organs of special senses. They reach 60% and reach 90% of adult size at two and six years of age respectively.

***Lymphoid type***

Lymphoid tissues including thymus, tonsils and lymph nodes throughout the body grow rapidly in early childhood (40% of adult size by the age of two years) and reach their maximum size at puberty, after this lymphoid tissue degenerates.

***Reproductive type***

The gonads and accessory organs of reproduction remain undeveloped until puberty, when very rapid growth begins and continues throughout adolescence. The reproductive system atrophies in women after the menopause.

***Note:*** Certain organs show different type of growth. For example, adrenal glands and uterus. These organs are relatively large at birth, then they lose weight rapidly and then regains just before puberty.

## Factors Affecting Growth

### Genetic Factors

Genetic factors are very important in relation to growth and stature and they are mainly responsible for certain racial differences in the height. For example, achondroplasia. The timing of the adolescent spurt in both males and females appears to be genetically controlled via hypothalamus.

### Nutritional Factors

The food supply is the most important extrinsic factor affecting growth. The diet must be adequate not only in protein content but also in essential vitamins and minerals and in calories so that ingested protein is not burned for energy. Once the pubertal growth spurt has commenced, considerable linear growth continues even if caloric intake is reduced. Diet deficient in quantity and energy, in proteins, minerals and vitamins, inhibits growth markedly and adversely; therefore:

- If the lack of diet is sufficiently prolonged, the stunting of growth may be irreversible.
- If the lack is less severe or for shorter period, restoration of normal diet leads to a compensatory increase in the rate of growth.
- Undernutrition affects the growth of different organs and tissues unevenly.

### Environmental Factors

***Diseases***

Ill health causes temporary depression of growth, but ring recovery the lost ground is regained. Thus, following illness and starvation in children, there is a period of catch-up growth during which takes place during which the growth rate is greater than the normal. The accelerated growth usually continues until the previous growth curve is reached at which point growth slows to normal.

***Exercise***

Repeated exercise of skeletal can increase in their mass by producing enlargement of individual fibers.

***Emotional disturbances***

Emotional disturbances can cause decrease in rate of growth in children taking an adequate diet.

***Old age***

Aging is characterized by:

- Cellular degeneration due to degradative changes in the properties of multiplying cells
- Impairment of various functions due to loss of non-multiplying cells.

### Hormonal Factors

Contribution of hormones to growth after birth:

- Rapid growth during infancy—GH and TH
- Spurt of growth at puberty—GH and androgens
- In between continuous growth—TH and GH
- After attainment of puberty and rest of life—TH, GH, androgens.

***Growth hormone***

Growth *in utero* and neonatal growth are independent of growth hormones (GHs).

*Clinical features due to GH deficiency:*

Normal birth weight, subsequent severe retardation of growth and tendency to obesity, low fasting blood sugar and delayed recovery from insulin hypoglycemia.

***Thyroid hormone***

It is necessary for a completely normal rate of GH secretion. Hypothyroidism decreases the synthesis, storage, and release of growth hormone and retards growth.

Thyroid hormone (TH) has widespread effects on ossification of cartilage, growth of teeth, contours of face and proportions of body. Cretins are therefore dwarfed and have infantile features.

Patients who are dwarfed due to panhypopituitarism have features consistent with their chronological age until puberty, but since they do not mature sexually, they have juvenile features in the adulthood.

***Note:*** GH and TH show *permissive action,* i.e. either of the two cannot produce normal growth, but when administered together they will stimulate growth (possibly *via* potentiation of the actions of somatomedins).

#### *Androgens*

In males, testes (mainly) and adrenal cortex whereas in females the main androgen sources are adrenal cortex (mainly) and ovaries.

- It is a protein anabolic hormone and is responsible for growth spurt
- It produces an increase in GH secretion that in turn increase IGF-I secretion
- Although androgen stimulates growth but, ultimately it terminates growth by causing epiphysial closure thereby decreases linear growth
- Estrogen have similar effects due to stimulation of androgen secretion by the adrenals. Sex steroids (estrogen and androgen) stimulate both synthesis and release of GH which in turn increases IGF-I secretion to cause growth.

#### *Others*

- Adrenocortical hormones exert permissive action on growth.
- *Insulin:* Diabetic children fail to grow because of increased breakdown of proteins and fats.

## PROLACTIN

It is called lactogenic/mammotrophic/galactopoietic hormone.

### *Actions*

#### *Breast growth*

During pregnancy under the influence of prolactin, mammary duct gives rise to lobules of alveoli.

#### *Lactogenic effect*

Prolactin acts on alveolar epithelium and stimulates the secretory activity. It stimulates galactosyltransferase activity, leading to the synthesis of lactose.

#### *Suppression of ovarian cycle in nursing mothers*

It inhibits the secretion of GnRH from hypothalamus. Therefore, FSH and LH secretion from anterior pituitary decreases and account for the antireproductive and antigonadal effects of prolactin, which account for amenorrhea (stoppage of periods) during postpartum lactation.

### *Regulation of Prolactin Secretion (Table 8.2)*

1. *By hypothalamus:* Prolactin releasing hormone (PRH) and prolactin inhibiting hormone (PIH) regulate prolactin secretion. PIH is a dopamine and is more important than PRH. Prolactin stimulates the secretion of PIH from hypothalamus and brings about its inhibition.
2. *Estrogen and progesterone:* High levels of these hormones inhibit and low levels facilitate prolactin secretion.
3. *Suckling of breast* and stimulation of the vagina during coitus stimulate prolactin secretion.
4. *Bromocriptine* is a dopamine agonist and so it decreases prolactin secretion. This is used in the treatment of prolactin dependant breast tumors.

## OXYTOCIN

Synthesized by paraventricular nucleus of hypothalamus. It acts on the myoepithelial cells of mammary gland and the uterus.

### *Actions*

#### *On mammary glands*

It causes the ejection of milk from the mammary gland. Oxytocin causes the contraction of myoepithelial cells. It squeezes milk from alveoli to the exterior through the duct system and nipple. The process by which the milk is ejected from the alveoli of lactating breast-milk ejection reflex (details given in reproductive system).

#### *On uterus*

*On pregnant uterus:* It causes contraction of smooth muscles of uterus and helps in the expulsion of fetus. Sensitivity of

**Table 8.2: Factors influencing prolactin secretion**

| *Stimuli that increases secretion* | *Stimuli that decreases secretion* |
|---|---|
| Exercise and stress | Prolactin inhibitory factor |
| Dopamine antagonists (phenothiazine, tranquilizers), adrenergic blockers, serotonin agonist | Dopamine agonist (bromocriptine, apomorphine) |
| Pregnancy | Serotonin antagonist |
| TRH | |

the uterine musculature to oxytocin is enhanced by estrogen and inhibited by progesterone. In late pregnancy, the uterus becomes very sensitive to oxytocin (due to increase in oxytocin receptors). Oxytocin secretion is increased during labor. At the onset of labor, cervix dilates and the fetus descends through the birth canal. Expansion of birth canal stimulate stretch receptors.

From them impulses goes to pituitary through afferent fibers which in turn increases oxytocin in blood. This will reach uterus through general circulation. This enhances further strong contraction of uterus and favors delivery of the baby.

*On nonpregnant uterus:* Oxytocin acts on the nonpregnant uterus to facilitate sperm transport. Oxytocin released causes uterine contraction and facilitate sperm transport.

***Other actions***

In males at the time of ejaculation it causes increased contraction of smooth muscle of vas deferens, propelling sperm towards the urethra.

## VASOPRESSIN

Antidiuretic hormone (ADH) is secreted mainly by supraoptic nucleus of hypothalamus. It is an antidiuretic hormone.

### *Vasopressin Receptors*

$V_{1A}$: Located in blood vessels, liver brain.
$V_{1B}$ (also called V3 receptors): Located in anterior pituitary.
$V_{2}$-: Located in kidney.

### *Actions*

***Water retention***

The major function of ADH is retention of water by acting on kidney (activated by $V_2$). Main site of action is at distal nephron. It increases the permeability of collecting ducts of kidney. Due to increased permeability water enters hypertonic medullary interstitium. Thus diuresis is prevented. Water is retained in the kidney and urine becomes concentrated. Water is reabsorbed through aquaporin II (ADH responsive water channel).

***Vascular effect***

In large amounts ADH causes constriction of vascular smooth muscles (mediated by $V_{1A}$). Due to vasoconstriction BP increases.

***Other actions***

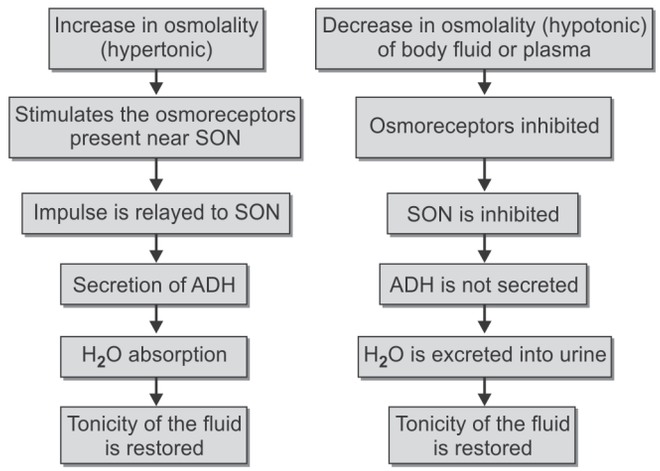
Acts on anterior pituitary and cause ACTH release (mediated by $V_{1B}$). It is a neurotransmitter in brain and spinal cord. Vasopressin causes glycogenolysis in the liver (mediated by $V_{1A}$).

### Regulation of ADH Secretion

Two important factors that regulate ADH secretion are osmolality and ECF volume.

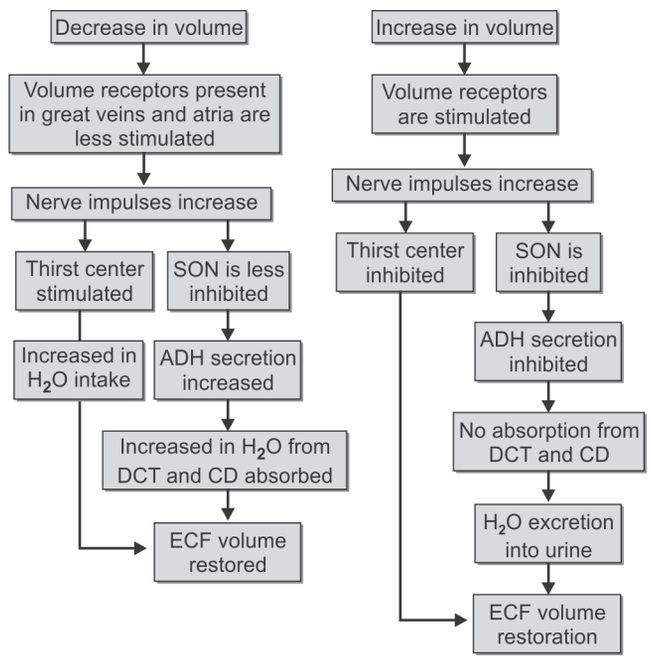
#### *Effect of Osmolality (Flow chart 8.2)*

**Flow chart 8.2:** Effect of osmolality on ADH secretion




#### *Effect of ECF Volume (Flow chart 8.3)*

**Flow chart 8.3:** Effect of ECF volume on ADH secretion



### *Other Stimulants*

Pain, emotion, stress, exercise, vomiting, angiotensin II.

### *Other Inhibitors*

Alcohol

## Clinical

1. Patients highly sensitive to vasopressin are prone to hypertension.
2. In massive hemorrhage and shock, vasopressin is secreted in high amounts. The pressor action of vasopressin raises the BP.
3. *Diabetes insipidus:* The deficiency of ADH causes diabetes insipidus. This disease is characterized by excessive excretion of water through urine (polyuria), increased water intake (polydypsia).

### *Causes*

It can be due to failure of production of ADH (cental diabetes insipidus) or due to inability of the kidneys to respond to ADH (nephrogenic diabetes insipidus).

***Central diabetes insipidus***

It is due to inability to produce or release ADH from the posterior pituitary. It can be caused by head injuries or infections, or it can be congenital. Because the distal tubular segments cannot reabsorb water in the absence of ADH, this condition, called "central" diabetes insipidus, results in the formation of a large volume of dilute urine, with urine volumes that can exceed 15 L/day.

The treatment for central diabetes insipidus is administration of a synthetic analog of ADH, desmopressin, which acts selectively on $V_2$ receptors to increase water permeability in the late distal and collecting tubules.

***Nephrogenic diabetes insipidus***

It is a condition in which normal or elevated levels of ADH are present but the renal tubular segments cannot respond appropriately. This condition is referred to as "nephrogenic" diabetes insipidus because the abnormality resides in the kidneys. This abnormality can be due to either failure of the countercurrent mechanism to form a hyperosmotic renal medullary interstitium or failure of the distal and collecting tubules and collecting ducts to respond to ADH. In either case, large volumes of dilute urine are formed. Many types of renal diseases can impair the concentrating mechanism, especially those that damage the renal medulla. Also, impairment of the function of the loop of Henle, as occurs with diuretics that inhibit electrolyte reabsorption by this segment, can compromise urine concentrating ability.

The treatment for nephrogenic diabetes insipidus is to correct the underlying renal disorder. The hypernatremia can also be attenuated by a low-sodium diet and administration of a diuretic that enhances renal sodium excretion, such as a thiazide diuretic.

## THYROID GLAND

The two principal hormone secreted by thyroid gland are thyroxine ($T_4$) and triiodothyronine ($T_3$). Small amount of reverse $T_3$ are also found (inactive form). $T_3$ is more active than $T_4$.

Parafollicular cells of thyroid gland secretes calcitonin, a calcium-lowering hormone. The thyroid gland is composed of large number follicles. Each follicle is lined with cuboidal epithelial cells (thyroid cells) and filled with a secretory substance called colloid.

***Note:*** When the gland is inactive, the colloid is abundant, follicles are large and the cells lining them are flat. When the gland is active, the follicles are small, the cells are cuboid or columnar and the edge of the colloid is scalloped forming many small reabsorption lacunae (Fig. 8.10).

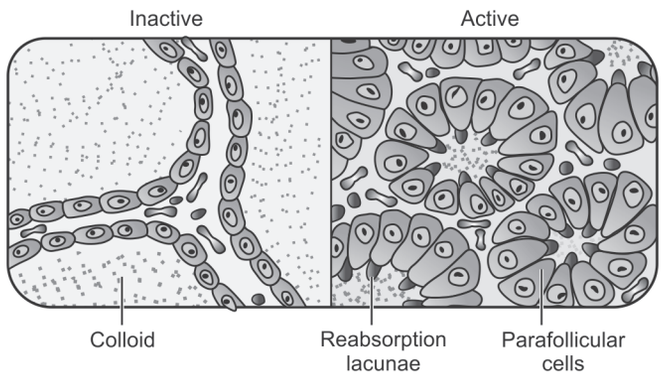



**Fig. 8.10:** Histology of thyroid gland during inactive and active state

### Synthesis of Thyroid Hormones

Iodine and tyrosine are essential for the formation of thyroid hormones. Iodine consumed through diet is converted into iodide and is absorbed from GIT. Tyrosine is also consumed through diet.

### *Stages in the Synthesis of Thyroid Hormones*

#### *Thyroglobulin Synthesis*

The ER and golgi apparatus in the thyroid cells synthesize and secrete a glycoprotein molecule called thyroglobulin into the colloid. It contains 123 tyrosine residues that combines with iodine to form thyroid hormones. The hormone remain bound to thyroglobulin until secreted (Fig. 8.11).

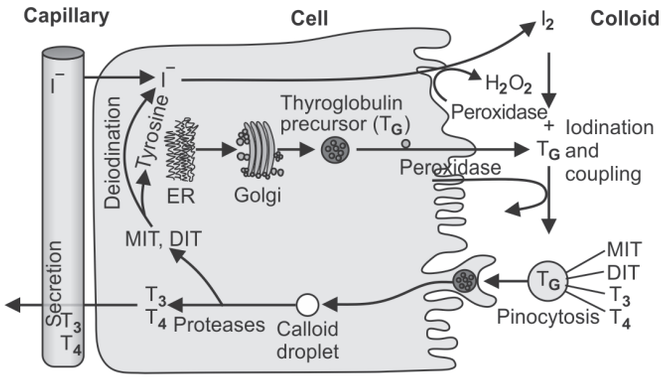



**Fig. 8.11:** Stages in the synthesis of thyroid hormones

### *Iodide Trapping*

Iodide trapping is the picking up of iodide by thyroid gland. $Na^+$ and $I^-$ are co-transported into the thyroid gland and the $Na^+$ is pumped into the interstitium by $Na^+$- $K^+$ ATPase (secondary active transport).

### *Oxidation of Iodide*

Iodide has to be oxidized to iodine because only iodine is capable of combining with tyrosine. The process of oxidation is promoted by an enzyme thyroid peroxidase ($H_2O_2$ accepts the electron).

### *Iodination of Tyrosine*

The binding of iodine with thyroglobulin molecule is called organification of thyroglobulin. Tyrosine (of thyroglobulin) is 1st iodinated (at 3rd position) to form monoiodotyrosine. (MIT). MIT is next iodinated (at 5th position) to diiodotyrosine (DIT).

### *Coupling*

DIT+MIT = $T_3$ (Triiodothyronine)
DIT+DIT = $T_4$ (Tetraidothyronine/thyroxine)
The enzyme peroxidase is required for coupling.

***Note:*** MIT + DIT = Reverse $T_3$.

### *Storage*

In combination with thyroglobulins, thyroid hormone can be stored in the follicles for several months. Therefore, when synthesis of thyroid hormones ceases, the physiological effects of deficiency are not observed for several months.

### *Release of Thyroid Hormones*

Thyoglobulin itself is not released into the bloodstream. The hormones are 1st cleaved from thyroglobulin. The process occurs as follows:

The apical surface of thyroid cells sends out pseudopod like extensions, that close around small portions of colloid to form pinocytic vesicles. These vesicles then enter the thyroid cell. Then the lysosomes of the cell fuses with the vesicles. The digestive enzymes present in the lysosomes digest the thyroglobulin and release $T_3$ and $T_4$ in free form. These then diffuses through the base of thyroid cell into the surrounding capillaries. The $T_4$-$T_3$ secretion ratio is 10 : 1.

### *Transport of $T_3$ and $T_4$*

Over 99% of $T_3$ and $T_4$ combines immediately with plasma proteins like thyroxine binding globulin (mainly) and thyroxine binding prealbumin and albumin (to lesser extent). The rest circulate unbound in the plasma.

## Differences Between $T_4$ and $T_3$ (Table 8.3)

## *Actions*

### *Metabolic*

#### *Calorigenic action*

Thyroid hormone in general stimulates the metabolic activities and increases $O_2$ consumption and heat production in most tissues of the body except adult brain, testis uterus, lymph nodes, spleen and anterior pituitary. Thus, it increases the BMR. They increases activity of $Na^+$- $K^+$ ATPase.

#### *Effects on carbohydrate metabolism*

- Increased uptake of glucose by the cells
- Enhanced gluconeogenesis
- Increased rate of absorption from GIT
- Increased insulin secretion.

**Table 8.3: Comparison of $T_4$ and $T_3$**

| $T_4$ | $T_3$ |
|---|---|
| 1. Considered as a precursor of $T_3$ and is solely secreted by the gland | 1. Considered as a physiologically active form and plasma $T_3$ comes from<br>a. Deiodination of $T_4$ in the tissue<br>b. Secretion by the gland |
| 2. $T_4$ combines less freely with DNA receptor | 2. It has more affinity to the receptor on the DNA |
| 3. Amount secreted is ten to twenty times more | 3. Amout secreted is less |
| 4. More bound to protein, less free form | 4. Less bound to protein, more free form |
| 5. Slow and sustained | 5. Fast action |
| 6. Gets metabolized slowly | 6. Gets metabolize faster |

***Effects on fat metabolism***

- Mobilization of fat from adipose tissue
- Increase the level of free fatty acids
- Enhances the oxidation of free fatty acids by cells
- Lowers circulating cholesterol levels (due to increased secretion of cholesterol in bile; cholesterol secretion is increased by inducing the formation of LDL receptors in the liver, resulting in increased hepatic removal of cholesterol)
- Plasma levels of triglycerides and phospholipids are also decreased.

***Effects on protein metabolism***

In physiological amounts thyroid hormones function as anabolic hormone. They cause increase in RNA and protein synthesis. In high concentration they have catabolic effect.

***Effect on vitamin metabolism***

Thyroid hormones increase the quantity of enzymes. Vitamins are essential parts of some enzymes and coenzymes. Therefore, thyroid hormones cause increased need for vitamins leading to relative vitamin deficiency in hyperthyroidism.

## Growth and Development

***Effects on growth***

Thyroid hormones are essential for normal growth and skeletal maturation. They exert their effect directly by increasing protein synthesis and enzymes and indirectly by increasing the production of GH and potentiating their effect on the tissues. They also promote growth and development of brain during fetal life and for 1st few years of postnatal life.

***Effect on other endocrine glands***

They increases the rate of secretion of other endocrine glands. They also increases the need of tissues for hormones (insulin, parathyroid, catacholamines, etc.).

***Effect on body weight***

Greatly increased thyroid hormone always decreases the body weight, and greatly decreased hormone almost increases the body weight.

## Systemic

***Cardiovascular effects***

*Effect on heart*

1. Increased heart rate
2. Increased stroke volume
3. Increased cardiac output.

Cardiac output is increased due to increase in metabolism, increase in β-adrenergic receptors (both number and affinity) and increase in level of α- MHC (Myosin heavy chain).

*Effect on blood vessels*

Systolic BP is increased due to increase in cardiac output. Diastolic BP is decreased due to the peripheral vasodilatation. Vasodilatation is due to increase in heat production and increased metabolites. This results into the increased pulse pressure and increased velocity of blood flow causing increase in circulation (hyperdynamic circulation).

***Respiratory effects***

The increased rate of metabolism increases the utilization of $O_2$ and formation of $CO_2$. These effects activate all the mechanisms that increases rate and depth of respiration.

***Effect on GIT***

They increase appetite and food intake. Thyroid hormones also increases secretions and motility of GI tract.

***Effect on CNS***

They are essential for brain development (especially cortex, basal ganglia and cochlea) during fetal life and for 1st few years of postnatal life. Normal functioning of brain need thyroid hormone. The hyperthyroid individuals may develop psychoneurotic problems like anxiety, complexes, extreme worry, etc. Reaction time of stretch reflex is shortened in hyperthyroidism and it is prolonged in hypothyroidism.

Thyroid hormones are essential for normal formation of synapses and myelination in the developing brain. In hypothyroidism there will be abnormal development of synapses, decreased myelination and decreased growth and branching of dendrites. This decrease in number of neurons is responsible for mental retardation.

***Effect on skeletal muscle***

Slight increase in thyroid hormone can make the muscle to work with more vigor. But excessive secretion causes weakness in muscles due to catabolism of proteins. Fine muscle tremor is a characteristic sign of hyperthyroidism.

***Effect on sleep (due to activity on RAS)***

Hypersecretion of thyroid hormone causes excessive stimulation of muscles and CNS. So the person feels tired but because of excitable effects of thyroid hormone on synapses it is difficult to sleep. On the other hand hyposecretion causes excessive sleep (somnolence).

***Effect on reproductive system***

For normal function thyroid hormones are essential. In males, lack causes loss of libido and excess causes impotence. In females lack causes menorrhagia (excessive bleeding) and polymenorrhagia (frequent menstruation). Hypersecretion in women causes oligomenorrhea (reduced bleeding).

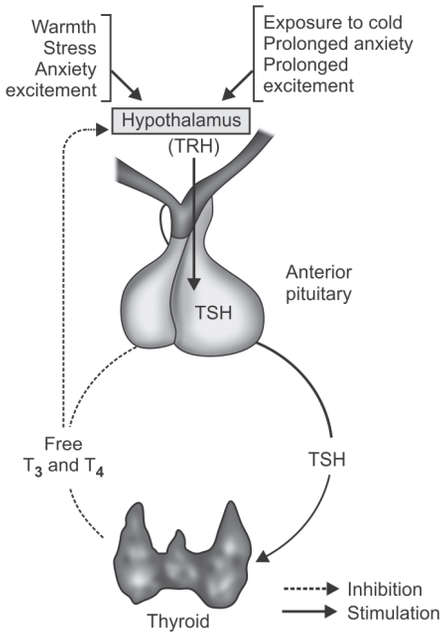



**Fig. 8.12:** Negative feedback mechanism through hypothalamus-anterior pituitary-thyroid gland axis

## Regulation of Secretion

The secretion of thyroid hormone is regulated by:

### *Negative Feedback Mechanism Through*

### *Hypothalamus-anterior Pituitary-thyroid Gland Axis (Fig. 8.12)*

### *Autoregulation of Thyroid Gland*

The secretions of thyroid gland is regulated by food iodine contents. If there is deficiency of iodine content in the diet then the iodine trapping mechanism of the thyroid cells become super efficient and vice versa if there is excess of iodine content in the diet. In this way iodine availability for thyroid hormone synthesis remains constant and this phenomenon is called autoregulation.

***Note:*** In normal individuals, large doses of iodines act directly on thyroid to produce a mild and transient inhibition of organic binding of iodide and hence of hormone synthesis. This inhibition is known as the ***Wolff-Chaikoff effect.***

## Antithyroid Drugs

Drugs that depresses thyroid secretion are called antithyroid drugs.

*Mechanism:*

- Interfering iodide trapping
- Blocking the organic binding of iodine.

For example: (1) Thiocyanate, (2) Propylthiouracil, (3) High concentrations of inorganic iodides.

*Thiocyanate ions decrease iodide trapping:* Administration of thiocyanate in high concentration causes competitive inhibition of iodide transport into the cell (thiocyanate and iodide ions have the same active pump).

Propylthiouracil decreases thyroid hormone formation: Prevents formation of thyroid hormone from iodides and tyrosine. Mechanism-block the peroxidase enzyme required for iodination of tyrosine and partly to block the coupling of two iodinated tyrosines to form thyroxine and triiodothyronine.

Iodides of high concentration decrease thyroid activity and thyroid gland size. When iodides are present in high concentration most activities of thyroid gland are decreased to reduce rate of iodide trapping. So the rate of iodination of tyrosine to form thyroid hormones are decreased.

## Thyroid Function Test

1. Sleeping pulse rate >100 in hyperthyroidism.
2. BMR: Normal value is 37–40 kcal/$m^2$ of body surface/hours. BMR increased in hyperthyroidism (50), decreased in hypothyroidism (20).
3. Serum cholesterol: Increases in hypothyroidism, decreases in hyperthyroidism.
4. Serum $T_3$ and $T_4$: Estimated by radioimmunoassay. Normal $T_3$ = 0.15μg/dl, $T_4$ = 8 μg/dl.
5. Ankle jerk (Achilles reaction time): Normally 2–3 msec. In hypothyroidism it is prolonged, and in hyperthyroidism it is shortened.
6. Radioactive iodine uptake studies: $I_{131}$ is given orally in 100 ml water and thyroid uptake is determined by placing a X-ray counter over the neck. Normally 20–40% is taken up.
7. Scanning technique.
8. Thyroid biopsy: To detect any malignant process.
9. TRH/TSH stimulation test: To know whether pituitary/thyroid disorder.

## Applied Aspects

### *Hypothyroidism*

Caused by low levels of circulating thyroid hormones. Depending upon the cause it can be:

a. Primary hypothyroidism: Disorder of thyroid gland.
b. Secondary hypothyroidism: Diseases of anterior pituitary or hypothalamus.

It leads to myxedema in adults and cretinism in children.

***Cretinism***

*Cause*

1. Congenital absence of thyroid gland
2. Genetic disorder
3. Lack of $I_2$.

*Symptoms*

- Appear 1–3 weeks after birth
- Appearance-idiotic, ugly, obese, short child
- Mental retardation in children
- All milestones of development are delayed
- Skeletal growth is more affected than soft tissues (so stunted body with pot belly)
- Tongue larger (macroglossia) and protrude out of the mouth
- Big tongue obstructs swallowing and breathing
- Sexual development is affected
- Skin is dry, coarse and wrinkled
- Hair is sparse and scanty
- Temperature is subnormal.

*Treatment*

Treatment of neonate with cretinism at any time with adequate iodine or thyroxine returns normal physical growth, but unless the cretinism is treated within few weeks after birth, mental growth remains permanently retarded.

***Myxedema***

*General features:* Tiredness, weight gain, intolerance to cold, mental sluggishness, poor memory, decreased BMR, lower body temperature, husky and slow voice (frog like voice), hair coarse and sparse, extreme sleep (Fig. 8.13).

*Cardiovascular features:* Adrenergic activity is decreased causing bradycardia, atherosclerosis (due to increased cholesterol level) and atherosclerosis increases BP.

*Neuromuscular features:* Fatigue, stretch reflex reaction time is prolonged.

*Dermatological features:* Skin is dry and yellowish (carotenemia, since the conversion of vitamin A require $T_3$ and $T_4$), swelling of the face, puffiness under the eyes, nonpitting edema.

*Reproductive features:* Menorrhagia and infertility.

*Gastrointestinal features:* Constipation.

*Hematological changes:* Anemia.

## Hyperthyroidism

Its common causes are Graves' disease, toxic goiter, TSH secreting tumors of anterior pituitary, mutations that causes the activation of TSH receptors.

***Symptoms***

Intolerance to heat, increased sweating, weight loss, nervousness, muscle weakness, extreme fatigue but inability to sleep, diarrhea, tremor of hands, goiter, atrial fibrillation, tachycardia, exophthalmos.

**Fig. 8.13:** Patient with myxedema

***Treatment***

Surgical removal of thyroid gland.

***Graves' disease***

It is an autoimmune disease. It is characterized by development of TSH receptor stimulating antibodies. These antibodies bind to TSH receptors and mimic TSH action, making the gland hyperactive. In Graves' disease there is marked stimulation of secretion of thyroid hormones and high circulating $T_4$ and $T_3$ levels. This will inhibit TSH secretion. Increased levels of thyroid hormones tend to cause increased formation of antibodies. Exophthalmos is often seen.

***Exophthalmos***

Exophthalmos means protrusion of eyeballs. The cause of protruding eyes is edematous swelling of retro-orbital tissues and degenerative changes in the extraocular muscles (Fig. 8.14). Sometimes eyeball protrusion stretches the optic nerve enough to damage the vision. Due to the protrusion of eyeballs, the eyelids cannot be closed completely while blinking or sleep. So the constant exposure of eyeball to atmosphere causes dryness of the cornea leading to irritation and infection, finally resulting in ulceration of cornea.

**Fig. 8.14:** Exophthalmos

***Goiter***

Goiter refers to any abnormal increase in size of thyroid gland. Goiter does not denote functional state of the thyroid gland. It may be associated with euthyroid, hypothyroidism or hyperthyroidism. Antithyroid substances that cause enlargement are called goitrogens. Goitrogens decreases thyroid hormone synthesis leading to feedback increase in TSH secretion. TSH is responsible for the formation of hypertrophic thyroid gland (goiter).

Goiter in hyperthyroidism-toxic goiter

Goiter in hypothyroidism are of two types

*Endemic colloid goiter:* Also called iodine deficiency goiter (intake below 10 μg/day). TSH (produced due to feedback mechanism) stimulates thyroid cells to secrete tremendous amounts of thyroglobulin. Due to iodine deficiency $T_3$ and $T_4$ production does not occur and the thyroglobulin remains as such and gets accumulated in the follicles of the gland. This increases size of gland.

*Idiopathic nontoxic colloid goiter:* Enlargement of thyroid gland occurs even without iodine deficiency.

*Causes*: Thyroiditis, abnormal enzyme system, goitrogenic substances like propylthiouracil present in turnips and cabbages.

## PARATHYROID GLANDS

Parathormone secreted by parathyroid gland is essential for maintenance of blood calcium level.

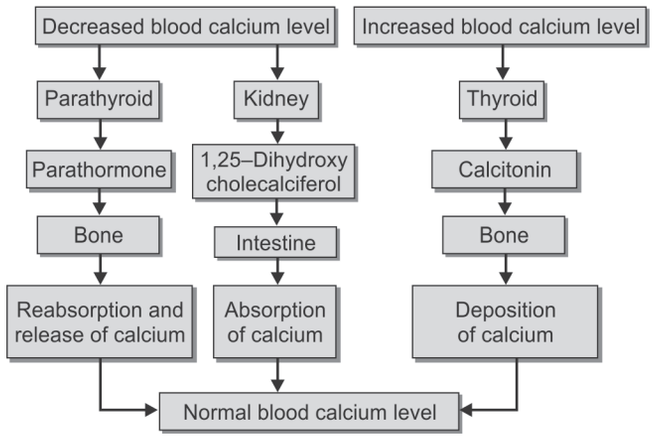
### Calcium Metabolism

Calcium is essential for bone formation, neuromuscular activity, normal cardiac rhythmicity, coagulation of blood, formation of milk, mediation of intercellular action of hormones, fetal development during pregnancy, membrane integrity and permeability. Normal Ca level in blood is 9–11 mg/dl.

#### *Types of Calcium*

1. *Calcium in plasma exists in diffusible and non-diffusible forms.*
   - Diffusible Ca is in the form of ionic Ca (about 50%) or complexed to $HCO_3^-$, citrate, etc. (about 10%). Ionized $Ca^{2+}$ is required for—(a) muscle contraction, (b) cardiac activity, (c) blood coagulation.
   - Non-diffusible is bound with albumin or globulin (about 40%).
2. *Calcium in bones is of two types:*
   - Readily exchangeable form (1%)
   - Stable calcium (99%) can be mobilized only through the action of PTH.

**Flow chart 8.4:** Regulation of blood calcium level




### *Regulation of Blood Calcium Level*

Calcium that is taken through dietary sources are absorbed from GI tract. Through blood it is distributed to various parts of the body. Depending upon the blood level, the calcium is either deposited or removed from the bone. All these process are finely regulated by three hormones (Flow chart 8.4).

1. Parathormone.
2. 1,25–dihydroxycholecalciferol.
3. Calcitonin.

In addition to the above mentioned three hormones, growth hormone and glucocorticoids also regulates blood calcium level. Growth hormone increases the blood calcium level by increasing intestinal calcium absorption. Glucocorticoids decreases blood calcium level by inhibiting intestinal absorption and increasing the renal excretion of calcium.

## PARATHORMONE

PTH controls extracellular calcium and phosphate concentration. PTH increases:

1. Resorption of calcium from the bones.
2. Reabsorption of calcium from renal tubules.
3. Absorption of calcium from the GI tract.

### *Actions*

***Effect on bones***

PTH increases plasma $Ca^{2+}$ and decreases plasma phosphate concentration by promoting bone resorption (osteolytic effect). It occurs in two phases: rapid and slow phase.

*Rapid phase*

It is seen within few minutes of administration of PTH. Plasma $Ca^{2+}$ is raised by increasing the permeability of osteoclasts, osteoblast and osteocytes to calcium. It increases calcium

pump mechanism, allowing $Ca^{2+}$ ions to move from these cells to plasma.

*Slow phase*

It occurs hours or days after PTH administration. There occurs increased osteoclastic activity. Osteoclasts are large phagocytic multinucleated cells formed in the bone marrow. When osteoclasts are activated by PTH some proteolytic enzymes and several acids like citric acid and lactic acid are released. The enzymes digest or dissolve the organic matrix of the bone and acids dissolves the bone salts. Eventually $Ca^{2+}$ ions are released into plasma. Along with $Ca^{2+}$ resorption, PTH also increases phosphate absorption from the bones.

***Effect on kidney***

PTH increases the resorption of calcium mainly from distal tubules, collecting tubules and to a lesser extent from ascending limb of loop of Henle. It decreases phosphate reabsorption.

Reabsorption of $Mg^{2+}$ and $H^+$ are increased while the reabsorption of $Na^+$, $K^+$ ions and amino acids are decreased.

***Effect on intestine***

Increases intestinal absorption of Ca and phosphates.

***Role of PTH in activation of vitamin D***

Vitamin D is essential for calcium absorption from intestine. But vitamin D has to be converted to 1,25–dihydroxycholecalciferol (active form).

*Steps (Fig. 8.15)*

1. Cholecalciferol (vitamin $D_3$) is formed in the skin.
2. Cholecalciferol is converted to 25-hydroxycholecalciferol in liver.
3. 1,25-dihydroxycholecalciferol is formed in the kidney. This step is under the control of PTH

When blood Ca level increases it inhibits the formation of 1, 25-dihydroxycholecalciferol. The mechanism involved in the inhibition of formation of 1,25-dihydroxycholecalciferol is:

- Ca ion itself has a slight effect in preventing the conversion of 25 hydroxycholecalciferol to 1,25-dihydroxycholecalciferol.
- Increase in Ca ion concentration decreases the PTH secretion which in turn suppresses the conversion of 25 hydroxycholecalciferol to 1,25 dihydroxycholecalciferol.

### *Actions of 1,25-dihydroxycholecalciferol*

- Promotes intestinal Ca absorption
- Promotes intestinal phosphate absorption
- Decreases excretion of Ca and phosphate from kidney

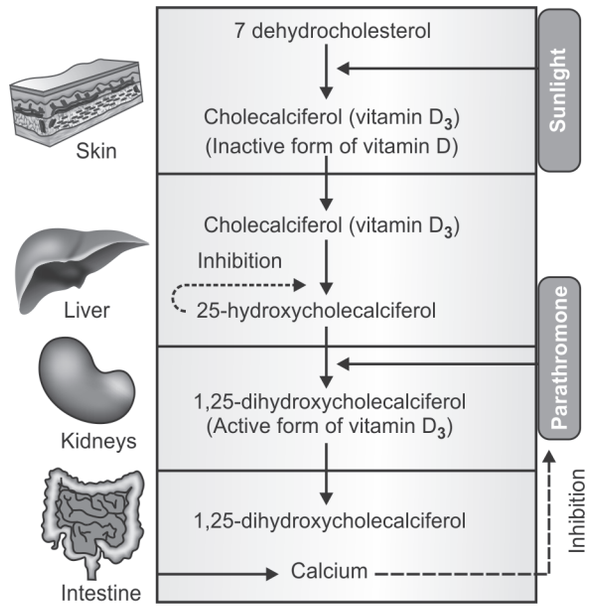



**Fig. 8.15:** Activation of vitamin D

- Extreme quantities of vitamin D causes absorption of bone. In the absence of vitamin D the effect of PTH in causing bone absorption is greatly reduced
- Vitamin D in smaller quantities promotes bone calcification.

### *Regulation of Parathyroid Secretion*

1. Ca concentration in the blood is the main factor.
2. Increased phosphate stimulates PTH secretion (by lowering plasma Ca and 1,25-dihydroxycholecalciferol).
3. 1, 25-dihydroxycholecalciferol acts directly to decrease prepro PTH mRNA and decreases PTH secretion.
4. Mg deficiency cause impaired PTH release along with diminished target organ responses to PTH.

## Calcitonin

Calcitonin tends to decrease plasma Ca concentration and in general counteracts PTH.

### *Actions*

***On Bones***

- Facilitates the deposition of Ca on bones
- Suppresses the activity of osteoclast
- Inhibits development of new osteoclast in bones.

***On Kidney (minor effect)***

Increases the excretion of Ca through urine.

***On Intestine (minor effect)***

Prevents the absorption of Ca from intestine into blood.

## Applied Aspects

### *Hypoparathyroidism*

Decreased secretion of PTH.

***Causes***

- Surgical removal of parathyroid gland
- Removal of parathyroid glands during surgical removal of thyroid gland
- Deficiency of receptors for PTH in target cells.

When total serum Ca level is decreased below six mg%, it results in hypocalcemic tetany. Simultaneously serum phosphate is also decreased.

***Treatment***

1. Administration of 1,25-dihydrocholecalciferol.
2. Administration of PTH (usually not treated).

***Tetany***

Refers to a clinical condition resulting from increased neuromuscular excitability. When ECF concentration of Ca ions falls below normal, neuronal membrane permeability to Na increases, allowing easy initiation of action potentials.

***Clinical features***

*Carpopedal spasm (obstetric hand) (Fig. 8.16):* It is a peculiar attitude of hand in tetany.

There is flexion at the wrist and thumb with hyperextension of remaining fingers.

*Laryngeal stridor:* Due to the spasm of laryngeal muscles.

*Visceral manifestations:* It includes intestinal colic, biliary colic, bronchospasm, profuse sweating.

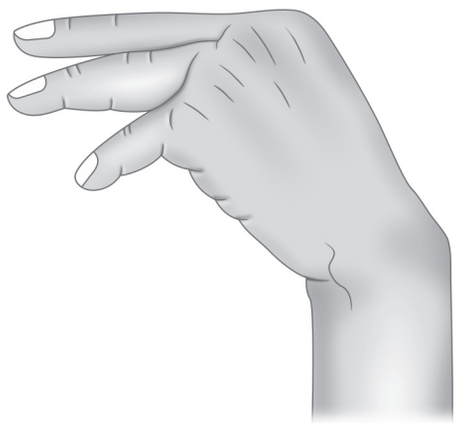


**Fig. 8.16:** Carpopedal spasm (obstetric hand)

*ECG changes:* ST segment is prolonged with abnormal T wave.

*Trousseau's sign:* Occluding the blood supply to a limb by inflation of sphygmomanometer cuff produces characteristic carpopedal spasm.

*Chvostek's sign:* Tapping the facial nerve at the angle of jaw produces ipsilateral contraction of the facial muscles (due to increased excitability of nerves to mechanical stimuli.

### *Hyperparathyroidism*

Increased secretion of PTH. Based on cause, it is divided into primary and secondary hyperparathyroidism.

***Primary hyperparathyroidism***

Abnormality of parathyroid causes excess PTH secretion.

*Cause*: Tumor of parathyroid gland.

Here Ca ion concentration is elevated (due to extreme osteoclastic activity). Phosphate ion concentration is decreased (due to increased renal excretion of phosphate).

***Secondary hyperparathyroidism***

Here high levels of PTH occurs as a compensation for hypocalcemia.

*Cause:* Vitamin D deficiency or kidney damage.

***Clinical features***

- Depression of central and peripheral nervous system, muscle weakness, constipation, abdominal pain, peptic ulcer, depressed relaxation of heart during diastole.
- Increase in serum alkaline phosphatase.
- The cystic bone disease of hyperparathyroidism is called osteitis fibrosa cystic.

## Physiology of Bone

Bone is a special type of connective tissue with a collagen framework impregnated with $Ca^{2+}$, $PO_4^{3-}$ salts particularly hydroxyapatites. It is a living tissue that is well vascularized and has a total blood flow of 200–400 ml/min in adult humans. The protein in bone matrix is mostly type 1 collagen. Bone is of two types:

### *Compact/Cortical Bone*

It makes up the outer layer of most bones. It accounts for 80% of the bone in the body. Surface-to-volume ratio is low. Bone cells (osteocytes) lie in lacunae and they receive nutrients via Haversian canals.

### *Trabecular/Spongy Bone*

It lies inside the cortical bone. They are made up of spicules or plates makes up remaining 20% of bone in the body. Surface

to volume ratio is high. Bone cells lie on the surface of plates. In spongy bone, nutrients diffuse from bone ECF into the trabeculae.

### Bone Growth

During fetal development, most of the bone are modelled in cartilage and then transformed into bone by ossification-endochondral bone formation.

Certain bones (bones of skull) are formed directly from mesenchymal cells-intramembranous bone formation.

During growth, specialized areas at the ends of each long bone (epiphysis) are separated from the shaft of bone by a plate of actively proliferating cartilage, the epiphysial plate. The width of the epiphysial plate is proportionate to the rate of growth and is affected by a number of hormones like growth hormone and IGF-1. Linear bone growth ceases after the epiphyses unit with the shaft (epiphysial closure).

### Bone Formation and Resorption

Bone is constantly being reabsorbed and reformed, which is under the cellular control of osteoblasts, osteocytes and osteoclasts. The cells responsible for bone formation are osteoblasts and the cells responsible for bone resorption are osteoclasts.

#### *Osteoblasts*

They are bone forming cells. They are found on the outer surfaces of the bones and in bone cavities. They synthesize and secrete collagen, forming a matrix around themselves which then calcify and form new bone. They have abundant alkaline phosphatase activity.

#### *Osteoclasts*

They are phagocytic multinuclear giant cells containing numerous lysosomes. They erode and resorb previously formed bone. They contain several acids and appear to phagocytose bone, digesting it in their cytoplasm.

#### *Osteocytes*

They are bone cells surrounded by calcified matrix. Osteocytes remain in contact with one another and with osteoblasts via long protoplasmic processes that run through channels in the bone forming functional syncytium. Osteocytes provide rapid and transient movement of Ca from bone into the ECF space.

### Mechanism of Bone Formation

1. The initial stage in bone production is secretion of collagen molecules (called collagen monomers) and ground substances (proteoglycans) by osteoblasts. The collagen monomers polymerize rapidly to form collagen fibers; the resultant tissue becomes osteoid. As the osteoid is formed, some of the osteoblasts become entrapped in the osteoid. At this stage they are called osteocytes.
2. During the normal process of mineralization, minerals accumulate within membrane bound vesicles. Within a few days after osteoid is formed, calcium salts begin to precipitate on the surfaces of collagen fibers. This process is controlled by PTH, calcitonin, 1-25 DHCC (Fig. 8.17).
3. PTH increase and CT decreases the permeability of the bone cells to $Ca^{2+}$ while 1-25 DHCC facilitates the active transport of $Ca^{2+}$ from osteoblasts into ECF. In this way calcium and phosphate concentrations in bone fluid is regulated.
4. Osteoblast secrete an alkaline phosphatase that hydrolysis phosphate esters and the phosphate is released. Thus whenever $[Ca^{2+}]$ x $[PO_4^{3-}]$ exceeds solubility product, calcium phosphate precipitates.

### Reabsorption of Bone

It is a process that involves the destruction of entire matrix followed by the removal of calcium. It is brought about by osteoclasts. Osteoclasts are large phagocytic multinucleated cells formed in the bone marrow. When osteoclasts are activated by PTH some proteolytic enzymes and several acids like citric acid and lactic acid are released. The enzymes digest or dissolve the organic matrix of the bone and the acids cause solution of the bone salts. All the dissolved materials are then released into the blood.

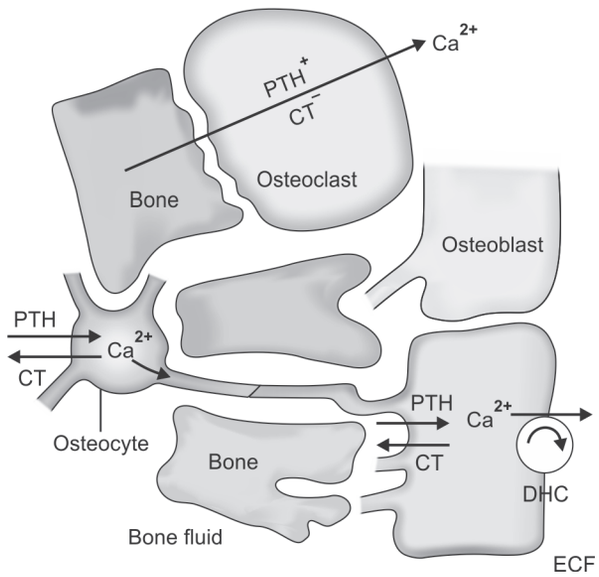



**Fig. 8.17:** Organization of bone cells and mechanism of bone formation

## Metabolic Bone Diseases

### *Rickets*

Defective calcification of bone matrix in children due to Ca or phosphate deficiency caused by the lack of vitamin D.

*Causes:* Inadequate intake of provitamins, inadequate exposure to sun, kidney failure, liver failure, congenital hypophosphatemia (congenital reduced uptake of phosphate by renal tubules).

***Clinical features***

- Weakness and bowing of weight-bearing bones
- Thickening of wrist and ankles
- Retarded growth and shortness of stature
- Dental defects
- Hypocalcemia, hypotonia, rickety rosary (beading of costochondrial junction of ribs)
- In prolonged cases, usual signs of tetany develop.

***Treatment***

1. Supplying adequate Ca and phosphate in diet.
2. Administration of vitamin D.

### *Osteomalacia*

Adult counterpart of rickets. Adults seldom have dietary deficiency of vitamin D or Ca because large quantities of Ca are not needed for bone growth as in children.

*Causes:* Steatorrhea (failure to absorb fat, so that vitamin D which is fat soluble is not absorbed), congenital hypophosphatemia.

Usually the complications of tetany are not seen.

***Note***

1. *Vitamin D resistant rickets:* Rickets due to congenital hypophosphatemia (congenital reduced reabsorption of phosphates by renal tubules) must be treated with phosphate compounds instead of Ca and vitamin D.
2. *Renal rickets:* It is a type of osteomalacia that results from prolonged kidney damage. The cause of this condition is mainly failure of the damaged kidneys to form 1,25-dihydrocholecalciferol.

### *Osteoporosis*

Decreased bone matrix. Usually occurs in old age.

*Causes:* Lack of physical stress on bones, malnutrition, lack of vitamin C (essential for secretion of intercellular substances), lack of estrogen secretion (estrogen decrease the number and activity of osteoclast), old age, Cushing's syndrome (here osteoblastic activity as well as deposition of protein in bone is decreased).

## PANCREAS

Secretes enzymes and hormone. Exocrine-secrete enzymes that promote the digestion of carbohydrates, proteins and fats. Cells in endocrine part secrete hormones.

*A cells or α cells (15–20%):* Glucagon (hyperglycemic hormone).

*B or β cells (70–80%):* Insulin-hypoglycemic hormone.

*D cells (1–8%):* Somatostatin (GHIH) and gastrin (in small amounts).

*F Cell:* Pancreatic polypeptide (decreases the absorption of food from GIT).

*Nerve supply:* ANS

*Blood supply:* Portal vein

## Insulin

### *Structure of Insulin*

Consist of two chains -α and β connected by two S-S bonds and a 3rd disulfide bridge on a chain. α has 21 amino acids and β has 30 amino acids (total 51 amino acids).

### *Synthesis and Excretion*

Insulin is synthesized by ribosomes on ER (proinsulin). It is then transported to the Golgi apparatus to form insulin. Here the formation of insulin continues within the storage granules which, therefore contain proinsulin, insulin and C peptide. These granules move to the cell wall and their membranes fuse with the membrane of the cell, expelling the insulin to the exterior by exocytosis. Insulin is formed after detaching connecting (C) peptide before secretion. The process of release of insulin requires ATP, cAMP and presence of $Ca^{2+}$ and $K^{+}$. Normal fasting insulin concentration is 10–50 U/ml. Insulin is 10–20 times more active than proinsulin.

### *Transport and Distribution*

Binds with circulating plasma protein of *anti-insulin* activity called synalbumin. Insulin fixes to insulin receptors (glycoprotein) on the cell membrane of may tissues. Insulin exerts its effect without entering the cell on which it acts.

### *Metabolism*

Half life is about 5 minutes. 80% gets metabolized by the liver and kidneys by hepatic glutathione insulin dehydrogenase (HGIT) which breaks disulfide bridge to SH groups with separation of α and β chains. 20% in rest of body tissues and is destroyed by insulin protease.

## Actions

***On cell membrane permeability***

Promotes glucose entry into cell (except RBC liver and brain cell).

***On metabolism***

a. *Carbohydrate metabolism:*
- Peripheral utilization of glucose increased.
- Increased uptake of carbohydrates (by liver cells)
- Insulin responsible for stimulation of GLUT
- Stimulates phosphorylation of glucose by stimulating glucokinase
- Activates glycogen synthetase. Helps glycogen synthesis in liver and muscle
- Inhibits glycogenolysis and gluconeogenesis
- Inhibits secretion of glucagons.

In hyperinsulinemia, patients suffer from hypoglycemia (decrease in blood sugar), brain cells are affected and produce convulsions.

Insulin dysfunction-glucose utilization severely affected.

b. *Protein metabolism:*
- Its action is anabolic.
- Facilitates the transport of amino acids into the cell from blood (by increasing the permeability of cell membrane)
- Accelerates protein synthesis by influencing translation of mRNA.
- Inhibits gluconeogenesis, thus decrease protein breakdown.
- Promotes growth-acts synergistically with GH.

c. *Fat metabolism.*

*Promotes fat synthesis by:*
- Increasing the transport of glucose into liver cells and this glucose is utilized for synthesis of fatty acids and triglycerides
- Acetyl CoA carboxylase is activated (enzyme for fatty acid synthesis)
- Increases the deposition of TGs by breaking down circulating TGs by lipoprotein lipase.

*Promotes Storage by:*

Inhibiting the action of lipases.

***Miscellaneous action***
- Insulin increase urea output from liver and increases uptake of $K^+$ and phosphate
- Insulin increases $K^+$ entry into the cell thereby decreasing ECF $[K^+]$
- It activates ATPase activity thus increases $K^+$ entry to cell.

## Glucose Transporters

Glucose enters the cell by facilitated diffusion. But in the intestine and kidneys glucose entry is by the secondary active transport with $Na^+$. In muscle, fat and other tissues, insulin facilitates glucose entry into the cells by increasing the number of glucose transporters.

There are 14 varieties (isomers) of glucose transporters (GLUT). Glucose entry in the cells of muscles and adipose tissue is dependent on GLUT-4. GLUT- 4 is insulin dependent, i.e. insulin is required for its activity. Normally GLUT-4 is present in the cytoplasm of muscle and adipose tissue cell. But in presence of insulin GLUT- 4 are translocated in the cell membrane.

GLUT is a sort of channel protein, i.e. it contains a channel within it. Normally glucose cannot cross the cell membrane, but when GLUT- 4 is present, the cell membrane contains a channel, through which glucose enters from the ECF to the cytoplasm. As cytoplasmic glucose is speedily metabolized, the ECF glucose concentration remains higher than the glucose concentration in the cytoplasm and glucose entry occurs due to concentration gradient. Insulin receptor substrates facilitate the translocation of GLUT-4 from the cytoplasm to membrane.

## Regulation of Insulin Secretion

Insulin is mainly regulated by blood glucose level. In addition other factors like amino acids, fat derivatives, hormones, autonomic nerves also regulates insulin secretion.

***Substrate control***

*Blood glucose:* Stimulates insulin secretion. Note that sugars like 2-deoxyglucose, mannoheptulose decreases secretion.

*Amino acids:* Arginine and lysine (most potent) and certain other amino acids stimulates.

*Fat derivatives:* β ketoacids stimulates.

***cAMP and various cAMP generating substances***

Stimuli that increase cAMP levels in β cells increase insulin secretion (increasing intracellular $Ca^{2+}$).

***Autonomic nerves***

Stimulation of sympathetic nerves to pancreas inhibit secretion (via α adrenergic receptors). Neurotransmitter is norepinephrine. Parasympathetic stimulation increases secretion (via $M_4$ receptors). Neurotransmitter is ACh.

***GI hormones*** like glucagon, secretin, gastrin, CCK, GIP stimulates.

***Hormones*** like glucagon, GH, cortisol stimulates and insulin, somatostatin inhibits secretion.

***$K^+$ depletion*** decreases insulin secretion.

Drugs like sulfonylureas ***(antidiabetic agents)*** stimulates and diazoxide ***(antihypertensive)***, thiazides, phenytoin, alloxan decreses secretion.

## Diabetes Mellitus

A syndrome of impaired carbohydrate, fat and protein metabolism caused by either lack of insulin secretion or decresed sensitivity of the tissues to insulin. There are two general types DM.

1. *Type I diabetes:* Insulin dependent; caused by lack of insulin.
2. *Type II diabetes:* Noninsulin dependent; caused by decreased sensitivity of target tissues to the metabolic effect of insulin (insulin resistance).

### *Clinical Characteristics (Table 8.4)*

**Table 8.4: Differentiating features of type I and type II diabetes mellitus**

| *Feature* | *Type I* | *Type II* |
|---|---|---|
| Age of onset | Usually <20 years | Usually >30 years |
| Body mass | Low (wasted) to normal | Obese |
| Plasma insulin | Low or absent | Normal to high initially |
| Plasma glucagon | High, can be suppressed | High, resistant to suppression |
| Plasma glucose | Increased | Increased |
| Insulin sensitivity | Normal | Reduced |
| Therapy | Insulin | Weight loss, thiazolidinediones Metformin Sulfonylureas, insulin |

### *Signs and Symptoms*

Various manifestations develop because of three major setbacks of insulin deficiency:

1. Increased blood sugar level due to reduced utilization by tissues.
2. Mobilization of fat from adipose tissue (for energy purpose) elevates fatty acid content in the blood; atherosclerosis.
3. Depletion of proteins from tissue.

### *Features*

Polyuria (due to osmotic effect, more water accompanies the glucose), polydypsia (to compensate for the loss of water, thirst center is activated and more water is taken), polyphagia (to compensate the loss of glucose and protein), glucosuria, osmotic diuresis, asthenia (lack of energy), ketoacidosis, acetone breathing, Kussmaul breathing, coma. Difference between diabetes mellitus and diabetes insipidus is given in Table 8.5.

### *Complications of DM (Flow chart 8.5)*

1. Predisposition to infection (intracellular glucose are converted to advanced glycosylation end products (AGEs) and these AGEs interfere with leukocyte response to infection).
2. Atherosclerosis.
3. Diabetic neuropathy-degeneration of autonomic and peripheral nerve.
4. Diabetic retinopathy-degenerative changes in retina.
5. Diabetic nephropathy-degenerative changes in kidney.
6. Stroke and MI.

**Table 8.5: Comparison between diabetes mellitus and diabetes insipidus**

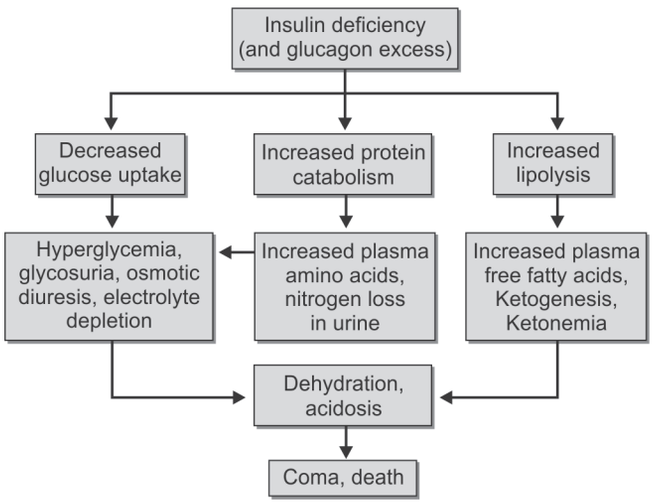
| | ***Features*** | ***Diabetes mellitus*** | ***Diabetes insipidus*** |
|---|---|---|---|
| 1. | Etiology | a. Deficient insulin secretion from pancreas | Deficient ADH secretion from posterior pituitary |
| | | b. Lesions of pancreas | Lesions of pancreas supraoptic nucleus of hypothalamus |
| 2. | Major metabolic changes | a. Storage of glucose as glycogen in muscles is impaired | |
| | | b. Liver glycogen breakdown is increased | No such effects |
| | | c. Fat breakdown increased | |
| | | d. Ketone bodies formation increased | |
| 3. | Urine output | Large volume of urine is voided-polyuria | Large volume of urine is voided-polyuria |
| 4. | Cause of polyuria | Water reabsorption is prevented by the osmotic pressure effect of glucose in the lumen of renal tubule. So more water is lost through urine. | ADH deficiency decreases water reabsorbtion at DCT and collecting duct. So more water is lost |
| 5. | Presence of glucose in urine | Present-glycosuria | Absent |
| 6. | Taste of urine | Sweet | No sweet taste |

*Contd...*

*Contd...*

| | | | |
|---|---|---|---|
| 7. | Specific gravity | High-as glucose is present in urine | Low-dilute hypotonic urine. Specific gravity-1.002–1.006 |
| 8. | Blood glucose level | High-hyperglycemia | Normal |
| 9. | Ketone body concentration in blood | High-ketosis | Not seen |
| 10. | Symptoms | Increased thirst, hunger, ketonuria, poor wound healing | Increased thirst. Other effects are absent. |
| 11. | Treatment | a. Oral hypoglycemic agents, b. Insulin injection | ADH injection |

**Flow chart 8.5:** Complications of DM




### *Treatment*

*Type I:* Administration of insulin.
*Type II:* Diet controlling, exercise (to induce weight loss and reverse insulin resistance). If this fails drugs are administrated to stimulate increased production of insulin.

## Glucagon

Secreted from α cells in islets of Langerhans. It has several functions that are opposite to that of insulin. Normal fasting glucagons concentration is 100–150 pg/ml. Metabolism same as that of insulin.

### *Actions*

Glucagons is glycogenolytic, gluconeogenic, lipolytic and ketogenic. It favors breakdown of stored nutrients.

### *On Carbohydrate Metabolism*

Glucagon increases the blood glucose level by:

***Stimulates glycogenolysis***

It increases breakdown of liver glycogen to glucose, which in turn increases blood glucose by:

a. Inhibiting glycogen synthetase.
b. By activating cAMP formation (via its action on Gs) → activates protein kinase → activates phosphorylase enzyme which converts glycogen to glucose-6-phosphate.

$$\text{Glucose-6-phosphate} \xrightarrow{\text{Liver phosphatase}} \text{glucose}$$

c. Act on liver cells to activate phospholipase C and results in intracellular $Ca^{2+}$, thus stimulating glycogenolysis.

***Promotes gluconeogenesis***

Promotes formation of glucose from lactate, pyruvate, glycerol and amino acids by:

a. Increases rate of amino acid uptake by liver cells.
b. Activates the enzymes, which convert pyruvate to phosphoenol pyruvate (rate limiting step).
c. Increasing deamination of amino acids in the liver.

### *On Protein Metabolism*

Increases transport of amino acids into liver cell.

### *On Lipid Metabolism*

Shows lipolytic and ketogenic actions. It increases the release of free fatty acids from adipose tissue and makes free fatty acids available for peripheral utilization. The lipolytic activity of glucagon in turn promotes ketogenesis.

### *Other Actions*

- Inhibits secretion of gastric juice
- Stimulates secretion of GH, insulin and pancreatic somatostatin
- Increases force of contraction of heart by increasing cAMP.
- Increases blood flow in some tissues like kidney
- Enhances bile secretion.

### *Regulation of Glucagon Secretion*

Controlled mainly by blood glucose amino acid level in blood.

***Blood glucose level (most potent factor)***

Increased blood inhibits glucagon secretion.

***Amino acid level in blood***

Increased amino acids stimulates the secretion of glucagon. Thus in this instance glucagon and insulin responses are not opposite.

***Other factors***

*Stimulators:* Exercise, stress, gastrin, CCK, cortisol, β adrenergic stimulations.

*Inhibitors:* Somatostatin, secretin, FFA, insulin, ketones, GABA, α adrenergic stimulations.

### Somatostatin

Somatostatin is secreted by δ cells of the islets. It inhibits glucagon, insulin and pancreatic polypeptide. Somatostatin secretion is stimulated by glucose-amino acid meals. It is also increased by CCK. Apart from islet cells, somatostatin is secreted from various sites of our body, like: (i) Brain and CNS (ii) GI tract. Hypothalamic somatostatin inhibits GH hormone. That is why, it is also called growth hormone inhibiting hormone (GHIH). Somatostatin inhibits gastric secretion and gastric motility.

### Pancreatic Polypeptide

F-cells of the islets produce pancreatic polypeptide which is a polypeptide hormone containing 36 amino acids and is structurally related to the neurotransmitter neuropeptide Y in the CNS and polypeptide YY found in the intestine. Fasting and hypoglycemia increase the secretion of pancreatic polypeptide. Physiological significance of this hormone is uncertain.

## ADRENAL CORTEX

Adrenal cortex has three layers:

1. Zona glomerulosa—mineralocorticoids
2. Zona fasciculata—glucocorticoids
3. Zona reticularis—sex steroids (androgens).

### Mineralocorticoids

*Aldosterone:* The chief mineralocorticoid (90%). Other mineralocorticoids are deoxycorticosterone, 9 α-fluorocortisol (synthetic). They are life saving hormones.

#### *Effects on Renal Tubules*

- Na reabsorbtion from the tubular fluid into tubular epithelial cell.
- Potassium excretion (active reabsorption of Na occurs in exchange of K and H).
- $H^+$ excretion.

#### *Effect on ECF Volume*

When Na are reabsorbed from renal tubules, simultaneously water is also reabsorbed which causes increase in volume of ECF.

#### *Effect on Blood Pressure*

Blood pressure (BP) is increased due to increase in ECF volume or blood volume.

***Aldosterone escape***

When aldosterone secretion increases**,** ECF volume and blood volume, is increased leading to rise in BP elevated BP stimulates the secretion of ANP from atrial muscles. It causes excretion of excess salt and water through urine *(pressure natriuresis and pressure diuresis)*. Content of salt and water in ECF comes to normal in spite of increase in secretion of aldosterone.

#### *Effect on Salivary Gland and Sweat Gland*

$Na^+$ reabsorption from sweat gland and loss of $Na^+$ is prevented.

#### *Effect on Intestine*

Enhance $Na^+$ absorption from intestine especially in the colon and prevents loss of $Na^+$ through feces.

### *Mechanism of Action*

Aldosterone binds to a cytoplasm receptor, and the receptor-hormone complex moves to the nucleus where it alters the transcription of mRNAs. This in turn increases the production of proteins that alter cell function. The aldosterone-stimulated proteins have two effects-a rapid effect, to increase the activity of epithelial sodium channels (ENaCs); and a slower effect to increase the synthesis of ENaCs. Aldosterone activates the gene for ***serum and glucocorticoid regulated kinase (sgk)*** and sgk increases ENaC activity. Aldosterone also increases the mRN. As for the three subunits that make up ENaCs. Aldosterone increases the activity of membrane $Na^+$-$K^+$ exchangers. This produces an increase in intracellular $Na^+$.

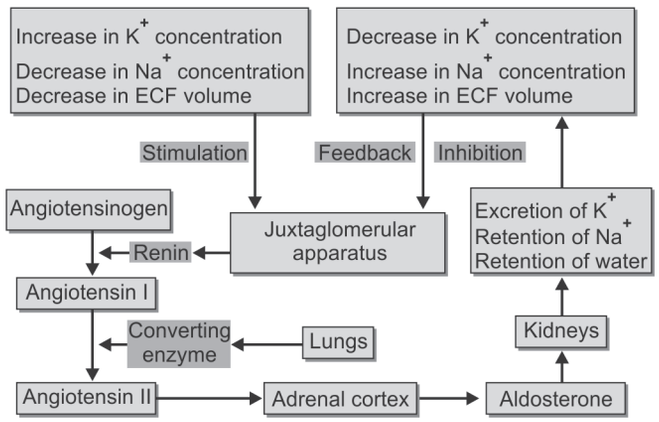
### *Regulation of Aldosterone Secretion (Flow chart 8.6)*

Four factors are involved in the regulation.

The stimulatory agents for aldosterone secretion are given below in the order of importance:

- Increase in $K^+$ ion concentration in the ECF
- Increased activity of renin-angiotensin system
- Decrease in Na ion concentration
- ACTH.

**Flow chart 8.6:** Regulation of aldosterone secretion




## Glucocorticoids

Cortisol is the chief glucocorticoid. Other glucocorticoids are corticosterone, cortisone. They are life protecting hormone.

## Actions

### *Metabolic Effects*

#### *Effects on Carbohydrate Metabolism*

Exerts anti-insulin effect by

a. Increases gluconeogenesis by:
   i. Enhancing breakdown of protein in extrahepatic cells.
   ii. Increasing synthesis of enzymes required for gluconeogenesis.
b. Inhibiting glucose uptake and utilization by peripheral cells.

#### *Effects on Protein Metabolism*

Decrease cellular protein and increase liver and plasma proteins by:

- Decreasing the protein synthesis by inhibiting amino acid transport into extrahepatic cells and inhibiting the formation of RNA
- Stimulates catabolism of proteins in all body cells except in liver
- Enhance amino acid transport into liver cells and also enhances liver enzymes required for protein synthesis.

#### *Effect on Fat Metabolism*

- Mobilizes fat from adipose tissue
- Enhance the oxidation of fatty acids in cells
- Increases the utilization of fat for energy.

#### *Effects on Electrolyte and Water Metabolism*

- Increase the retention of $Na^+$ and excretion of $K^+$ by the kidney
- Accelerates the excretion of water; adrenal insufficiency causes water retention.

### *Physiological Actions on Various Organs and Systems*

#### *Effects on Muscle*

Hypersecretion causes muscular weakness (due to protein catabolism).

#### *Effects on Bone*

- Increased bone resorption.
- Inhibition of bone formation.

#### *Effects on Vascular System*

Essential for constrictor action of adrenaline and noradrenaline. In adrenal insufficiency, blood vessels fail to respond to adrenaline and noradrenaline leading to vascular collapse.

#### *Effects on CNS*

Insufficiency causes personality changes like irritability and lack of concentration.

#### *Effects on Blood Cells and Lymphatic Organs*

- Decrease circulating eosinophils and basophils
- Increase number of neutrophils, platelets and RBCs
- Decrease circulating lymphocyte count and size of lymph nodes and thymus.

#### *Permissive Action*

Actions of some hormones are executed only in presence of glucocorticoids. For example:

- Calorigenic action of glucagon
- Pressor activity of catecholamine
- Bronchodilation of catecholamine
- Lipolytic effect of catecholamine.

#### *Effects in Resistance to Stress*

Exposure to any type of stress increases secretion of ACTH, which in turn increases the secretion of glucocorticoids. It enhance resistance by:

- Immediate release of amino acids → synthesis of new protein.
- FA released from cell → energy supply.

- Enhances vascular reactivity to catecholamine.
- Prevent the severity of other changes in body caused by stress.

### *Anti-inflammatory Effects*

Blocks the early stages of inflammation process before inflammation begins. If inflammation has already begun, it causes rapid resolution of inflammation and increased rapidity of healing. These effects are by:

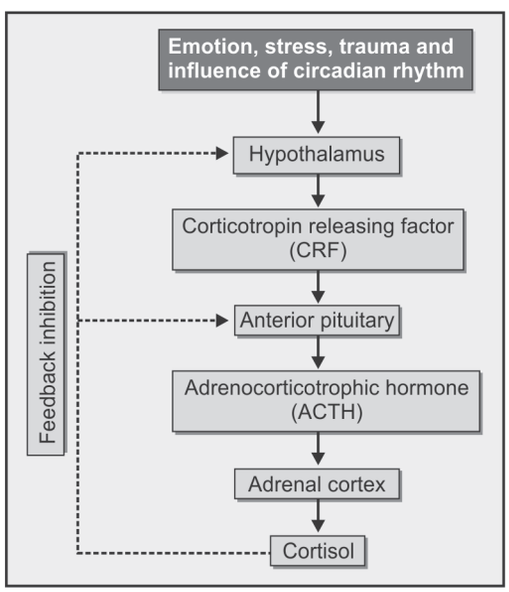
- Stabilizing lysosomal membranes so that proteolytic enzymes are not released
- Decreasing permeability of capillaries so that loss of plasma is prevented
- Decreasing both migration of WBCs into inflamed area and phagocytosis of damaged cell (by decreasing the release of PG and leukotrienes)
- Suppression of T-cells and other leukocytes so that there is decrease in reaction of tissue
- Reducing the release of IL-1 (so temperature is reduced, which in turn reduces vasodilation)
- Inhibit phospholipase $A_2 \rightarrow$ less arachidonic acid is formed.

### *Anti-allergic Effects*

Prevents various reactions in allergic condition.

## Regulation of Cortisol Secretion (Flow chart 8.7)

**Flow chart 8.7:** Regulation of cortisol secretion




### *Circadian Rhythm of Glucocorticoid Secretion*

The secretory rates of CRF, ACTH and cortisol are high in the early morning but low in the late evening. This effect results from a 24 hours cyclical alteration in the signals from the hypothalamus that cause cortisol secretion.

***Note***

*Stages of inflammation:*

a. Substances that activate inflammation process such as histamine, bradykinin, proteolytic enzymes, PG and leukotrienes are released from damaged cells.
b. Increase in blood flow in the inflamed area.
c. Leakage of plasma out of the capillaries into the damaged areas (due to increased capillary permeability) followed by clotting of tissue fluid causing nonpitting type of edema.
d. Infiltration of the area by leukocytes.
e. After days or weeks, ingrowth of fibros tissue that often help in healing process.

## ADRENAL SEX HORMONES

Most of the hormone are androgens. Estrogen and progesterone are also secreted in very small amounts.

### Applied Aspects

### *Hyperactivity of Adrenal Cortex*

***Cushing's syndrome***

Hypersecretion of glucocorticoids. Increase in glucocorticoid secretion is accompanied by increased secretion of adrenal androgens.

*Causes*

a. Adenomas of anterior pituitary that secrete ACTH.
b. Abnormal functions of hypothalamus that causes high levels of CRH.
c. Ectopic secretion of ACTH by a tumor elsewhere in the body.
d. Adenomas of adrenal cortex.

Cushing's syndrome due to anterior pituitary tumors are called ***Cushing's disease.***

*Signs and symptoms (Fig. 8.18)*

1. Disproportionate distribution of body fat producing following features:
   a. Moon face-due to fat accumulation on face.
   b. Buffalo hump-due to fat accumulation in upper back.
   c. Pot belly-due to fat accumulation in upper abdomen.
   d. Purple striae-reddish purple stripes on abdomen due to:

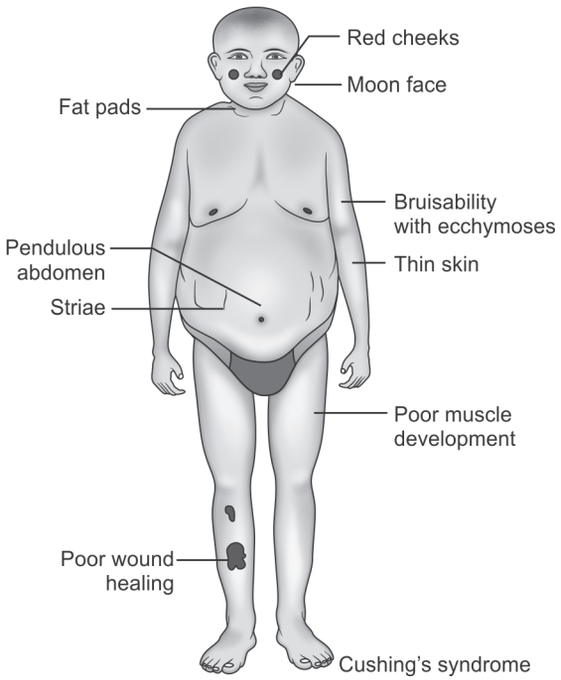



**Fig. 8.18:** Clinical features of Cushing's syndrome

- Stretching of abdominal wall by increased subcutaneous fat
- Deficiency of collagen fibers due to protein depletion (cause thinning of skin)
- Rupture of subdermal tissues due to stretching.

2. Thinning of extremities.
3. Muscle are poorly developed due to protein catabolism.
4. Facial hair growth and acne (effect of androgens).
5. Wounds heal poorly and minor injuries cause bruises and ecchymoses.
6. Hyperglycemia due to gluconeogenesis.
7. Bone resorption and osteoporosis.
8. Mental abnormalities.
9. Blackening of skin due to pigmentation of skin by MSH like activity of ACTH.
10. Hypertension due to increased retention of Na and water.

*Treatment*

1. Removal of adrenal tumor.
2. Tumors in the pituitary gland that over secrete ACTH can be surgically removed or destroyed by radiation.
3. Serotonin antagonist and GABA transaminase inhibitors (inhibit ACTH secretion).
4. Bilateral adrenalectomy if ACTH secretion cannot be decreased.

***Hyperaldosteronism***

Depending upon the causes, it is classified as:

*Primary hyperaldosteronism:* It is called *Conn's syndrome.* Renin secretion is depressed (due to feedback suppression). The most important effects are hypokalemia, slight increase in ECF and blood volume, hypertension. Due to hypokalemia muscles are paralyzed.

*Causes:* Adenoma of zona glomerulosa, adrenal hyperplasia, adrenal carcinoma.

*Treatment*

Surgical removal of tumor or adrenal tissue when hyperplasia is the cause.

*Secondary hyperaldosteronism:* Occurs due to extraadrenal causes.

*Causes:* Cirrhosis, heart failure and nephrosis.

***Adrenogenital Syndrome (Virilism)***

Tumor of zona reticularies of adrenal cortex cause intense musculinizing effects through out the body. In females they cause development of male secondary sexual characteristics such as beard, deeper voice, muscular body, enlargement of clitoris, baldness, etc. In prepubertal males it produces same characteristics as in females along with rapid development of male sex organs. In males the effects are usually masked due to effects produced by testosterone.

## Hypoactivity of Adrenal Cortex

*Addison's disease*

Due to insufficiency of mineralocorticoids as well as glucocorticoids.

*Cause:* Complication of TB, autoimmune inflammation of adrenal.

*Signs and symptoms*

Glucocorticoid deficiency produces weight loss, nausea, vomiting, weakness, tiredness, etc. Since glucocorticoids are essential for adaptation to stress, therefore in Addison's disease, exposure to any type of stress may be fatal. Mineralocorticoid deficiency produces hyponatremia, hyperkalemia, acidosis, decreased ECF volume with hypotension. They have small heart (hypotension decreases work of heart). Increased ACTH secretion occurs due to feedback mechanism and causes pigmentation of skin and mucous membrane (because of its MSH like activity).

*Treatment*

Administration of mineralocorticoids and glucocorticoids daily.

***Note***

*Addisonian crisis*

Great quantities of glucocorticoids are occasionally secreted in response to different types of physical or mental stress. In a person with Addison's disease, the output of glucocorticoids does not increase during stress. Yet whenever different types of trauma, disease, or other stresses, a person is likely to have an acute need for excessive amounts of glucocorticoids (often must be given 10 or more times the normal quantities of glucocorticoids to prevent death). This critical need for extra glucocorticoids and the associated severe debility in times of stress is called an addisonian crisis.

## Adrenal Medulla

Adrenal medulla constitutes central 20% of the gland. Epinephrine (adrenaline), norepinephrine (noradrenaline) and dopamine are secreted by adrenal medulla. These hormones are called catecholamines. It secretes epinephrine and norepinephrine in response to sympathetic stimulation. Adrenal medulla is referred as a modified sympathetic ganglion.

### *Mechanism of Release of Catecholamines*

Stimulation of preganglionic splanchnic fibers → release of ACh → stimulate medullary chromaffin cells, by promoting inward movement of $Ca^{2+}$ → secretion of epinephrine and NE into blood by exocytosis.

### *Adrenergic Receptors*

Adrenergic receptors are divided into α and β types: Epinephrine and norepinephrine both act on α and β receptors, with norepinephrine having greater affinity for α adrenergic receptors and epinephrine for β adrenergic receptors.

***Alpha adrenergic receptors***

They are sensitive to both epinephrine and NE. They are mainly excitatory, except inhibition of intestinal motility. They are of two kinds $\alpha_1$ and $\alpha_2$.

α-mainly excitatory (receptor located on postsynaptic membranes).

$\alpha_2$-are inhibitory (located on presynaptic nerve terminals of cholinergic and adrenergic nerves).

***Beta adrenergic receptors***

They respond to epinephrine and in general are relatively insensitive to NE. They are mainly inhibitory except excitation of myocardium. They are of three types: $\beta_1$ $\beta_2$ and $\beta_3$.

$\beta_1$: Its activation produce tachycardia and increased myocardial contractility (receptors located on cardiac muscle).

$\beta_2$: Associated with relaxation of smooth muscle.

In humans $\beta_1$-adrenergic mechanism predominates.

## Actions of Epinephrine and Norepinephrine

### *On CVS*

***Heart***

Epinephrine and norepinephrine are powerful cardiac stimulants. They act mainly by interacting with $\beta_1$ receptors and produces various effects as follows:

1. Increase in heart rate (positive chronotropic)
2. Increased myocardial contractility (positive inotropic)
3. Increase in conduction velocity (positive dromotropic)
4. Increase in cardiac output
5. Increase in automaticity
6. Increase in cardiac work and its oxygen requirement
7. Increase in excitability and tendency to cause cardiac arrhythmias.

***Blood vessels and blood pressure***

Blood vessels of the skin and mucous membranes predominantly contain $\alpha_1$ receptors, hence are constricted by epinephrine and norepinephrine. Both epinephrine and norepinephrine also constricts renal, mesenteric, pulmonary and splanchnic vessels. But epinephrine dilates the blood vessels of skeletal muscle and coronary vessels; via $\beta_2$ (norepinephrine does not produce this action as it has no $\beta_2$ action).

Intravenous administration of adrenaline in moderate doses produces typical biphasic effect.

There is an initial rise in BP due to $\alpha_1$ (blood vessels) and $\beta_1$ (heart) actions, followed by a fall in BP due to $\beta_2$ mediated vasodilatation in skeletal muscle. Administration of adrenaline after $\alpha_1$ blocker produces only a fall in BP ($\beta_2$). This is referred to as ***Dales vasomotor reversal.***

### *Carbohydrate Metabolism*

Catecholamines increase blood sugar (via β receptors increases glycogenolysis by increasing phosphorylase activity and via α receptors increases glycogenolysis by increasing intracellular $Ca^{2+}$).

Catecholamines via β receptors increases the secretion of insulin and glucagon, but inhibit the secretion of these hormones via α receptors.

### *Lipid Metabolism*

Catecholamines by β receptors stimulates hormone sensitive lipase, breaks down stored triglycerides to free FFA and glycerol. In liver, excess fatty acids are converted in to ketone bodies.

### On BMR

Catecholamines increase BMR (calorigenic action) in the presence of $T_4$ and adrenal cortex. Epinephrine shows more calorigenic action than norepinephrine.

### On CNS

Catecholamines show stimulatory effect on CNS and produce anxiety, hyperventilation and coarse tremors of extremities. It inhibits the release of ADH.

### On Eyes

Receptors cause contraction of radial muscles producing mydriasis. β receptors cause relaxation on ciliary muscles and increases tone of eye muscles.

### On GIT

Epinephrine decreases tone and mobility (via β receptors). It causes sphincteric constriction (via β receptors), thus produces constipation.

### On Urinary Bladder

Epinephrine via β receptors causes relaxation of detruser muscle and via α receptors cause contraction of trigone and shinctors; thus produces retention of urine.

### On Skin

Catecholamines (via α receptors) produce piloerection of hair.

### On Sweat Glands

Produce localized sweating on palm and sole called adrenergic sweating.

### On Skeletal Muscles

Improves skeletal muscle blood supply (via $\beta_2$) and increases force of contraction.

### On Bronchial Muscles

Epinephrine relaxes bronchial musculature producing bronchodilatation (via $\beta_2$ receptors).

### On Blood

*Epinephrine:*

- Decreases clotting time due to increase in activity of factor five.
- Increases RBC count, PCV, Hb concentration.
- Increases plasma protein concentration.
- Cause increase in neutrophils.

### Miscellaneous

Initially cause hyperkalemia followed by hypokalemia due to increased $K^+$ influx into skeletal muscle.

Summary of the different hormones in human body (Table 8.6).

***Actions of Dopamine***

1. It produces generalized vasoconstriction by releasing NE.
2. It increases contractility of heart (via β receptors).

**Table 8.6: Hormones showing type, excess, deficiency and effects**

| *Hormone* | *Source* | *Type* | *Excess* | *Deficiency* | *Effects* |
|---|---|---|---|---|---|
| Insulin | Beta cells of pancreas | Small protein or polypeptide | Hypoglycemia | Diabetes mellitus | a. Glycogen synthesis in liver and muscle<br>b. Lipogenesis in adipose tissue |
| Glucagon | Alpha cells of pancreas | Polypeptide | Hyperglycemia | Hypoglycemia | Glycogen breakdown, glyconeogenesis |
| Parathormone (PTH) | Chief cells, parathyroid | Polypeptide | Hypercalcemia, Hypercalcuria, Phosphate bone | Tetany, abnormal conduction, calcification | Increased vitamin D activity, increase bone reabsorption |
| Calcitonin | Parafollicular cells of thyroid | Polypeptide | No known effects | No known effects | Decreased serum calcium and decreased bone reabsorption |
| ADH | Posterior pituitary | Peptide | Hypertension, Hyponatremia, SIADH | Diabetes insipidus | Increased reabsorption of water, increased permeability of the collecting ducts |
| Oxytocin | Posterior pituitary | Peptide | — | — | Uterine contraction and milk ejection reflex |
| GH | Acidophils of anterior pituitary | Polypeptide | Acromegaly (adults) | Dwarfism | Increased protein synthesis, somatomedins, lipolysis, and calcium absorption |

*Contd...*

*Contd...*

| | | | | | |
|---|---|---|---|---|---|
| ACTH | Basophils of anterior pituitary | Protein | Cushing's syndrome | Secondary Addison's disease | Increase cortisol and androgen |
| Cortisol | Adrenal zona fasciculata | Steroid | Cushing's syndrome | Stress intolerance, Addison's disease | Increased protein and fat catabolism and increased glycogenesis and increased gluconeogenesis |
| Aldosterone | Adrenal zona glomerulosa | Steroid | Conn's syndrome | Hypotension | $Na^+$ retention in the kidneys |
| Adrenal androgens | Adrenal zona reticularis | Steroid | Virilism | Poor secondary sexual character development, hypogonadism | Contribute to the secondary sexual characters |

3. Increases in SBP and does not affect DBP.
4. On kidneys it produces natriuresis (by inhibiting $Na^+$- $K^+$ ATPase) and vasodilation.

Because of these actions, dopamine is usefuel in the treatment of traumatic and cardiogenic shock.

## Regulation of Catecholamine Secretion

1. Secretion is entirely controlled by splanchnic nerves. These fibers are preganglionic sympathetic fibers and release ACh as their transmitter. Splanchnic nerve activities are controlled by centers in the reticular formation in the medulla and hypothalamus. Adrenal medullary activation occurs as a part of sympathetic response to any emergency situation like fear, anxiety, pain, trauma, hemorrhage, hypoxia.
2. Secretion of glucocorticoids promotes conversion of NE to epinephrine.
3. Hypoglycemia is a potent stimulus to catecholamine secretion.

### *Applied Aspect*

***Hyposecretion of catecholamines***

It usully produces no clinical signs and symptoms because catecholamine production from sympathetic nerve endings appears to satisfy the normal biological requirements.

***Hypersecretion of catecholamines***

Seen in tumors of chromaffin tissue called pheochromocytoma.

*Features*

a. Sustained hypertension, headaches
b. Sweating, anxiety
c. Palpitations and chest pain
d. Increased body temperature, hyperglycemia, glycosurea and increase in BMR
e. Increased in urinary excretion of catecholamines, metanephrines and VMA.

Chapter

# 9 Reproductive System

Reproductive system is unique because it ensures the continuation of the species. The main difference from other system like cardiovascular system, respiratory system is that other system function for the survival of the individual but function of reproductive system is not necessary for the survival of the individual.

The organs of reproductive system can be divided into two portions:

1. Internal reproductive organs
2. External genital organs.

## ABNORMAL SEXUAL DIFFERENTIATION

### Chromosomal Abnormalities

***Turner's syndrome*** (44-XO) (gonadal dysgenesis or ovarian agenesis)

1. Here gonads are rudimentary and absent.
2. Female external and internal genitalia.
3. Stature is short and puberty changes do not occur.

***Klinefelter's syndrome*** (44-XXY)

1. Genitalia of a normal male.
2. Testosterone secretion at puberty is normal but the seminiferous tubule are absent.
3. Mental retardation.

***Down's Syndrome***

Autosomal dysjunction of chromosome 21 produce trisomy 21(mongolism). Symptoms are broad face, epicanthus, hand with single transverse crease and consistent infections that leads to death.

### Hormonal Abnormalities

***Female pseudohermaphroditism:*** Male genetic development occur in genetic female exposed to androgens from other source during the 8th to 13th week of gestation.

***Male pseudohermaphroditism:*** Development of female external genitalia in genetic males.

#### *Causes*

1. Embryonic testes are defective.
2. Androgen resistance.

***Note***

*Barr bodies/sex chromatin*

A Barr body is highly coiled, genetically inactive X chromosome seen in the female (where other X chromosome is active). It can be detected in sex chromosome from buccal cells, vaginal mucous cells and spinous epidermal cells.

No. of barr bodies = No. of X Chromosome–1

## MALE REPRODUCTIVE SYSTEM

The reproductive functions of male can be divided into three major subdivisions which includes:

1. Spermatogenesis: Formation of sperm.
2. Performance of male sexual act.
3. Regulation of male reproductive functions by various hormones.

### Blood-Testis Barrier

Tight junctions between adjacent Sertoli cells near the basal lamina form a blood-testis barrier (Fig. 9.1). These creates a specialized, immunological safe microenvironment for developing sperm. Steroids can penetrate this barrier with ease. Mature germ cell pass through this barrier as they move to lumen through the formation and breakdown of these junctions.

#### *Functions*

1. Prevents large molecules from passing from the interstitial tissue and the part of tubule near the basal lamina.
2. Maintenance of composition of fluid in the lumen of seminiferous tubule (little protein, glucose but rich in androgens, estrogens, $K^+$, inositol and glutamic and aspartic acids) depends on blood-testis barrier (BTB).

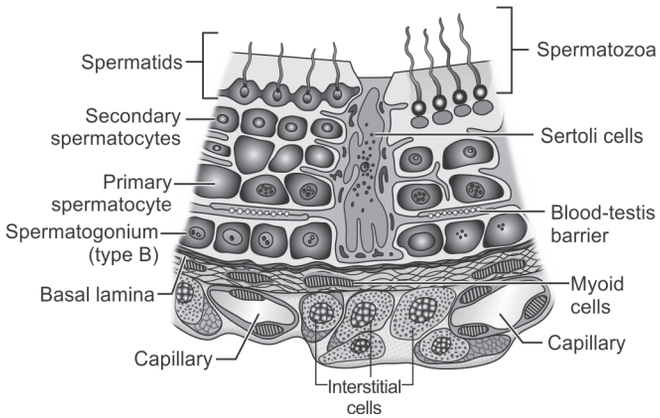



**Fig. 9.1:** Stages in the development of sperm from spermatogonia

3. Protect the germ cell from blood borne noxious agent.
4. Establish an osmotic gradient that facilitates movement of fluid into the tubular lumen.

## Spermatogenesis (Fig. 9.2)

The process by which new spermatozoa are created from spermatogonia is called spermatogenesis (Fig. 9.2). In human it takes an average of 74 days. The estimated number of spermatids formed from single spermatogonia is 512.

### *Phases of Spermatogenesis*

1. *Phase of mitotic division of spermatogonia:* Spermatogonia divides mitotically 7 times to form 128 spermatogonia
2. *Phase of formation of primary spermatocyte by maturation:* 128 spermatogonia undergoes maturation to form 128 primary spermatocytes. They are large cell with diploid number of chromosome.
3. *Phase of formation of secondary spermatocyte by 1st meiotic division:* During 1st meiotic (reductional division), 128 primary spermatocyte is converted into 256 secondary spermatocytes with haploid number of chromosomes.
4. *Phase of formation of spermatid:* Each secondary spermatocyte undergoes 2nd meiotic division(similar to mitotis) to give rise to 2 spermatids. Thus a total of 512 spermatids is formed having haploid number of chromosomes.
5. *Phase of formation of spermatozoan:* Spermatids do not divide further but undergoes morphological changes to form sperms or spermatozoa.

### *Spermiogenesis*

Conversion of spermatids to sperms. This process takes place within the cytoplasm of the Sertoli cells and depends on the presence of androgen.

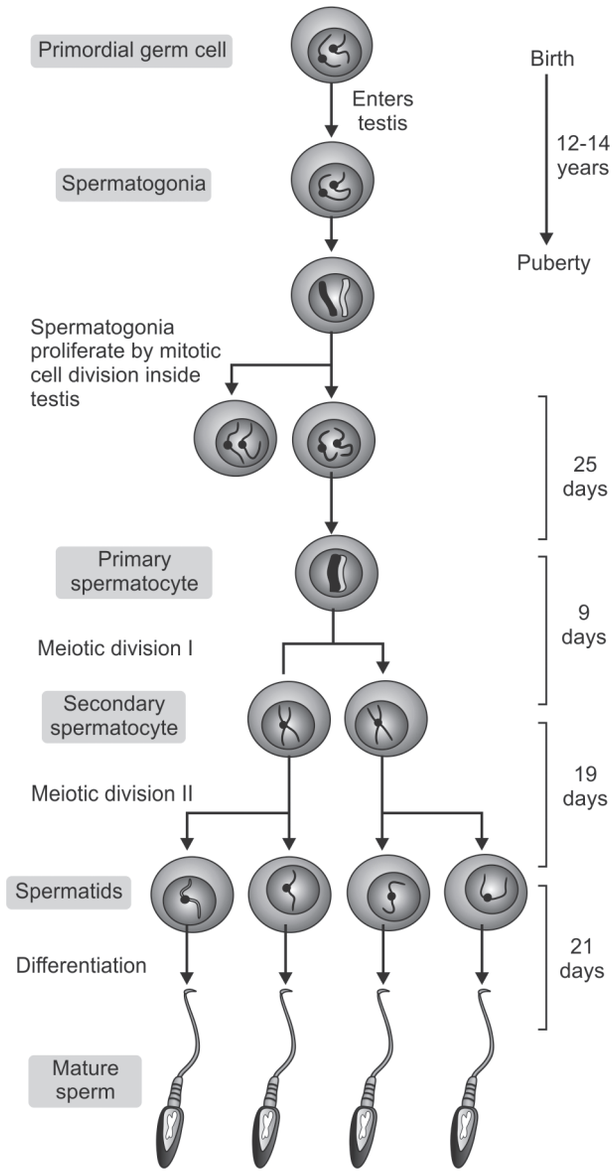



**Fig. 9.2:** Cell division during spermatogenesis

### *Factors Influencing Spermatogenesis (Table 9.1)*

1. Testosterone in high concentration is essential for growth and division of testicular germinal cells, which is the first stage in forming sperm.
2. *LH:* It is secreted by anterior pituitary gland helps by stimulating the Leydig cells to produce testosterone which is essential for spermatogenesis.
3. *FSH:* It is the key gonadotropin for spermatogenesis. It is secreted by anterior pituitary. It help in the conversion of spermatid to sperm by stimulating the Sertoli cells to produce some local factors.

4. *Growth hormone:* It is necessary for controlling the background metabolic functions of the testis. It specially promotes early division of spermatogonia themselves.
5. *Estrogen:* It is formed from testosterone by the Sertoli cells when they are stimulated by FSH. They are also essential for spermiogenesis.
6. Sertoli cells secrete androgen binding factors (ABP), inhibin and MIS (mullerian inhibiting substance). They do not synthesize androgens, but contain aromatase, the enzyme responsible for conversion of androgens to estrogens (promotes spermatogenesis)
   - ABP helps to maintain a high stable supply of androgens in the tubular fluid.
   - Inhibin inhibits FSH secretion.
   - MIS causes regression of the mullerian ducts in males during fetal life.
7. Seminal fluid with fructose content help in maturation of sperms.
8. Vitamin E, C and several members of B complex are required for normal spermatogenesis.
9. *General factors:*
   a. Temperature—optimum 32°C.
   b. Radiation—degenerates seminiferous tubule.
   c. Vasectomy.
   d. Age.

## Spermatozoan (The sperm)

The sperm (Fig. 9.3) about 60 μm long is a long single cell which has a 'head' and a 'tail'. The head is the nucleus of the cell containing the DNA material. Head is capped by 'acrosome' made up of mucopolysaccharide and acid phosphatase enzyme. The acrosome is covered by a membrane called acrosomal membrane. In the fallopian tube the acrosomal membrane is removed so that the acrosomal enzymes are exposed. These enzymes are digestive in nature that facilitate their activity by enabling the sperm to penetrate the ovum to cause fertilization. The removal of acrosomal membrane is called *sperm capacitance*. The highly elongated structure of the sperm enable it to swim forward in the female genital tract at a speed of 3 mm/min. Sperm reach the uterine tube 30–60 min after copulation.

**Table 9.1: Factors influencing spermatogenesis**

| *Stage of spermatogenesis* | *Hormone necessary* |
|---|---|
| 1. Stage of proliferation | FSH<br>Growth hormone |
| 2. Stage of growth | Testosterone<br>Growth hormone |
| 3. Stage of maturation | Testosterone<br>Growth hormone |
| 4. Stage of transformation | Testosterone<br>Estrogen |

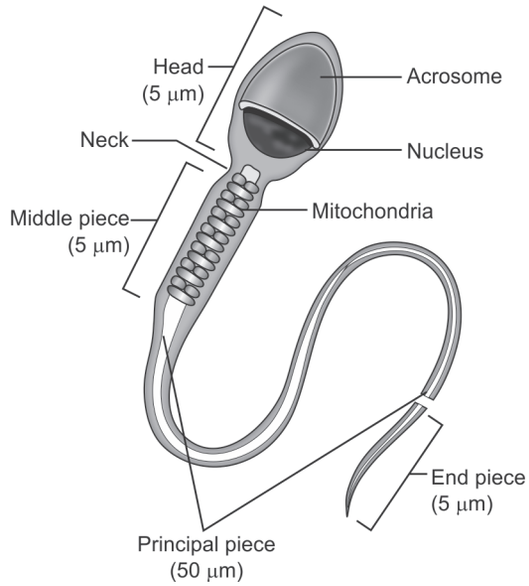



**Fig. 9.3:** Structure of human spermatozoan

## Semen

The fluid that is ejaculated at the time of orgasm. It contains sperms and the secretion of the seminal vesicle, prostate, Cowper's glands and urethral gland.

### *Composition*

| | |
|---|---|
| Fructose<br>Phosphorylcholine<br>Ergothioneine<br>Ascorbic acid<br>Flavins<br>Prostaglandins | From seminal vesicles (contributes 60% of the total volume) |
| Spermine<br>Citric acid<br>Cholesterol<br>Phospholipids<br>Fibrolysin<br>Fibrinogenase<br>Zinc<br>Acid phosphatase | From prostate (contributes 20% of the total volume) |
| Phosphate<br>Bicarbonate | Buffers |
| Hyaluronidase | |

- Specific gravity: 1.028
- pH: 7.35-7.50

- Average volume per ejaculate is 2.5–3.5 ml.
- *Sperm count:* 80–120 million/ml with fewer than 20% abnormal forms.

Seminal vesicles contribute to 60% of total volume of semen and prostate 20%.

***Note:***

a. Clotting enzyme from the prostatic fluid causes the fibrinogen of the seminal vesicle fluid to form a weak fibrin coagulum that hold the semen in the deeper regions of the vagina. The coagulum then dissolves during the next 15 to 30 minutes because of lysis by fibrinolysin formed from the prostatic profibrinolysin.
b. Nutrition to sperms is mainly provided by fructose.
c. Fertilization is enhanced by the prostaglandin present in seminal vesicle.

## Sertoli Cells

Sertoli cells are large, complex glycogen containing cells that stretch from the basal lamina of the tubule to the lumen.

### *Functions*

1. Sertoli cell (Fig. 9.1) secrete androgen binding factors (ABP), inhibin, activin, MIS (mullerian inhibiting substance).
2. They have receptors for FSH and testosterone. After combining with FSH, Sertoli cells stimulates the first half of spermatogenesis. Subsequently testosterone-Sertoli cells binding causes development of last half of spermatogenesis
3. Sertoli cells are components of blood-testis barrier.
4. They produce estradiol from testosterone.
5. They provide nutrition to the germ cells.
6. Converts testosterone into 5 alpha dihydrotestosterone.
7. Sertoli cells and epithelium of the epididymis secrete a special nutrient fluid that is ejaculated along with the sperm.

## Testosterone

Testosterone, the principal hormone of the testis is a C19 steroid with an OH group in the 17th position.

### *Synthesis*

It is produced from cholesterol in the Leydig cells and is also formed from androstenedione secreted by the adrenal cortex.

### *Secretion*

The testosterone secretion rate is 4-9 mg/day in normal adult males. Small amount of testosterone are also secreted in females. The secretion is under the control of LH.

### *Transport*

Ninety-eight percent of testosterone in plasma is bound to plasma protein. Sixty-five percent is bound to β globulin called gonadal steroid binding globulin or sex-binding globulin and thirty-three percent bound to albumin.

### *Mechanism of Action of Testosterone*

Testosterone has several target cells.

In the target cell of prostate, seminal vesicles, epididymis, penis and skin testosterone crosses the cell membrane and is converted to dihydrotestosterone (DHT) by an enzyme 5 alpha reductase. In these cells DHT is the final hormone (testosterone in these cells is merely a prohormone).

In the hypothalamus, muscle mass and anterior pituitary, testosterone is the final active agent as no DHT is formed.

The androgen (either DHT or testosterone itself, depending upon the tissue) combines with its receptor and the receptor losses its heat shock protein. Now the androgen receptor complex moves to the target chromosome and various proteins are synthesized and acts on target cells.

### *Actions*

#### *On the Sex Organs, Secondary Sex Characteristics and Sex Behavior*

*In the fetus:*

i. Testosterone is formed in the 7th week of intrauterine life. It is responsible for the sex differentiation of male fetus.
ii. Exposure of some part of brain to testosterone in fetal life, determines the sexual behavior in adult life.

*In the puberty:*

i. Testosterone causes growth of the external genitalia and accessory sex organs in pubertal stage.
ii. It also causes the appearance of secondary sexual characters in boys, i.e. beard, moustache, hairs (on chest and abdomen, as well as axillary and pubic hairs), linear growth, muscular growth, deepening of voice and male psyche.

*In adults:*

i. Maintenance of the accessory sex organs.
ii. Development of sebaceous glands and acne vulgaris.
iii. Necessary for spermatogenesis and sperm motility.

#### *On Metabolism*

Anabolic effects.

***Proteins***

i. Increase the synthesis and decrease the breakdown of protein, leading to an increase in the rate of growth.

***Bone***

ii. Cause epiphysis to fuse with the long bone.
iii. Increase growth.
iv. Favors calcium deposition.

***Muscle***

v. Promotes growth of muscle and muscle mass get doubled.

*On Electrolytes*

Retention of Na, K, Ca, $H_2O$, $PO_4$, $SO_4$.

***Note***

Androgenic drugs like nandrolone are used as anabolic steroids. These agents are not easily converted into DHT. So they have minimal action on sex organs, but they act on muscles to increase muscle bulk and strength. Unscrupulous sports persons misuse this drug to increase their muscular efficiency, this is called **doping.**

## Regulation of Secretion (Fig. 9.4)

Secretion of testosterone from Leydig cells during fetal stage is caused by hCG from placenta. After birth, its secretion is absent till adolescence. During adolescence it starts again under the influence of GnRH.

### *Applied Aspects*

1. *Cryptorchidism:* The testis develops in the abdominal cavity and migrate to scrotum during the fetal development in the 7th week. The failure of descent of testis cause the testis to remain in abdominal cavity or inguinal canal leading to sterility called cryptorchidism.
2. *Testicular feminizing syndrome:* Due to congenital lack of androgen receptors. Testis and testosterone secretion is normal but testosterone cannot act due to lack of receptors. So, there is development of female genitalia and there is also enlargement of breast.

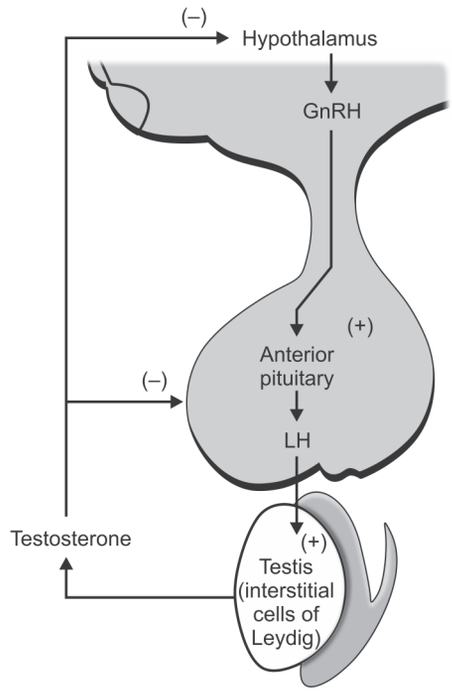



**Fig. 9.4:** Regulation of testosterone secretion

## Test for Male Infertility

1. *Semen analysis:* Here the masturbation sample of semen is obtained and examined for sperm morphology, motility and count. Normally, the volume of an ejaculate is 2-6 ml. If analyzed within an hour of ejaculation, more than 60% of the sperm should be normal in morphology, more than 60% of the sperm should be motile, and the sperm number in the ejaculate should be more than 60 million.
2. At testicular level, function may be assessed by measuring testosterone levels—free and protein bound.
3. *Sex hormone binding globulin (SHBG)* may be measured in abnormal testosterone levels.

# FEMALE REPRODUCTIVE SYSTEM

During the reproductive years of female, between 13–46 years of age, 400–500 primordial follicles develop enough to expel their ova. One ova is expelled each month and the remaining degenerate at the end of reproductive life. At menopause only few primordial follicle remains and even this degenerate. The most prominent part of this reproductive cycle is menstrual cycle.

## Menstrual Cycle

Menstrual cycle is defined as periodic regular rhythmic changes that occur in female reproductive organs characterized by periodic vaginal bleeding associated with endometrial shedding. The average duration of the cycle is 28 days but the normal range is quite wide (20-45 days). The days are numbered in terms of menstrual bleeding, day one of the cycle being the 1st day of menstrual bleeding. Ovulation takes place at about 14th day of the cycle. If the cycle length is shorter or longer than 28 days, the variation is generally in the period before ovulation. That is, the interval between ovulation and end of the cycle is essentially constant at 14 days irrespective of the cycle length. It consists of four cycles:

1. Ovarian cycle
2. Uterine cycle
3. Cervical cycle
4. Vaginal cycle.

## Ovarian Cycle

Depends on gonadotropin secretion which begins at puberty (8-13 yrs). During 8th year, large quantity of GnRH is secreted which initiates the monthly sexual cycle. GnRH shows increase or decrease in secretion which is responsible for the cyclical changes in the ovary. There are three phases in ovarian cycle:

a. Follicular phase/estrogenic
b. Ovulation
c. Luteal phase/progestational phase.

a. *Follicular phase:* During fetal development, ovaries contain seven million primordial follicles. However, many undergo atresia (involution) before birth and others are lost after birth. At the time of birth, there are two million ova, 50% of these are atretic. The normal ova undergo the 1st part of the first meiotic division and enter a stage of arrest in the prophase which persists until adulthood. Atresia continues during development, and the number of ova in the both of the ovaries at puberty is less than 300,000. Only one of those ova per cycle (500 in a normal reproductive life) normally reaches maturity; the remaining degenerates. Just before ovulation the first meiotic division is completed. One of the daughter cells, the secondary oocyte immediately begins the 2nd meiotic division, but this division stops at metaphase and is completed only when a sperm penetrates the oocyte.

   At the start of each cycle, several of these follicles enlarges, one of follicle in one ovary start to grow at 6th day and become dominant follicle and other regress forming atretic follicle (Fig. 9.5). Follicle secretes estrogen for final maturation. The cells of the theca interna of follicle are the primary source of circulating estrogen.

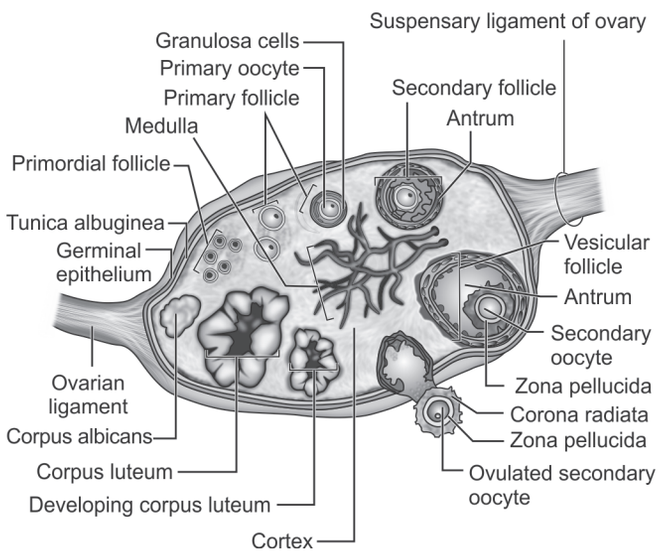



**Fig. 9.5:** Stages of follicular growth in ovary

b. *Ovulation:* The rupture of graffian follicle releases 2° oocyte occurs on 14th day by LH hormone. This process is called ovulation. The 2° oocyte moves towards surface of ovary and protrudes through the outer layer. The protruding outer wall of follicle swells rapidly and a small area in the center of the follicular capsule, called the stigma protrudes like a nipple. In another 30 minutes the fluid begins to ooze from the follicle through the stigma. And about 2 minutes later the stigma ruptures widely allowing more viscous fluid, which has occupied the central portion of the follicle to evaginate outward. This viscous fluid contain ovum surrounded by a mass of several thousand small granulosa cells called corona radiata.

   The follicle that ruptures at the time of ovulation is promptly filled with blood and is called as corpus hemorrhagicum. The granulosa and theca cells of the follicle lining promptly begins to proliferate, and the clotted blood is rapidly replaced by yellowish, lipid-rich luteal cells, forming the corpus luteum. This initiates the luteal phase of the menstrual cycle.

***Mechanism of ovulation***

Follicle secrete estrogen which stimulate hypothalamus and pituitary to release LH (6-10 times called LH surge) and FSH (2 folds). LH and FSH is required for the final maturation of follicle. Estrogen in high dose results in positive feedback effect where as in moderate dose negative feedback effect is produced.

c. *Luteal phase:* Granulosa and theca cells of follicle begin to proliferate, and the clotted blood is replaced by yellowish, lipid rich luteal cells, forming corpus luteum. Luteal cells secrete estrogens and progesterone.
   - If fertilization persists LH maintains pregnancy.
   - No pregnancy corpus luteum degenerates to form corpus albicans.

## Uterine Cycle

Changes occurring in endometrium to prepare it to receive the fertilized ovum, then for implantation constitute the uterine cycle (Fig. 9.6).

### Phases

a. Proliferative phase (5–14 days)-Estrogen.
b. Secretory phase (15–28 days)-Progesterone and estrogen
c. Menstrual phase (1–4 days) can prolong up to 8 days.

a. *Proliferative phase/Estrogenic phase:* It is the period between menstruation and ovulation and it represents the restoration of the epithelium from the preceding menstruation. It corresponds to follicular phase of ovarian cycle. The

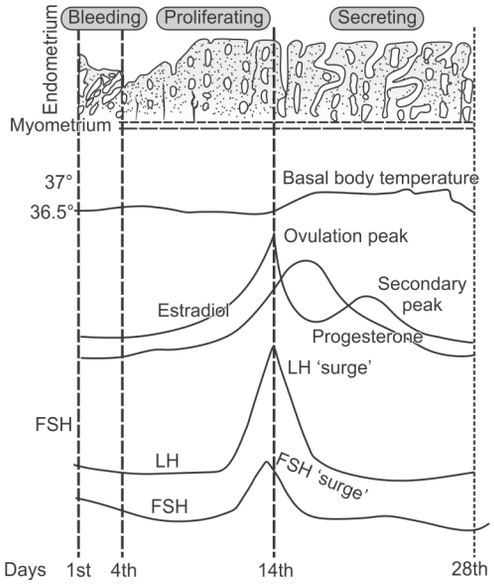



**Fig. 9.6:** Uterine cycle

estrogen secreted from the developing ovarian follicles under the influence of FSH is responsible for this phase.

Changes occurring during proliferation phase:

- Proliferation of endometrial tissue from 2-4.5 mm in 5 to 14 days of menstrual cycle. As the thickness increases, the uterine gland is drawn out so that they lengthen.
- Proliferation of glands and blood vessels.
- Restoration of epithelium of the endometrium within 7 days.

b. *Secretory/Progestational phase:* It is the period between ovulation and next menstruation. It corresponds to luteal phase of ovarian cycle and so the hormone responsible is progesterone and estrogen. Here endometrial thickness increase from 6 to 8 mm. Endometrial gland become tortuous and begins to secrete.

Proliferation of cytoplasm, deposition of lipids and glycogen is seen. There is increased vascularity of endometrium which is proportional to activity of gland. The spiral arteries become more tortuous. Arteriovenous anastomosis and anastomosis between veins occur.

c. *Menstrual phase:* Corpus luteum regresses, so that the hormone support is withdrawn and thus endometrium becomes thin. The spiral arteries become more tortuous and they undergo vasospasm by PGF2α. This leads to ischemia and necrosis of tissue and the walls rupture. Sequential shedding occurs layer by layer in 3–5 days.

Menstrual blood is predominantly arterial with only 25% of blood being venous in origin. Menstrual blood consists of shed endometrium, secretion of glands and blood from spinal artery. The amount of blood lost may range normally from slight spotting to 80 ml, average amount of blood lose is 30 ml. The clotting of blood is resolved by fibrolysin system.

## Cervical Cycle

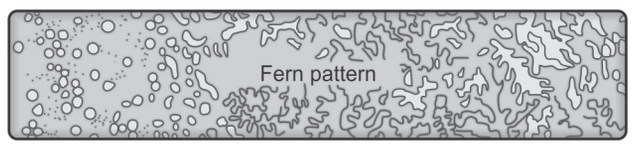
Though cervix is continuous with uterus it shows a separate cycle. Here no shedding of mucosa occurs, but mucous show changes due to action of hormone.

### Changes in Cervical Cycle (Fig. 9.9)

a. *During proliferative phase:* Cervical secretion is thin alkaline due to estrogen; this is to enable sperm survival and transportation.

b. *During ovulatary phase:* Cervical secretion is thinnest, increase elasticity or spinnbarkeit, therefore can be stretched to 8–12 cm. More ever it dries in an arborizing fern-like pattern when a thin layer is spread on a slide (Fig. 9.7).

c. *Secretory phase:* Cervical secretion is thick, tenacious and cellular (Fig. 9.8).




Normal cycle, 14th day estrogen

**Fig. 9.7:** Fern pattern in proliferative phase

Midluteal phase, normal cycle (progesterone)

**Fig. 9.8:** Cervical mucus thick and cellular in secretory phase

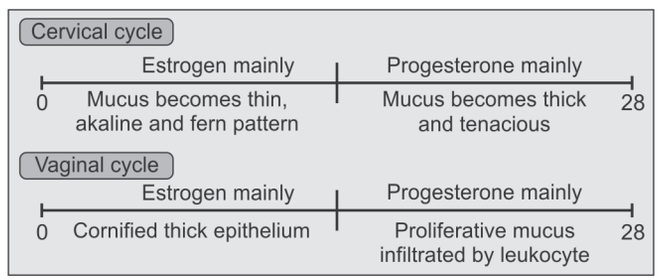



**Fig. 9.9:** Cervical and vaginal cycle

### *Vaginal Cycle*

During proliferative phase under the influence of estrogen, vaginal epithelium becomes cornified and can be identified as vaginal smear. During secretory phase under influence of progesterone, a thick mucus is secreted and the epithelium proliferates and become infiltrated with leukocytes.

## Hormonal Control of the Menstrual Cycle (Fig. 9.10)

The regulation is based on the hypothalamo-pitutary-gonadal axis and feedback actions of estrogen and progesterone(1). GnRH is secreted in episodic bursts to stimulate secretion of FSH and LH from anterior pituitary which then act on ovary(2).

At the start of cycle there are very low levels of estrogen and progesterone, therefore minimum feedback inhibition. So GnRH secretion increases and there is increased FSH and LH.

Follicle stimulating hormone now causes development of the follicle and LH receptors (LH does not act on follicle). The LH acts on the theca cells which produces androgens. These androgens are subsequentially converted into estrogen in granulosa cell. Estrogen at this stage causes feedback inhibition of LH, FSH, and GnRH(3), but more on FSH, which is further helped by inhibin acting at the level of pituitary. Towards the middle of the cycle, due to further development of the follicle, estrogen secretion increases further(4). This persistent high level of estrogen increases responsiveness of the pituitary gonadotropins to GnRH. There is also increased secretion of GnRH. All these result in positive feedback action and there is rapid rise of LH secretion(5), called LH surge which is thought to cause ovulation(6). The estrogen level increases 25 hours before and the LH surge occurs about 9 hours before the ovulation, i.e. after estrogen peak. At this time there is also FSH peak due to both estrogen and progesterone.

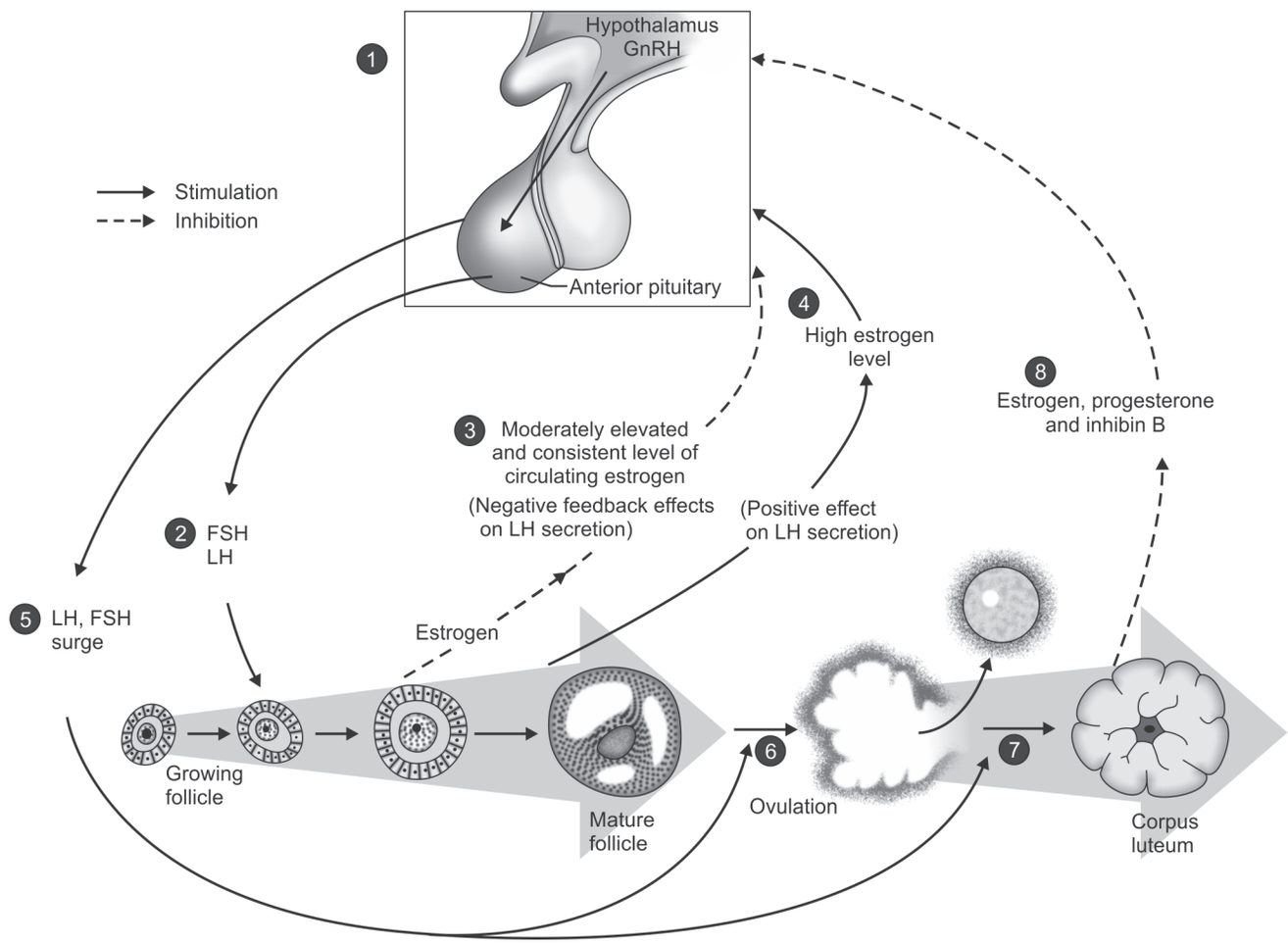



**Fig. 9.10:** Feedback interaction involved in the control of ovarian activity

After ovulation corpus luteum(7) is formed which secretes both estrogen and progesterone(8), so there is feedback inhibition on both LH and FSH. At this stage positive feedback action by estrogen cannot occur due to inhibitory effects of high levels of progesterone.

Towards the end of cycle, estrogen progesterone level become very much low again. This removes the feedback inhibition, so there is rise of GnRH pulses as well as increased output of FSH and LH to start the cycle again.

## *Ovarian Hormones*

### Estrogen

All estrogens are steroid hormones with cholesterol as the main precursor.

#### *Source*

a. Theca interna of the graffian follicle (major source)
b. Granulosa cells of the graffian follicle
c. Placenta
d. Adrenal cortex-(in small amounts)
e. Testis-(in small amounts).

#### *Secretion*

There are two peaks of secretion. One just before ovulation and one during midluteal phase.

#### *Actions*

1. *Effects on female genitalia:* It facilitates growth of ovarian follicle and increases the motility of uterine tubes. Their role in cyclic changes in endometrium, cervix and vagina is discussed above. They increase the uterine blood flow and have important effect on the smooth muscle of uterus. Estrogen increases the uterine muscle and its content of contractile proteins and muscle becomes more excitable. Under the influence of estrogens, the muscle becomes more active and excitable.
2. *Effects on endocrine organs:* They inhibit the secretion of both LH and FSH (negative feedback), but also produce LH surge(positive feedback). They increase the angiotensinogen and thyroid-binding globulin level of blood. High doses of estrogen prevent conception (morning after-pill by preventing implantation).
3. *Effects on CNS:* Estrogen is responsible for the female type of behavior and also it increases the libido in females. It also increases the proliferation of dendrites on neurons and the number of synaptic knobs.
4. *Effects on CVS:* Estrogens have a significant plasma cholesterol lowering action and they rapidly produce vasodilatation by increasing the local production of nitric oxide (NO). These action inhibit atherogenesis and contribute to low incidence of myocardial infarction (MI). However large doses of orally active estrogen promotes thrombosis, because they reach the liver in high concentration and alter hepatic production of clotting factors.
5. *Effect on female secondary sex characteristics:* The body changes that develop in girls at puberty in addition to enlargement of breast, uterus and vagina are due to estrogen, which is called the 'feminizing hormones'. Women have narrow shoulders and broad hips, thighs that converge and arms that diverge (carrying angle). This body configuration, plus the female distribution of fat in breast and buttocks is due to estrogen.
6. *Effect on water and electrolyte metabolism:* Estrogen cause some degree of salt and water retention.
7. *Effects on breasts:* Estrogen produce duct growth in breasts and is responsible for the breast enlargement at puberty in girls. So they are called as the growth hormone of the breast. Estrogen are responsible for the pigmentation of the areolas.

***Note:*** Growth of pubic and axillary hairs in females is mainly due to androgens.

### Progesterone

#### *Source*

a. Corpus luteum and placenta (major source)
b. Testis and adrenal cortex.

#### *Secretion*

In men, plasma progesterone is 0.3 ng/ml. In women, it is 0.9 ng/ml during follicular phase which increases by 20-folds during luteal phase.

#### *Actions*

1. *BMR:* Progesterone increases the body temperature due to its thermogenic actions. In the luteal phase of women, the basal body temperature (BBT) is raised due to progesterone from the corpus luetum.
2. *On respiration:* It stimulates breathing which may result into a decrease in alveolar $pCO_2$.
3. *On endocrine glands:* High levels of progesterone inhibit the LH secretion.
4. *On reproductive system:* Progesterone is responsible for the progestational changes in the endometrium and the cyclical changes in the cervix and vagina. It has an antiestrogenic effect on the myometrial cells, decreasing their excitability. It also decreases the number of estrogen receptors on the endometrium.

5. *On mammary gland:* It causes the development of alveoli of the mammary glands. Along with estrogen it prepares the gland for lactation.
6. *On renal system:* Large doses of progesterone produces natriuresis, probably by blocking the action of aldosterone on the kidney.

## Relaxin

Relaxin is a polypeptide hormone that is produced in the corpus luteum, uterus, placenta and mammary gland in women and in the prostate gland in men.

### *Actions*

During pregnancy, it relaxes the pubic symphysis and other pelvic joints, softens and dilates the uterine cervix. Thus it facilitates delivery. It also inhibits uterine contractions and may play an important role in the development of mammary glands.

## Indicators of Ovulation

1. *Basal body temperature:* It shows a rise by 0.3–0.5°C after ovulation due to increase in progesterone secretion, since progesterone is thermogenic (Fig. 9.11). The temperature (oral or rectal) should be recorded in the morning before leaving the bed.
2. *Cervical mucus pattern:* Cervical mucus when spread on a slide and dried, shows a fern-like pattern under microscope this pattern are lost after ovulation.
3. Vaginal cornification disappear after ovulation.
4. Pregnandiol, a metabolite of progesterone appears in urine after ovulation.
5. Estimation of plasma progesterone level shows a gradual rise after ovulation.
6. Estrogen, FSH, LH estimation –peaks just before ovulation.
7. *Mittelschmerz sign:* Pain in lower abdomen due to minor bleeding from the follicle into peritoneum.

## Mammary Gland

It is a modified apocrine gland for the supply of nutrition to the young ones.

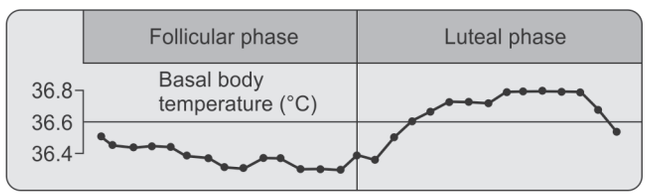
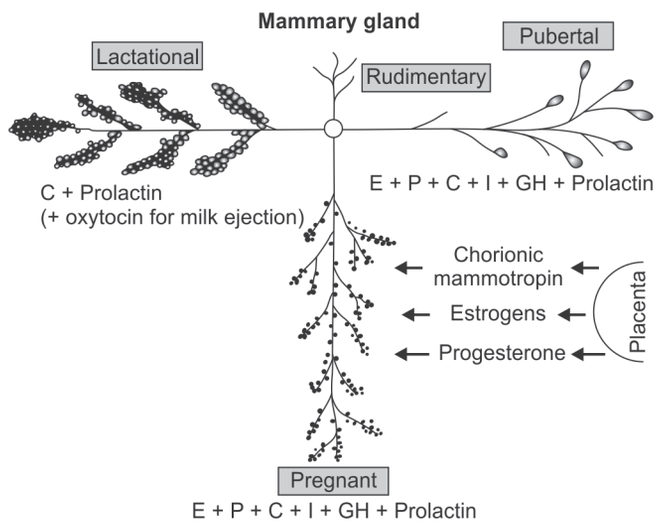



**Fig. 9.11:** Changes in basal body temperature in follicular and luteal phase

- Estrogen stimulates the proliferation of mammary duct and deposition of fat to give the breast mass. Far greater growth occurs during high estrogen state of pregnancy (Fig. 9.12).
- Progesterone is essential for the development of lobules.
- Glucocorticoids, insulin and growth hormone are necessary for mammary development in response to other hormones, but they do not themselves cause growth of breasts.
- Prolactin is not very high in nonpregnant state, hence not important for the mammary gland. During pregnancy its level increases to make alveolar cells ready for milk production. Prolactin needs prior activity of estrogen and progesterone and also presence of other hormones.




(E: Estrogen; P: Progesterone; G: Glucocorticoids; I: Insulin; GH: Growth hormone)

**Fig. 9.12:** Hormonal actions on mammary gland

# PREGNANCY

## Physiological Changes in Pregnancy

**I. Changes in uterus**

Uterus increase in weight from 30-60 gm in the nonparous women to 800-1000 gm at full term. This is due to:

a. Hypertrophy of pre-existing muscle cells (mainly) both in width and length by approximately 5-9 times.
b. Increase in amount of connective tissue and elastic tissue between the muscle fibers.

All these effect are seen during the first 2-3 months of pregnancy due to estrogen. Subsequent enlargement of uterus is due to growing fetus which causes uterine wall to become thinner.

**II. Changes in the body system and organs**

1. *Blood:*
   a. *Blood volume:* It increases by 30% (4 L to 5.4 L) mainly due to increase in plasma volume. Therefore RBC count, PCV, Hb concentration decreases producing anemia called physiological anemia of pregnancy. Its characteristic features are of iron deficiency anemia as iron demand increases during pregnancy.
   b. *Plasma proteins:* Total plasma concentration decreases. Serum fibrinogen increases which increases the ESR. Serum albumin is decreased but $\alpha$ and $\beta$ globulins concentration increases (compensatory increase).
2. *Heart:*
   a. Heart enlarges due to pressure of the enlarging uterus on the diaphragm.
   b. Cardiac output increases (5 L to 6 L) due to increase in stroke volume and HR.
   c. Systemic BP: Both SBP and DBP decrease. Antecubital venous pressure is normal. Femoral venous pressure increase due to pressure of enlarged uterus on the pelvic veins.
   d. Blood flow through the hand and forearm increases. This increased flow helps in loss of excess heat produced by increased body metabolism.
3. *Respiration:*
   a. *Vital capacity (VC):* No change as any change in VC due to upward displacement of the diaphragm gets compensated by increase in width of pleural cavity.
   b. Pulmonary ventilation increases due to increase in tidal volume (TV) and frequency of breathing. This may be due to increase in progesterone level which increase the sensitivity of respiratory center to $CO_2$ and causes fall in arterial $pCO_2$.
   c. Body $O_2$ consumption increases by 15%.
4. *GIT:*
   a. There is morning sickness feeling of nausea and vomiting in early months of pregnancy.
   b. Hypochlorhydria.
   c. Decrease in motility of stomach and colon.
5. *Urinary system:*
   a. RBF and GFR increases in parallel with increase in cardiac output.
   b. Increased GFR increases the load of solutes presented for reabsorbtion. This may account for the glycosuria of pregnancy.
6. *Endocrine glands:*
   a. Thyroid gland shows mild enlargement with hyperplasia and increased thyroxine output. But here there is no signs of hyperthyroidism.
   b. Adrenal cortex shows enlargement of zona fasciculata layer in particular, therefore cortisol secretion increases but no signs of Cushing's syndrome.
   c. Placental hormones are secreted.
7. *Nervous system: Nervous system* shows mild mental changes which vary from craving from unusual articles of diet to alteration in mood and behavior. In some, a true psychosis may also develop.
8. *Skin:* Skin shows pigmentation of the nipple, breast areolas and linea alba, brownish patches on the face and neck also develop. These changes are due to over secretion of ACTH or MSH.

**III. Metabolic changes**

1. During pregnancy there is marked ***increase in body weight,*** on an average, 12.5 kg.
2. *Water metabolism:* During the early months of pregnancy there is marked diuresis, sweating and a weight loss of approximately 2.5 kg. During later months (5-6 month onwards) of pregnancy excess of water is retained in the fetus, placenta, amniotic fluid, breast, uterus and other tissues. The retention of water is due to fall in plasma protein concentration, especially albumin (thus colloidal osmotic pressure decreases). Retention of sodium due to the steroidal sex hormones.
3. *Protein metabolism:* There is a positive nitrogen balance during pregnancy and lactation period.
4. *Carbohydrate metabolism:* Renal threshold of glucose decreases during pregnancy producing glycosuria.
5. *Fat metabolism:*
   a. There occurs increase in blood concentration of cholesterol, phospholipids and neutral fats.
   b. Adipose tissue fat increases to supply energy in the later stages of pregnancy and lactation.
6. *Mineral metabolism:* During pregnancy, the mother stores approximately 50 gm of calcium and 35-40 gm of phosphorus. Only half the calcium goes to the fetus especially during the last month, the rest being stored in the maternal tissues to be utilized during lactation.
7. *Iron metabolism:* The fetus contain 375 mg of iron which accumulate at a rate of approximately 0.4 mg/day in the first 6 month of pregnancy and about 4 mg/day during last 3 months of pregnancy. A further 500-700 mg of iron is required by the mother for increased Hb synthesis and myoglobin formation in the growing fetus. The iron in the newborn child and iron removed in the blood lost during delivery amounts to 400-500 mg; this represents 1/8-1/10 of the total body iron and must be compensated by the increased dietary intake of iron during pregnancy.

## Pregnancy Test

### *Earlier Bioassay Method (Ascheim–zondek test)*

a. The urine of the women (suspected to have developed pregnancy) will have hCG
b. This hCG when injected into immature mice (the animal which do not ovulate naturally due to its immaturity) will cause ovulation, which can be detected.

### *Immunological Test for Pregnancy*

### *Gravidex Test (Fig. 9.13)*

***Principle***

a. hCG being protein in nature will cause generation of antibody when injected in suitable animal. hCG is injected in rabbit, in whom antibodies develop in the serum (called rabbit antiserum). Rabbit antiserum is then collected.
b. Small globules of latex (rubber) particles are coated with pure hCG.
c. The urine suspected to contain hCG is now treated with rabbit antiserum. If the urine contains hCG, the antibodies in the antiserum are all used up. Subsequently, when hCG coated latex particles are added to the mixture, latex particles are not agglutinated whereas, if the urine is free from hCG, the antibodies in the rabbit serum remains free. In such a mixture, (i.e. where the suspected urine contains no hCG) when the latex mixture coated with the hCG are added, antigen-antibody reaction (between hCG of latex particles and the antibodies of the serum) occur and the latex particles are agglutinated. Therefore agglutination of latex particles means that the urine is from a nonpregnant woman. Apart from diagnosis of normal pregnancy this test is also used to diagnose some diseases of the placenta.

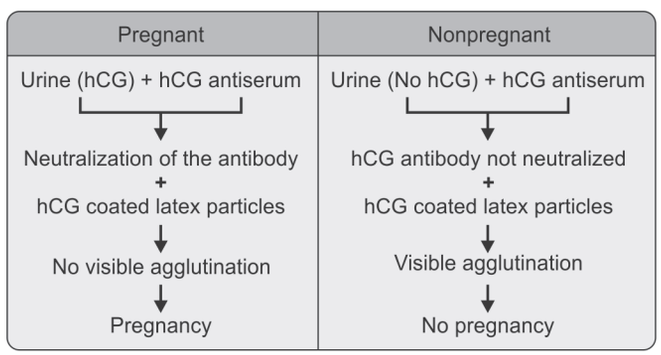



**Fig. 9.13:** Gravidex test

## Placenta

Placenta (Fig. 9.14) is the "fetal lung". It mainly consists of:

1. *Maternal part:* It is called decidua in which large blood sinuses partitioned by fibrous septa are present. Maternal blood circulates in these sinuses.
2. *Fetal part:* It consists of numerous finger-like processes called chorionic villi. These project into the maternal bloodsinuses. Chorionic villi has two layers; Cytotrophoblast and syncytiotrophoblast. Syncytiotrophoblast produces all hormones.

$O_2$ is taken up by the fetal blood and $CO_2$ is discharged into the maternal circulation across the walls of the villi in a fashion analogous to $O_2$ and $CO_2$ exchange in the lungs.

### *Function of Placenta*

1. *Respiratory:* Diffusion of $O_2$ and $CO_2$ through placental membrane.
2. *Excretory:* Excretion of waste products.
3. *Immunological:* Many immunoglobulin molecules (IgG) from maternal circulation cross the placental barrier to confer a passive immunity in the fetus.
4. Many drugs also cross placental barrier, e.g. pethidine and anesthetics. If used in labor, these drug cause damage to fetus.
5. *Endocrine:* Fetoplacental unit produces many hormones, vital to pregnancy. Hormones produced by placenta include hCG, human chorionic somatomammotropin (hCS), human chorionic thyrotropin (hCT), estrogen and progesterone.

### *Placental Hormones*

Hormones produced by placenta include:

1. Human chorionic gonadotropin (hCG)
2. Human chorionic somatomammotropin (hCS)

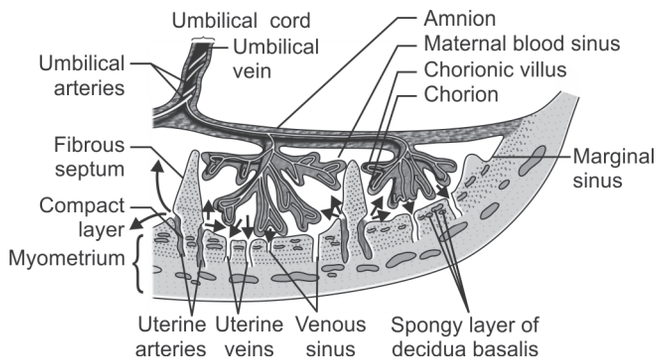



**Fig. 9.14:** Physiological anatomy of mature placenta. The direction of blood flow in the maternal blood sinuses is indicated by arrows

3. Human chorionic thyrotropin (hCT)
4. Estrogen and progesterone.

### *hCG*

Human chorionic gonadotropin (hCG) is a placental hormone. It is a glycoprotein that contains galactose and hexosamine. It is produced by syncytiotrophoblast. hCG is primarily luteinizing and luteotrophic and has little FSH activity. The hCG is detected in the blood at 6th day after conception and in urine after 14 days. It appears to act on the same receptor as LH. Clinically hCG is not absolutely specific for pregnancy. Small amounts are secreted by a variety of gastrointestinal and other tumor in both sex (hCG-as tumor indicator).

***Functions***

a. Maintains corpus luteum of pregnancy.
b. Increase interstitial GH, leading to testosterone secretion which promote development and descent of testis.
c. Development of stomal cells and decidual cells.

### *hCS*

It is synthesized by placental syncytiotrophoblastic cells. It resembles GH in amino acid content. It is maternal GH of pregnancy. The amount of hCS secreted is directly proportional to the size of the placenta. Therefore, low hCS levels are signs of placental insufficiency.

### *hCT*

It is a placental substance with properties like that of TSH.

### *Estrogen and Progesterone*

The fetus and placenta interact as a functional unit, called *fetoplacental* unit (Fig. 9.15) in the formation of estrogen and progesterone.

In connection with estrogen synthesis during pregnancy, both the placenta and the fetus cooperate with each other. Some enzyme are absent in the placenta but present in the fetus whereas some other are absent in the fetus but present in placenta. But when two system works in unison enzyme system is complete.

The placenta synthesize pregnenolone and progesterone from cholesterol. Some of the progesterone enters the fetal circulation and provides the substrate for the formation of cortisol and corticosterone in the fetal adrenal glands. Some of the pregnenolone enters the fetus and along with pregnenolone synthesized in the fetal liver is the substrate for the formation of dehydroepiandrosterone sulfate (DHEAS) and 16-hydroxy dehydroepiandrosterone sulfate in the fetal adrenal. The DHEAS and 16-OH DHEAS are transported back to the placenta, where DHEAS forms estradiol and 16-OH DHEAS forms estriol. Since fetal 16-OH DHEAS is the principal substrate for the estrogens, urinary estriol excretion of the mother can be monitored as an index of the state of the fetus.

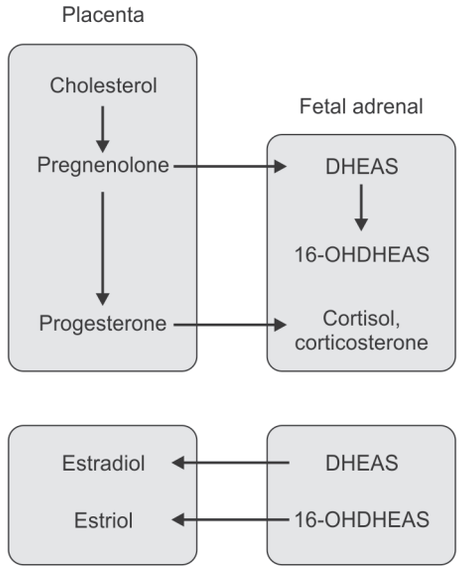



**Fig. 9.15:** Fetoplacental unit

***Note***

Increase uptake of $O_2$ by fetal blood as it traverses the placenta due to the double Bohr's effect because, while flowing through the placenta:

- $pCO_2$ of fetal blood decreases and its pH increases, this shifts $O_2$-hemoglobin dissociation curve to left to cause increased loading of $O_2$.
- $pCO_2$ of maternal blood increases and its pH decreases, this shift $O_2$- hemoglobin dissociation curve to right and causes increased unloading of $O_2$.

## Parturition

Parturition means birth of the baby. Towards the end of pregnancy, the uterus becomes progressively more excitable, until finally it develops strong rhythmic contractions so that the baby is expelled.

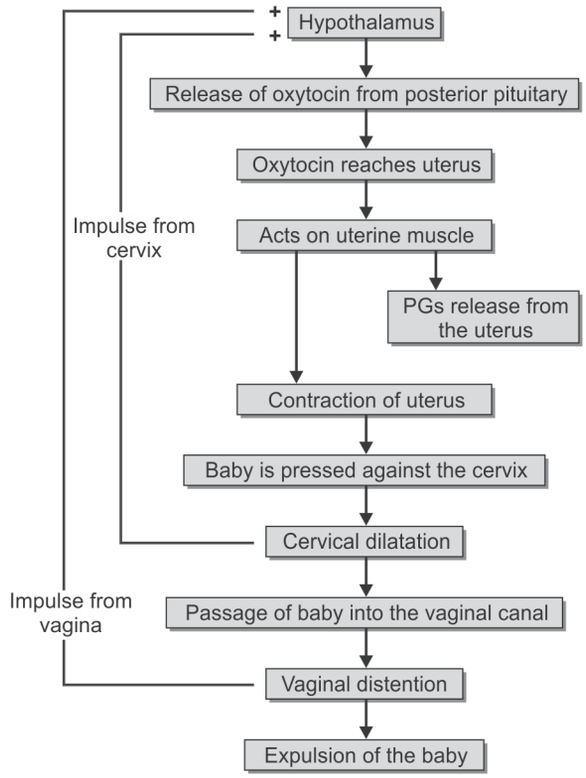
The process of parturition (labor) is divided into three stages (Flow chart 9.1):

1. Dilatation of cervix.
2. Expulsion of the fetus with membranes.
3. Expulsion of the placenta from the uterus.

***Initiation of Labor***

Initiation is usually indicated by the appearance of labor pains which are due to the conversion of slow and rhythmic

**Flow chart 9.1:** Mechanism of parturition




uterine contractions (Braxton Hicks contraction) to strong and powerful contractions. These contractions become stronger at full term and force the baby through the birth canal thereby causing parturition. Mainly two categories of effects lead up to the intense contractions responsible for parturition: (1) Hormonal factors that increases excitability of uterine musculature and (2) Mechanical factors that increases uterine contractility.

### *Hormonal Factors*

1. *Increased ratio of estrogens to progesterone:* The high estrogen to progesterone ratio sensitizes the uterus to stretch, prostaglandins (they are released locally) and oxytocin. Estrogen has a definite tendency to increase the degree of uterine contraction as they increase the number of gap junctions between adjacent uterine smooth muscle cells. From the seventh month of pregnancy, estrogen secretion continues to increase while progesterone secretion remains constant or even decreases slightly and thereby maintaining a high E/P ratio.
2. *Effect of oxytocin on uterus:* Oxytocin appears to play a prominent role in the processs of parturition. It facilitates parturition by causing contraction of the estrogen primed uterus. The uterine muscle increases its oxytocin receptors near term and also the rate of oxytocin secretion by neurohypophysis is considerably increased at the time of labor.
3. *Effect of fetal hormones on uterus:* The fetal pituitary gland secretes increasing quantities of oxytocin which plays a role in exciting the uterus. The fetal adrenal glands secrete large quantities of cortisol which is a uterine stimulant. The fetal membranes release PGs in high concentration at the time of labor which increases the intensity of uterine contraction.

### *Mechanical Factors*

1. *Stretch of the uterine musculature:* Uterine muscle being a visceral type of smooth muscle contracts when stretched. The sensitized uterus when stretched by the fully developed fetus brings out powerful contractions.
2. *Stretch or irritation of the cervix:* The stretching or irritation of nerves in the cervix initiates reflexes to the body of the uterus which may result in powerful uterine contractions.

## Lactation

Lactation is the process of milk output from mammary gland. It is divided into two stages: (1) Secretion and (2) Ejection.

### *Milk Secretion*

Initiation of milk secretion is called lactogenesis. After expulsion of placenta, there is decline in estrogens and progesterone. The drop in estrogen initiates lactation. Estrogen at low levels probably helps milk secretion by inhibiting prolactin inhibiting factor (PIF). Prolactin secretion increases during breastfeeding.

Maintenance of secretion is called galactopoiesis. This is the function of prolactin mainly with the aid of other hormones.

### *Effect of Lactation on Menstrual Cycle*

Women who do not nurse their infants have 1st menstrual cycle 6 weeks after delivery. Women who nurse regularly have amenorrhea for 25–30 weeks. Nursing stimulates the prolactin secretion, which in turn inhibits GnRH secretion and thereby ovulation is inhibited.

### *Milk Ejection*

Expulsion of formed milk from the gland is possible due to:
1. Suckling action by the baby.
2. Contraction of myoepithelial cells by oxytoxin secreted by suckling reflex.
3. Continuous production of milk creates a positive pressure which pushes the milk out.

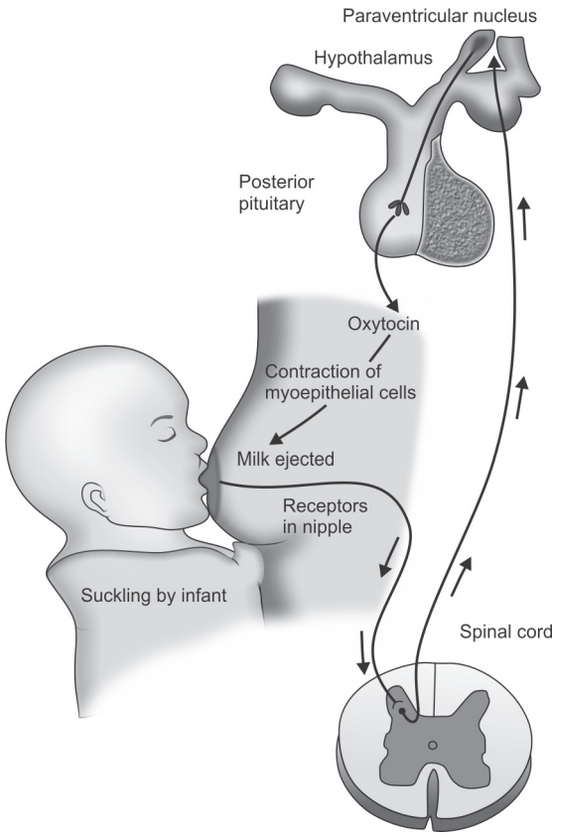



**Fig. 9.16:** Suckling reflex

### *Suckling Reflex (Fig. 9.16)*

It is a neuroendocrine reflex.

Due to suckling by baby → stimulation of tactile receptors in the areolor region of the breast → activate somesthetic neural pathway → transmit signal to paraventricular nuclei in hypothalamus → oxytoxin is formed and released through posterior pituitary → reach mammary gland through blood → contraction of myoepithelial cells → ejection of milk.

## CONTRACEPTION

Contraception means prevention of conception (fertilization of ovum) and thus to stop reproduction.

Various methods or agents used for contraception are contraceptives. These are as follows (Fig. 9.17):

### Contraceptive Measures in Males

i. **Barrier methods:** The aim of these methods is to prevent live sperms from meeting the ovum. For example, condom.

Condom is a sheath or covering made up of latex rubber, mostly coated with spermicides and made to fit over the male external genitalia.

*Advantages*

a. Prevents transmission of STDs including HIV and AIDS.
b. No hormonal side effects.

*Disadvantages*

a. Latex condoms can cause itching (allergy to latex) in few.
b. Hampers sexual pleasure.
c. Condom may rupture leading to fertilization.

ii. **Coitus interruptus**

*Disadvantage*

Slightest mistake in timing the withdrawal or even a drop of semen is sufficient to cause pregnancy.

iii. **Vasectomy**

*Advantages*

It is relatively safe and convenient method.

*Disadvantage*

About 50% of vasectomized patients develop antibodies against sperms. So in those patients wishing to restore fertility at a later stage success rate after restoration of vas is only 50%.

iv. **Drugs:** Gossypol (spermicide)

*Disadvantage*

Drugs are too toxic to be used clinically.

v. **Testosterone**

*Disadvantage*

In such high doses testosterone causes sodium and water retention.

### Contraceptive Measures in Female

**I. Conventional methods**

1. *Cervical diaphragm:*

   *Disadvantage*

   a. Trained persons will be needed to demonstrate the technique of use.
   b. Local infection can be caused if it is left in the vagina.

2. *Douches:*

   *Disadvantage*

   It produces burning sensation and irritation locally besides producing messiness.

3. *Rhythm method:* It involves confinement of sexual intercourse to safe period only.

**II. Tubectomy**

Bilateral ligation of the fallopian tubes.

*Advantages*

It is relatively safe and permanent means of terminating pregnancy.

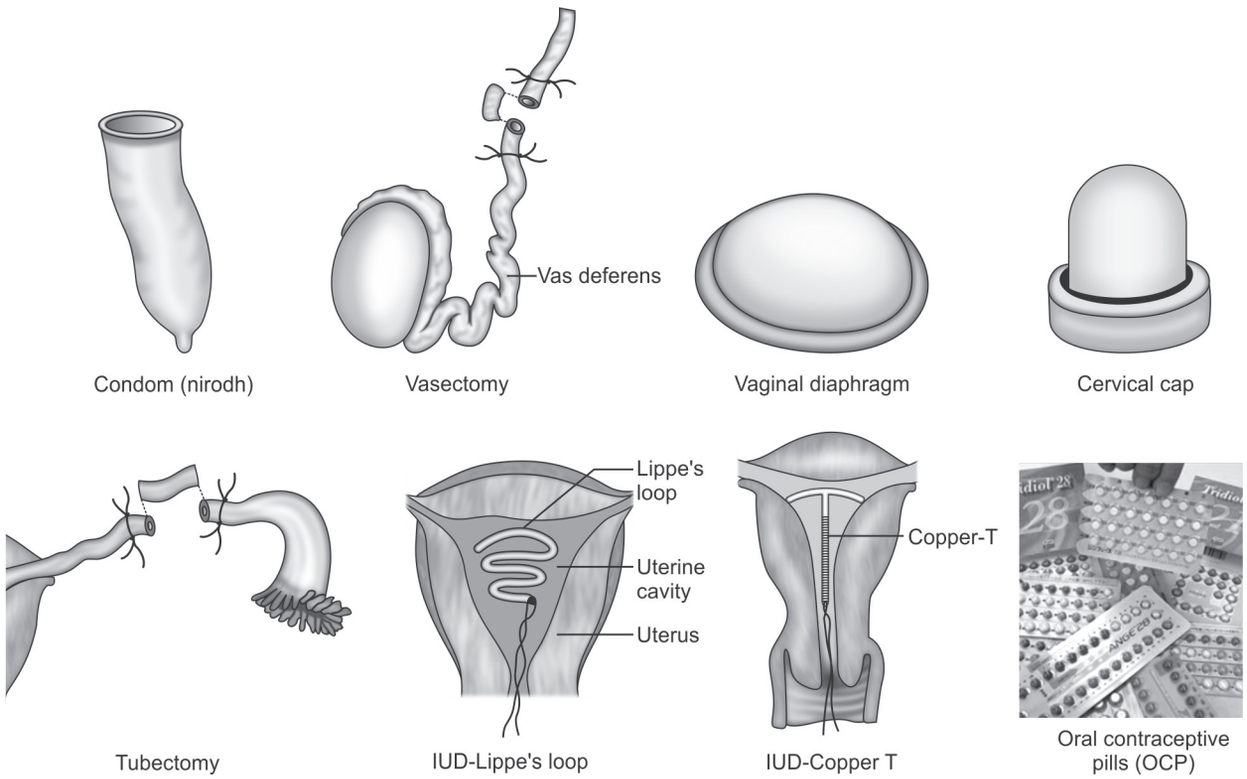



**Fig. 9.17:** Contraceptive measures

**III. Intrauterine device (IUD)**

Implantation of a foreign body into the uterine cavity for contraceptive purposes. Types of IUD's are:

1. *Nonmedicated IUD or inert IUD's:* These are referred to as 1st generation IUD's. It comprises of the inert or nonmedicated devices, usually made of polyethylene, or other polymers. They are available in different shapes and sizes—loops, spirals, coils, rings. The Lippes loop is the best known. The IUD causes a foreign body reaction in the uterus causing cellular and biochemical changes in the endometrium and uterine fluids that impair the viability of the gamete. They also prevent implantation.
2. *Copper IUD (second generation IUD's):* By adding copper to IUD. It was found that copper has strong anti-fertility effect, e.g. copper-T. Copper seems to enhance the cellular response in the endometrium. By altering the biochemical composition of cervical mucus, copper ions may affect sperm motility, capacitation, and survival. It also affects the enzymes in the uterus.
3. *Hormone releasing IUD (3rd generation):* The most widely used hormonal device is Progestasert, which is a T-shaped device filled with 38 mg of progesterone. It acts by increasing the viscosity of cervical mucus and thereby prevent sperm from entering the cervix.

*Advantages*

a. Long lasting and long-term prevention of pregnancy.
b. Very effective and no side effects.
c. No interactions with other medicines.

*Disadvantages*

a. Chances of ectopic pregnancy very high.
b. Menstrual changes in the first 3 months with occasional spotting between periods.
c. If left for longer intervals they tend to lose their efficiency and may cause intrauterine infection.
d. No protection against HIV, AIDS and other STDs.

**IV. Contraceptive pills**

1. *Classical or combined pills:* It contains orally active progesterone combined with small amounts of estrogens. The pill is given from the 5th to 25th day of the menstrual cycle.

*Mode of action*

a. Act on hypothalamus → inhibit secretion of LH → inhibit ovulation.
b. Make cervical mucus thick.

*Advantages*

a. Very effective when used correctly.
b. Helps to prevent endometrial and ovarian cancer, ectopic pregnancy, ovarian cyst.

*Disadvantages*

a. Nausea in the intial stages of taking combined pills.
b. Slight weight gain.
c. Breast tenderness.
d. Decreased milk quantity and quality in breast-feeding women.
e. On long-term use of oral contraceptives there is high risk of thromboembolic phenomenon.
f. Not effective unless taken every day.
g. Does not provide protection against STD including AIDS.

2. *Sequential pill:* High dose of estrogen for 15 days followed by 5 days of estrogen plus progesterone. This inhibit ovulation by suppressing the release of both FSH and LH.

*Disadvantage*

This increases the incidence of endometrial cancer.

3. *Postcoital pill or 'morning after pill:* Administration of large doses of estrogen. It is recommended within 48 hours of an unprotected intercourse. The method employed is to give a double dose of 'combined pill' that is 2 pills immediately followed by another 2 pills 12 hours later.

*Advantages*

a. Can be used by nursing mothers after child birth and it will not affect quantity and quality of breast milk.
b. May prevent endometrial and ovarian cancer.

*Disadvantages*

a. It leads to changes in menstrual bleeding patterns.
b. Breast tenderness.
c. Risk of ectopic pregnancy.
d. Headache.

4. *Mini pill or micro pill:* Low dose of progesterone throughout the menstrual cycle. This prevents fertility without inhibiting ovulation.
5. *Progesterone antagonist:* Progesterone antagonists like mifepristone is helpful in producing abortion.

PHYSICON—The Reliable Icon in Physiology

Chapter

# 10 Nerve and Muscle Physiology

## NEURON

Structural and functional unit of nervous system is called neuron. The term neuron is used to describe the nerve cell and its processes, the dendrites and the axon (Fig. 10.1).

### Structure

#### *Nerve Cell Body (Soma or Perikaryon)*

They are of various size and forms: stellate, round, pyramidal, fusiform, etc. Its principal constituents are similar to a generalized cell. However, after fixation with special stains its cytoplasm also reveals the presence of:

***Nissl granules/bodies***

These are basophilic granules composed of many thin, parallel arranged, membrane bounded cavities or cisternae which are covered by many minute particles consisting of ribose nucleoproteins, i.e. RNA with proteins. Granule's size and number varies with physiological condition of the cell.

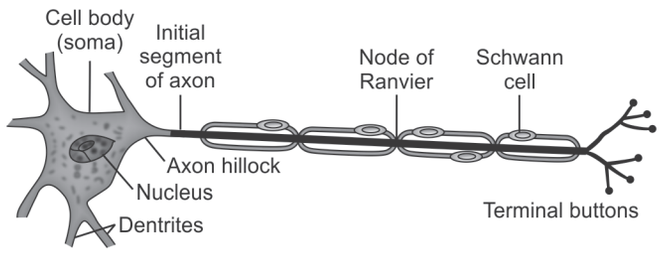



**Fig. 10.1:** Structure of neuron

***Neurofibrillae***

These are fine threads 6–10 nm in diameter and of variable length. They traverse the cytoplasmic matrix forming a loose framework of fibrils in the cytoplasm.

***Note***

There is no centriole which indicate that the highly specialized nerve cell lost its power of division. Nerve cell once destroyed are replaced merely by neuroglia, cells which support the nerve cell.

#### *Dendrites*

These are 5–7 processes extending out from the cell body and arborize extensively after they leave the cell. They also contains nissl granule, mitochondria and neurofibrillae. They are the receptive processes of the neuron. Impulse can be transmitted from one dendrite to another in the CNS.

#### *Axon (Axon Cylinder or Nerve Fiber)*

It originates from a thickened area of the cell body called axon hillock, in which there is no Nissl granules. The cytoplasmic fluid occupying the center of the axon is known as axoplasm. The cell membrane enveloping the cytoplasm is also continued on the axon as axolemma. Axon vary from a few microns in length to as long as 90 cm. Axon is the single elongated cytoplasmic extension with the specialized function of conducting impulses away from the cell body.

**Table 10.1: Differences between myelinated and unmyelinated nerves**

| *Myelinated nerves* | *Unmyelinated nerves* |
|---|---|
| 1. Multiple layers of Schwann cell membrane make myelin, formed by coiling of membrane many times round the axon. | 1. Axons are simply surrounded in the Schwann cell without wrap ping of myelin. |
| 2. Faster conduction of nerve impulse (50–100 times) than the unmyelinated fiber because of saltatory conduction, i.e. jumping of impulse from node to node over intersegmental region. | 2. Slower conduction of nerve impulses as it is a continuous process due to lack of myelination. |
| 3. For example:<br>i. All preganglionic fibers of ANS<br>ii. Nerve fibers in somatic nervous system more than 1 μm in diameter. | 3. For example<br>i. All post-ganglionic fibers of ANS<br>ii. Nerve fibers in somatic nervous system less than 1 μm in diameter |

### *Synaptic Knobs (Terminal Buttons or Axon Telodendria)*

The axon divides into terminal branches, each ending in a number of synaptic knobs. They contain granules or vesicles in which synaptic transmitter secreted by the nerve is stored.

### *Myelinogenesis*

Neurolemma or sheath of Schwann has got a cell, Schwann cell which takes part in the deposition of myelin sheath round the axon, a process called myelinogenesis. Myelination of axons in the CNS system is by the oligodendrocytes. One oligodendrocytes sends processes to up to 40 axons (Fig. 10.2).

### *Glial Cell (Neuroglia)*

Glial cell means glue, these are the cells which support the nerve cells. Glial cells are very numerous. There are approximate ten times as many glial cells as neurons. Unlike the neurons, the glial cells are capable of multiplying by mitosis. Glial cell are of three types:

1. ***Microglia:*** They are phagocytic cells that enter the CNS from meninges and blood vessels.
2. ***Astrocytes:*** They are found throughout the brain joining to the blood vessels and investing synaptic structures, neural bodies and neural processes.

***Function***

It plays an important role in support, transport mechanisms, inflammatory and repairative reactions and also helps in forming the blood-brain barrier. They also help in maintaining optimal concentration of ions and neurotransmitter (specially glutamine) in the brain neurons.

3. ***Oligodendrolia:*** These are cells that form myelin around within CNS. The axons in the CNS do not have Schwann cells.

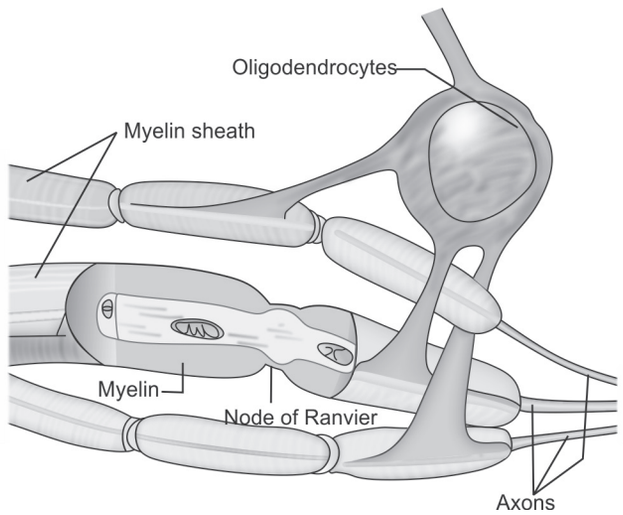



**Fig. 10.2:** Oligodendrocyte

### *Orthodromic and Antidromic Conduction*

Impulses normally pass in one direction only, i.e. from synaptic junction or receptor along axon to their termination. Such conduction is called *Orthodromic conduction.* Conduction in the opposite direction is called *Antidromic conduction,* seen in sensory nerve supplying the blood vessels.

## Nerve Fibers Types and Function

### *Erlanger and Gasser's Classification (Table 10.2)*

Nerve fibers have been divided into A, B and C groups. A group is further subdivided into α, β, γ and δ fibers.

### *Numerical Classification (Table 10.3)*

This is sometimes used for sensory neurons and is based on the origin of nerve fibers.

**Table 10.2: Erlanger and Gasser's classification**

| *Class of nerve fiber* | *Diameter of fiber (in μm)* | *Velocity of conduction (m/s)* | *Function* |
|---|---|---|---|
| **A** | | | |
| Aα | 12–20 (Thickest and heavily myelinated) | 70–120 | Proprioception, somatic motor |
| Aβ | 5–12 (Thinner than α; myelinated) | 30–70 | Touch, pressure, motor |
| Aγ | 3–6 (Still more thin; slightly myelinated) | 15–30 | Motor to muscle spindles |
| Aδ | 2–5 (Still thinner) | 12–30 | Pain, cold, touch |
| **B** | <3 (Myelinated) | 3–15 | Preganglionic fibers of ANS |
| **C** | | | |
| Dorsal root | 0.4–1.2 (Unmyelinated) | 0.5–2 | Pain, temperature, some mechanoreception, reflex responses |
| Sympathetic | 0.3–1.3 (Unmyelinated) | 0.7–2.3 | Postganglionic sympathetic |

**Table 10.3: Numerical classification for sensory neurons**

| *Number* | *Origin* | *Fiber Type* |
|---|---|---|
| Ia | Muscle spindle, annulospiral ending | Aα |
| Ib | Golgi tendon organ | Aα |
| II | Muscle spindle, flower-spray ending, touch, pressure | Aβ |
| III | Pain and temperature receptors, some touch, pressure | Aδ |
| IV | Pain and other receptors | Dorsal root 'C' fibers |

**Table 10.4: Physio-clinical classification**

| | *Most susceptible* | *Intermediate* | *Least susceptible* |
|---|---|---|---|
| Sensitivity to 'Hypoxia' | B | A | C |
| Sensitivity to 'Pressure' | A | B | C |
| Sensitivity to 'Local anesthetics | C | B | A |

### *Physio-clinical Classification (Table 10.4)*

It has clinical as well as physiological significance and is based on sensitivity to hypoxia, pressure and anesthetic agents.

## Degeneration and Regeneration of Nerve Fibers

When a nerve fiber is injured sufficiently, the part distal to the injury dies. Some changes in the proximal part are also seen. The entire process is known as degeneration (also called ***Wallerian degeneration***, after Waller who described it).

*Common causes of injury*

a. Transection
b. Crushing
c. Injection of toxic or poisonous substance into the nerve.
d. Ischemia-interference in blood supply.
e. Hyperpyrexia-increase in body temperature.

***Grading of injury (by "Sunderland")***

*First degree injuries:* Most commonly seen and is secondary to ischemia caused by direct pressure to a nerve for a limited time. Ischemia produces local anoxia with temporary impairment of nerve function. It gets corrected within hours to few weeks, because the axon is not destroyed but merely loses its functional properties for a short time.

*Second degree injuries:* Prolonged or severe pressure damages the nerve fibers at the pressure point eventually causing death of axon locally and distally.

*Third degree injuries:* Endoneurial tubes becoming interrupted.

*Forth degree injuries:* Fascicles becoming disorganized.

*Fifth degree injuries:* Through and through cutting of nerve fibers, i.e. complete transection.

***Degenerative changes occur at three levels***

1. Changes in nerve cell body (retrograde changes)
2. Changes in the distal stump
3. Changes at the site of injury.

### *Series of Degenerative Changes*

1. Change in nerve cell body begin within 48 hours of injury
   a. Chromatolysis: Nissl's granule disintegrate.
   b. Golgi apparatus, mitochondria, and neurofibrils are fragmented and disappear.
   c. Cell draws more fluid and become round.
   d. Nucleus increase in size and move to periphery.
2. Change in the distal stump begin within 24 hours of injury
   a. Axis cylinder breaks into short lengths and few days later little debris is left.
   b. Myelin sheath breaks up more slowly than axon into small oily droplets. It occurs in 2 stages: (i) physical destruction up to 8–10 days, (ii) chemical destruction starts at 8th day and goes on till 32 days.
   c. Nucleus of Schwann cell start multiplying mitotically, which fill up the endoneurial tubes.
   d. Macrophages from endoneurium start phagocytosing debris of axis cylinder and myelin sheath.
   e. Once the debris are cleared, Schwann cell cytoplasm starts proliferating and fills up the endoneurial tubes.
3. Changes in the site of injury
   Schwann cell differentiate into thin enlongated cells, mainly from the distal end and very little from the proximal end. It can bridge up the gap of 3 cm. Rate of progress of growth is 1–2 mm/day.

## Regenerative Changes

A degenerated nerve may regenerate, provided there is neurilemmal sheath. In places where the neurilemma is absent,

there can be no regeneration. Nerve fibers of CNS therefore, once degenerated, never regenerate as these nerves have no neurilemma. Degenerative and regenerative processes go side by side (Fig. 10.3).

1. **Changes in the nerve cell body**
   It begins in 20 days and is completed in 80 days. Nissl granules and Golgi apparatus gradually reappear, cell regains its normal size and nucleus returns to its central position. Repair of cell may even occur if the axon does not regenerate.
2. **Changes in the distal stump and at the site of injury**
   a. Axis cylinder from the proximal stump elongates and then grows out in all directions as rounded pseudopod like structures called fibrils towards the distal stump.
   b. Each axon gives rise to 50–100 fibrils which are guided by the strands of Schwann cell into the distal ends of the endoneurial tubes.
   c. 2–3 weeks after the nerve section the distal endoneurial tube contains varying number of developing fibrils.
   d. Eventually all the fibrils re-innervating one tube degenerate except one which thereupon progressively gets enlarged to fill the tube.
   e. To begin with, rate of growth is 0.25 mm/day, but once it enters the distal stump, the rate of growth becomes 3–4 mm/day. As it grows deeper down, the rate of growth further increases because mechanical conditions for regeneration are more suitable than those in a cut nerve end.

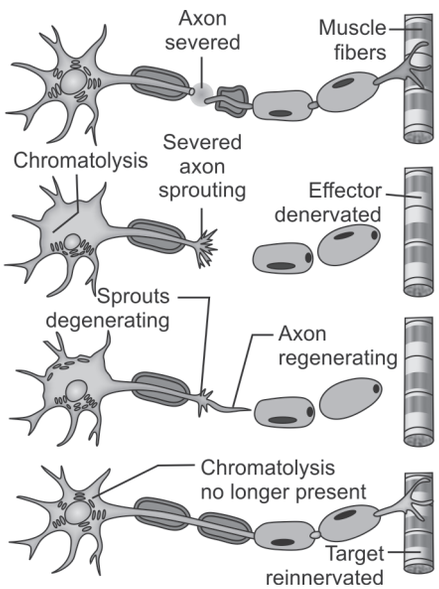



**Fig. 10.3:** Peripheral nerve damage and repair

   f. In approx 15 days, Schwann cell filling the endoneurial tube starts laying down myelin sheath round the successful fibril, which is completed by 1 year.
   g. Increase in fiber diameter takes place very slowly. Final diameter attained is 80–85% of normal. It is limited by the diameter of the distal tube and the size of the parent nerve cell. Therefore, functional recovery is not full which takes longer time and may be associated with different complications if it does not reach its own cut stump. That is why, for a motor nerve, recovery may be complete but for a mixed nerve it is rarely so.

***Note***

### *Denervation Hypersensitivity*

When the motor nerve to skeletal muscle is cut and allowed to degenerate, the muscle becomes extremely sensitive to ACh. This phenomenon is referred to as denervation hypersensitivity or supersensitivity and is seen in smooth muscles also. Smooth muscles, unlike skeletal muscle do not atrophy when denervated, but it becomes hyper-responsive to the chemical mediator that normally activates it. Hypersensitivity is limited to the structure immediately innervated by the destroyed neurons. For example, the response of the denervated iris. If the postganglionic sympathetic nerves to one iris are cut in an experimental animal and after several weeks, if norepinephrine is injected intravenously, the denervated pupil dilates widely. A much smaller, less prolonged response is observed on the intact side.

***Causes***

a. Synthesis and activation of more receptors
b. There is an increase in the area of muscle membrane sensitive to ACh
c. ACh receptors of fetal gamma subunit appears

In orthograde degeneration (wallerian degeneration), part distal to cut degenerates. Retrograde degeneration of axon is towards nearest collateral (Fig. 10.4).

## NEUROMUSCULAR JUNCTION (NMJ)

It is the junction between the motor nerve and skeletal muscle fiber. Nerve membrane which is in close approximation with the muscle membrane is called presynaptic membrane, while the muscle membrane is called postsynaptic membrane. The space between these membranes is called synaptic cleft (50-100 nm wide) which is filled with ECF.

Postsynaptic membrane has many folds of muscle membrane called subneural cleft which increases the surface area for the synaptic transmitter. Axon terminal has many mitochondria (for the synthesis of ACh) and minute vesicles or granules, which contain small packets of chemical transmitter,

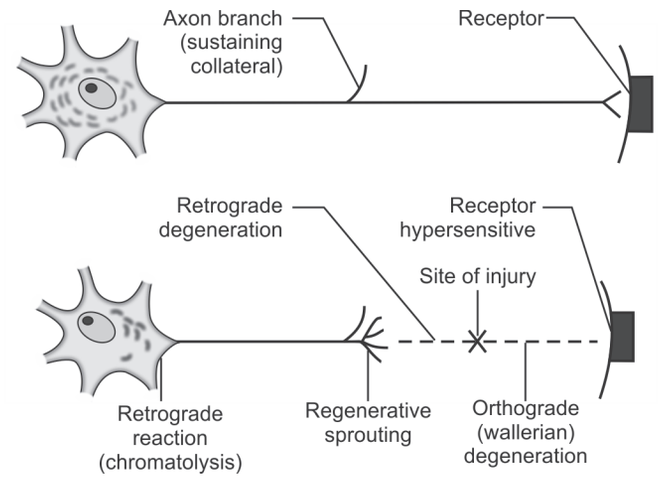



**Fig. 10.4:** Retrograde degeneration

acetylcholine (ACh) responsible for synaptic transmission. An enzyme specific acetylcholinesterase is found in high concentration in postsynaptic clefts, which destroys the ACh.

## Synthesis Storage and Release of ACh

Acetylcholine is synthesized within the mitochondria from 'choline' in the presence of enzyme Choline Acetyltransferase (Choline Acetylase). In addition, it requires acetyl Co-enzyme A, ATP and glucose. With the exception of choline all components required for synthesis of ACh are present within mitochondria or gain ready access to them.

Acetylcholine once formed is temporarily stored in minute vesicles (synaptic vesicles) (Fig. 10.5). Nerve impulse causes fusion of vesicles with membrane of terminal nerve fiber by increasing permeability of $Ca^{2+}$. $Ca^{2+}$ in ECF helps in fusion by changing ionic composition and thereby decreasing the flow of axoplasm, therefore, vesicles easily come in contact with the membrane. $Mg^{2+}$ decreases this process. The amount of transmitter released is directly proportional to the $Ca^{2+}$ influx.

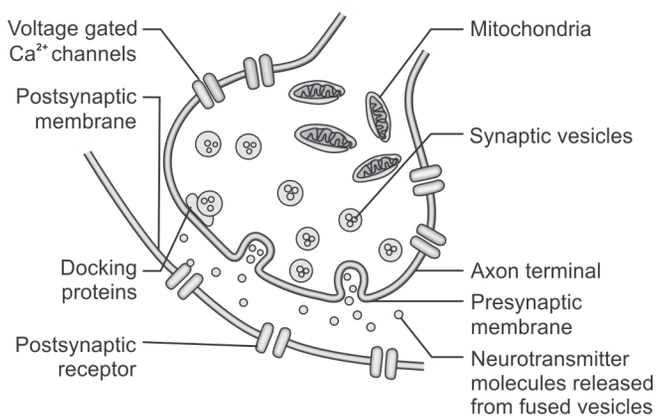
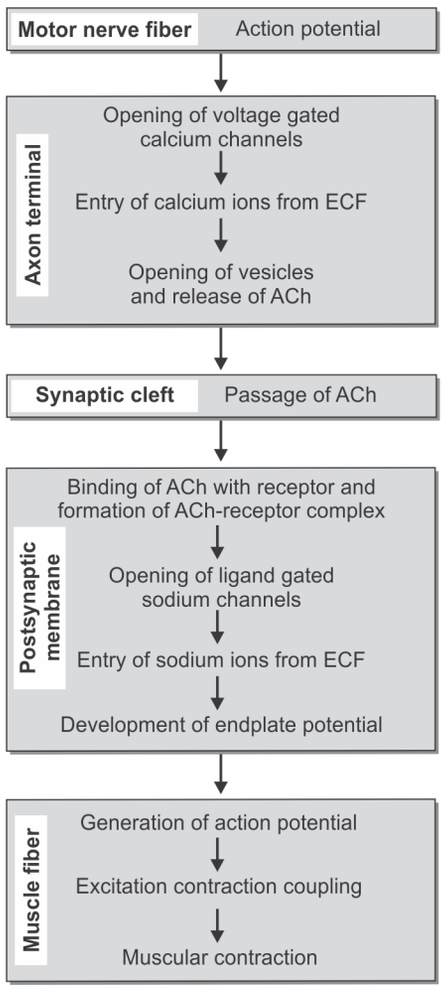



**Fig. 10.5:** Neuromuscular junction

## Sequence of Events (Flow chart 10.1)

**Flow chart 10.1:** Sequence of events during nerve impulse transmission




### *Final Step*

Destruction of ACh within 1 millisecond after ACh is released by acetylcholinesterase.

***Note***

It appears that vesicle breaks with the membrane when VAMP, a vesicle membrane protein connects with syntaxin, a cell membrane protein. The connection occurs in presence of G proteins-a SNAP, b SNAP, SNAP-25 and NSF.

***Toxins which blocks neurotransmitter release***

a. d tubucurarine competes with ACh for same nicotinic receptors on the motor endplate.
b. Tetanus and botulinum neurotoxin-b cleaves VAMP

c. Botulinum neurotoxin-b cleave SNAP-25
(Tetanus cause spastic paralysis, botulinum cause flaccid paralysis).

***Drug that stimulate neuromuscular junction by inactivating acetylcholinesterase***

a. Neostigmine
b. Physostgmine
c. Diisopropyl fluorophosphate.

### *Myasthenia Gravis*

Autoimmune disease in which patients have developed antibodies against their own ACh-activated ion channels. These antibodies destroy ACh receptors, thereby causing muscle paralysis due to the inability of the neuromuscular junctions to transmit enough signals from the nerve fibers to the muscle fibers. The disease is characterized by rapid onset of fatigue with marked generalized weakness of muscles. The most commonly affected muscle are extraocular muscle, facial, swallowing and mastication muscle. In severe form patient may die with paralysis of respiratory muscles.

#### *Treatment*

In myasthenia gravis (autoimmune disorder) antibodies are produced against nicotinic NM receptors in the NMJ. To prevent the action of the action of the antibody, we have to increase the release of ACh, for that the cholinesterase enzyme has to be inhibited by anticholinesterases such as neostigmine.

### *Lambert-eaten Syndrome*

In this muscle weakness is caused by antibodies against one of the $Ca^{2+}$ channels in the nerve endings at the neuromuscular junction. This decreases the normal $Ca^{2+}$ influx that causes ACh release.

## SKELETAL MUSCLE

Skeletal muscle is made up of many long thin cells called muscle fibers. Each muscle fiber is multinucleated, 1–40 mm long, cylindrical, 50–100 μm diameter and surrounded by a cell membrane, the sarcolemma. Muscle fibers are made up of many fibrils called myofibrils. Each myofibril is 1–2 μm in diameter. The cytoplasm in the muscle fibers is called sacroplasm.

#### *Light Microscopic Appearance*

The cross striations which are characteristic of skeletal muscle are due to difference in the refractive indices of various parts of muscle fiber. Therefore, the muscle fiber is seen to show alternate dark and light cross bands (Fig. 10.6).

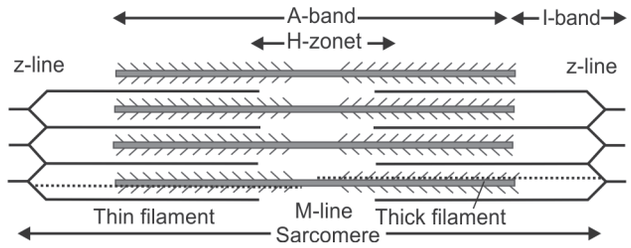



**Fig. 10.6:** Electron microscopic appearance of skeletal muscle

1. The dark band is made of highly refractile material (anisotropic) called A-band (1.5 μm in length).
2. In the center of each A-band is found a slight less refractile region called H-band.
3. M line is seen in the middle of H-band, due to central bulge of A-band.
4. The alternate light band is made of lower refractile material (isotropic), therefore looks lighter and is called I-band (1 μm).
5. In the center of each I-band is found a narrow line of highly refractile material which looks dark called Z-line.
6. Contractile unit of the muscle is the substance between two adjacent Z-lines called sarcomere (2.5 μm).

#### *Electron Microscopic View*

The myofibrils are made up of two sets of protein filaments, thick and thin filaments.

1. **Thick filament:** Made out of myosin (cause for A-band). Myosin molecule is made up of 6 polypeptide; 2 heavy chain and 4 light chain. Myosin treated with proteolytic enzyme (trypsin) reveals 2 fragments.
   i. *Short compact head of heavy meromyosin (HMM):* It has 2 important sites: (a) Actin binding site-where myosin comes in contact with actin, (b) ATPase (catalytic) site-that hydrolyses ATP (Fig. 10.7).
   ii. *Long chain of light meromyosin:* It has only structural function and acts as backbone for HMM.

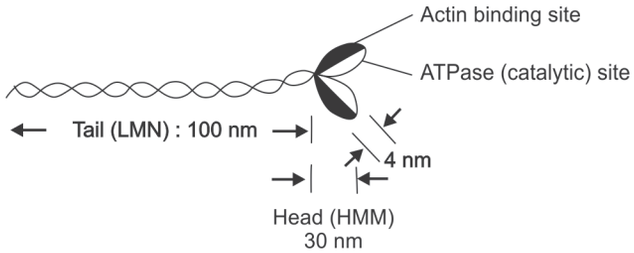



**Fig. 10.7:** Electron microscopic structure of thick filament

2. **Thin filament:** Made of actin, tropomyosin and troponin. They arrange themselves to form 2 chains of globular units that form a double helix (responsible for I-band formation). Each thin filament contains 300–400 actin molecules and 40–60 tropomyosin molecule.

### Actin

It occurs in two forms:
- *G actin:* Each molecule bind with 1 molecule of ATP firmly.
- *F actin:* Formed by polymerization of G actin.

### Tropomyosin

It covers the binding site of actin where myosin head comes in contact with actin, i.e. it prevents interaction between actin and myosin.

### Troponin

They are small globular proteins. It is made up of 3 subunits:
- Troponin 'T'- binds the other troponin components to tropomyosin
- Troponin 'I'- inhibits the interaction of myosin with actin
- Troponin 'C'-contains binding site for $Ca^{2+}$ that initiates muscle contraction.

### Sarcotubular System

It is highly specialized system of internal conduction of depolarization within the muscle fiber. It is made T-system (transverse tubular system) and a longitudinal sarcoplasmic reticulum (LSR).

***T-system***

They are inwardly directed extensions of the sarcolemma into the muscle fibers at the junction between 'A' and 'I' bands (A-I junctions). Its function is the rapid transmission of the action potential from the cell membrane to all the fibrils in the muscle. The T-tubule protein is a modified voltage-sensitive $Ca^{2+}$ channel known as the dihydropyridine receptor (so named because it binds the class of drugs called dihydropyridines). The main role of DHP receptor, however, is not to conduct $Ca^{2+}$, but rather to act as voltage sensor.

***LSR***

Longitudinally on either side of the tubular system are found the sacs of the dilated LSR. These sacs are called terminal cisternae, which are rich in glycogen and $Ca^{2+}$. $Ca^{2+}$ channels in sarcotubular reticulum are not voltage gated and allow the release of Ca into the cell. These are called ryanodine receptors. Traverse tubule with 2 terminal cisterns is called the Triad. There are 2 traid per sarcomere.

### Action

Depolarization of T-tubule cause the DHP receptors to induce a conformational change to open the ryanodine receptors channel. $Ca^{2+}$ is thus released from the lateral sac of sarcoplasmic reticulum. This $Ca^{2+}$ bind with the troponin, removes blocking action of tropomyosin.

## Excitation Contraction Coupling

Process by which depolarization of the muscle fiber initiates contraction. Sequence of events in excitation contraction coupling (Fig. 10.8).

a. ***Steps in muscular contraction:***
   i. Stimulation of motor neuron.
   ii. Release of ACh into synaptic cleft causing generation of endplate potential.
   iii. Depolarization of muscle membrane by increasing its permeability to $Na^{+}$.
   iv. Generation of action potential in the muscle fiber.
   v. Inward spread of action potential along the T-system.
   vi. Spread of depolarization to terminal cistern with release of $Ca^{+}$ in the myofibrils.
   vii. Increase of concentration of $Ca^{2+}$ in ICF by 2000 times.
   viii. Muscle contraction.

***Role of $Ca^{2+}$***

- $Ca^{2+}$ binds with troponin C causing tropomyosin to move laterally. This exposes the binding sites for the myosin heads on the actin.
- Activates prosthetic group of myosin filament which acts as enzyme (ATPase)

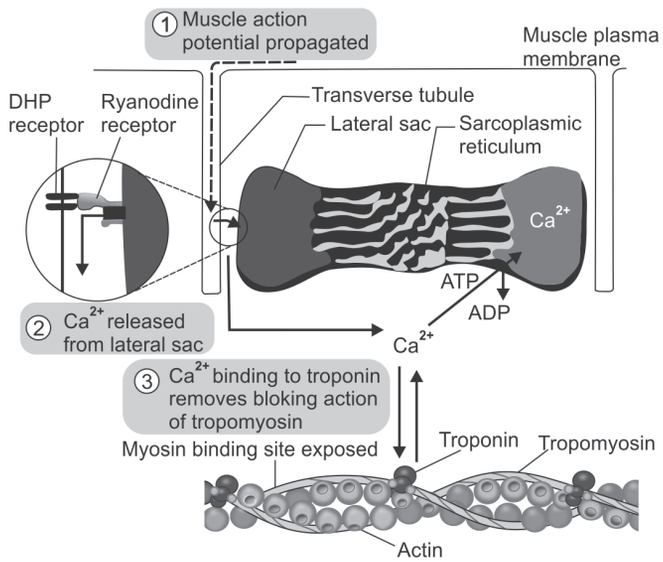



**Fig. 10.8:** Sequence of events in excitation contraction coupling

b. ***Steps in muscular relaxation:*** A few milliseconds after the action potential is over, sarcoplasmic reticulum begins to reaccumulate $Ca^{2+}$. The $Ca^{2+}$ ions are actively pumped by $Ca^{2+}$- $Mg^{2+}$ ATPase into longitudinal portion of the reticulum to terminal cistern for storage.

## *Molecular Basis of Muscular Contraction*

***Sliding filament theory (Ratchet theory):*** The process by which the shortening of the contractile elements in the muscle is brought about is by sliding of actin filament over the thick (myosin) filaments. The sliding of filaments is brought about by formation of the cross-bridges between the head of myosin and actin molecules.

***Events during formation of the cross-bridges***

i. In resting muscle no cross bridges are formed since troponin 'I' is lightly bound to actin and tropomyosin covers the actin sites where myosin bind to actin. Therefore, the troponin–tropomyosin complex constitutes a relaxing protein which inhibits the interaction between actin and myosin.
ii. $Ca^{2+}$ released from the terminal cisterns by the action potential, binds to troponin 'C' and causes.
   a. The binding of troponin 'I' to actin is weakened, this permits tropomyosin to move laterally uncovering the binding sites for myosin heads on actin filaments (Fig. 10.9).
   b. Hydrolysis of ATP by ATPase activity in the myosin heads produces energy.
iii. Seven myosin binding sites on actin filaments are uncovered for each molecule of troponin that binds a $Ca^{2+}$. The heads of the myosin molecules link to the actin, produce movements of myosin on actin by swiveling.

***Mechanism of sliding of thin filaments over thick filaments***

- The sliding during muscle contraction is produced by breaking and re-forming of cross bridges between actin and myosin, repeating the process in serial fashion for 5–6 times (Fig. 10.10).
- The width of 'A' bands is constant, whereas the 'Z' move closer together when the muscle contracts.

## Motor Unit

Motor unit is the functional unit of muscle contraction in the intact body. It consists of the single motor neuron cell body, its axon fibers and the muscle fibers innervated by it. The cell bodies of the motor neurons supplying the skeletal muscle fibers lie in the ventral horn of the spinal cord or the motor cranial nerve nuclei (Fig. 10.11). In simple words, each single motor neuron and all the muscle fibers it supplies constitutes a motor unit.

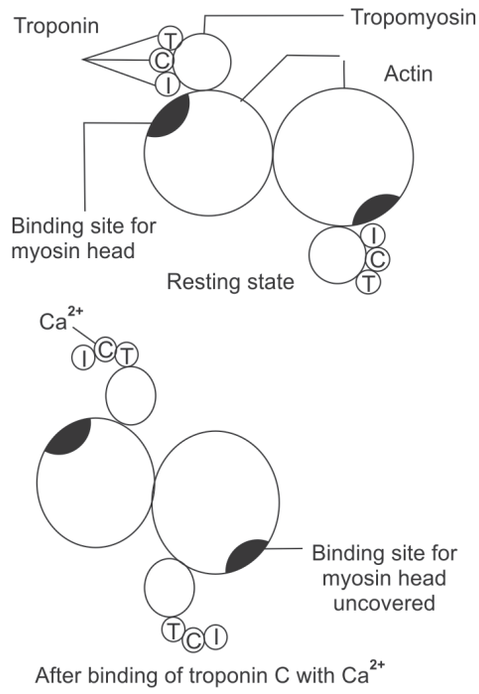



**Fig. 10.9:** Configurational change in thin filament

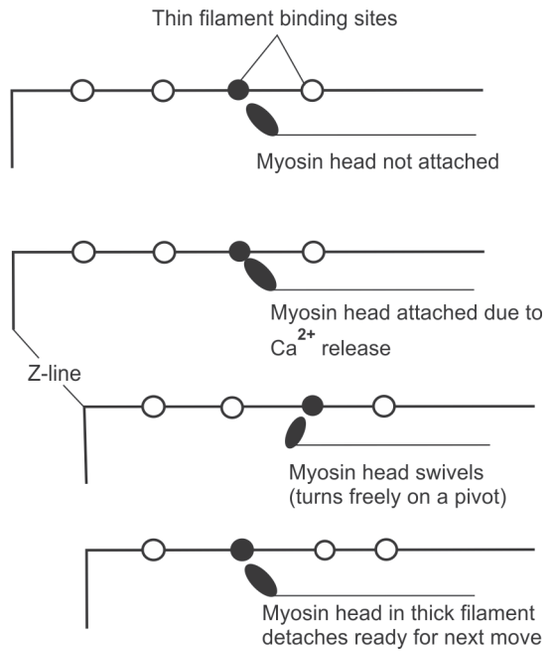



**Fig. 10.10:** Mechanism of formation of cross bridges

### *Properties of Motor Unit*

1. The number of muscle fibers in a motor unit varies inversely with the precision of movements performed by that part.
2. Each motor unit innervates only one type of muscle fiber. In other words, in a single motor unit the muscle fibers

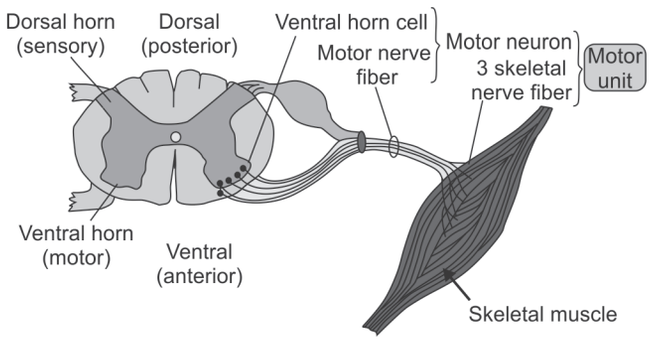



**Fig. 10.11:** Motor unit

supplied by it are of the same type. These are of 2 types- 'red' (Type I) and 'white' (Type II) muscle fibers.

3. All the efferent fibers passing to skeletal muscles are excitatory. There are no efferent nerves which on stimulation produce relaxation of the muscle, i.e. there are no inhibitory efferents to skeletal muscle (as compared to cardiac and smooth muscles where the efferent supply is both excitatory and inhibitory.
4. Depending on the type of muscle fibers they innervate, motor units are of two types, 'slow' and 'fast' motor units.

## Applied Aspect

1. When the motor nerve to a skeletal muscle is cut it causes:
   a. Disuse atrophy of the muscle, i.e. shrinkage of muscle fibers, which finally gets replaced by fibrous tissue (fibrous muscle)
   b. Complete paralysis of the muscle
   c. Appearance of fine, irregular contractions of individual fibers called fibrillations:
   d. Denervation hypersensitivity: These effects are the classical consequences of LMN (lower motor neuron), i.e. injury to the spinal/cranial motor neurons which directly innervate the muscles.
2. *Muscular dystrophy:* It is a syndrome characterized by progressive muscle weakness due to mutation in dystrophin gene, which results in congenital defect in dystrophin-glycoprotein complex. This is a large protein complex that connects the thin filaments to the transmembrane protein in the sarcolemma and thus provides support and strength to the fibers.
3. *Rigor mortis:* When muscle fibers are completely depleted of ATP and phosphocreatine, they develop a state of extremely rigidity called rigor. When this occurs after death, the condition is called rigormortis. In rigor, almost all of the myosin heads attach to actin but in an abnormal, fixed and resistant way.
4. *Myotonia:* A condition characterized by difficulty and slowness in relaxing muscle after voluntary effort. Various forms of myotonia defined clinically are due to abnormal genes on 7, 17 or 19 chromosomes, which results in abnormalities of $Na^+$ on $Cl^-$ channels.

## Types of Muscle Fibers

Muscles can be divided into two types: (i) fast muscles (white muscles) and (ii) slow muscles (red muscles). Fast muscles are pale looking, whereas slow muscles are more red (Table 10.5). This is so because, the slow muscles have greater capillary network. In human beings, most muscles contain a variable mixture of fast and slow muscle fibers. The postural muscles are largely slow muscles.

### *White Muscles*

White muscles constitute 3/4th of the total muscle mass and have greater speed of contractions. They have a resting blood flow of 3 ml/min/100 gm, which may increase to 60–70 ml/

**Table 10.5: Difference between white and red muscles**

| *White (fast) muscle fibers* | *Red (slow) muscle fibers* |
|---|---|
| 1. Muscle fibers are large in diameter with high glycogen capacity and ATPase activity. They are called 'white' muscle fibers because they are pale. | 1. Muscle fibers are of moderate diameter with moderate glycogen capacity and low ATPase activity. They are called 'red' muscle fibers because they are darker than other muscle fibers. |
| 2. They are called 'fast' muscle fibers because they are innervated by large, fast conducting motor neurons. | 2. They are called 'slow' muscle fibers because they are innervated by small, slow conducting motor neurons. |
| 3. These muscles get fatigued easily. | 3. These muscles are resistant to fatigue and are the most used muscles. |
| 4. These muscles are specialized for fine rapid and skilled movements and have short twitch durations (7.5 sec). For example, muscles of the hand and extraocular muscles. | 4. These muscles respond slowly (which duration 100 msec) and have long latency period. They are adapted for sustained, slow and posture maintaining contractions. For example, long muscles of limb and muscles of back. |
| 5. They are particularly suited to perform high intensity work that can be sustained for only short period of time. | 5. They are particularly suited to perform low intensity work over long periods of time such as for athletes, swimmers, etc. |

min/100 gm in maximal exercise. These muscles are prone to $O_2$ debt.

### *Red Muscles*

They comprise 25% of the total muscle mass and are concerned with maintenance of posture. Their activity is of the steady prolonged type which requires a relatively low $O_2$ usage. Their resting blood flow is 20–30 ml/min/100 gm due to low basal myogenic tone. They have vascular bed 3 times the size of white muscles with high flow capacity, approx. 150 ml/min/100 gm. Because of greater surface area of the capillary bed and their lower $O_2$ requirement, these muscles are unlikely to be exposed to $O_2$ debt.

## SMOOTH MUSCLE

Smooth muscle is distinguished anatomically from skeletal and cardiac muscle because it lacks visible cross striations. Actin and myosin-II are present and they slide on each other to produce contraction. However, they are not arranged in regular arrays, as in skeletal and cardiac muscle, and so the striations are absent.

### Types

There is considerable variation in the structure and function of smooth muscle in different parts of the body. In general, smooth muscle can be divided into visceral/unitary smooth muscle and multiunit smooth muscle (Table 10.6).

### *Visceral Smooth Muscle*

#### *Electrical and Mechanical Activity*

Visceral smooth muscle is characterized by the instability of its membrane potential and by the fact that it shows continuous, irregular contractions that are independent of its nerve supply. This maintained state of partial contraction is called tonus or tone.

The membrane potential has no true "resting" value, being relatively low when the tissue is active and higher when it is inhibited, but in periods of relative quiescence it averages about –50 mV. The excitation-contraction coupling in visceral smooth muscle is a very slow process compared with that in skeletal and cardiac muscle, in which the time from initial depolarization to initiation of contraction is less than 10 msec.

### Molecular Basis of Smooth Muscle Contraction

$Ca^{2+}$ is involved in the initiation of contraction of smooth muscle. However, visceral smooth muscle generally has a poorly developed sarcoplasmic reticulum and the increase in intracellular $Ca^{2+}$ concentration that initiates contraction is primarily due to $Ca^{2+}$ influx from the ECF via voltage-gated and ligand-gated $Ca^{2+}$ channels.

In addition, the myosin in smooth muscle must be phosphorylated for activation of the myosin ATPase. In smooth muscle, $Ca^{2+}$ binds to calmodulin and the resulting complex activates calmodulin-dependent myosin light chain kinase. This enzyme catalyzes the phosphorylation of the myosin light chain on serine at position 19. The phosphorylation allows the myosin ATPase to be activated and actin slides on myosin, producing contraction. This is in contrast to skeletal and cardiac muscle, where contraction is triggered by the binding of $Ca^{2+}$ to troponin C. Myosin is dephosphorylated by myosin light chain phosphatase in the cell. This enzyme is inhibited when it is phosphorylated and activated by dephosphorylation. It is dephosphorylated by a rho-associated kinase that is activated by ligands which produce inhibition of smooth muscle activity. However, dephosphorylation of myosin light chain kinase does not necessarily lead to relaxation of the smooth muscle. Various other mechanisms such as latch bridge mechanism by which myosin cross-bridges remain attached to actin for sometime after the cytoplasmic concentration falls. This produces sustained contraction with little expenditure of energy, which is especially important in vascular smooth muscle. Relaxation of the muscle presumably occurs when there is final dissociation of the $Ca^{2+}$-calmodulin complex or when some other mechanism comes into play. The events leading to contraction and relaxation of visceral smooth muscle are summarized.

1. Binding of acetylcholine to muscarinic receptors
2. Increased influx of $Ca^{2+}$ into the cell
3. Ca binds with calmodulin
4. Activation of calmodulin-dependent myosin light chain kinase
5. Phosphorylation of myosin
6. Increased myosin ATPase activity and binding of myosin to actin
7. Contraction
8. Dephosphorylation of myosin by myosin light chain phosphatase
9. Relaxation or sustained contraction due to the latch bridge and other mechanisms

**Table 10.6: Difference between single unit and multiunit muscle**

| *Single unit/Visceral smooth muscle* | *Multiunit smooth muscle* |
|---|---|
| 1. It is called single unit smooth muscles because it functions in a syncytial fashion. It occurs in large sheets and has low resistance fashion. Single unit smooth muscles have low resistance bridges between individual muscle cells. | 1. It is called multiunit smooth muscle because it is made up of individual units without interconnecting bridges, i.e. non-syncytial in character. So its contractions are discrete, fine and localized. |
| 2. Location-Wall of hollow viscera, i.e. GIT, ureters, bronchi, uterus and urinary bladder. | 2. *Location:* Ciliary muscles of eye, iris, pilomotor muscle of skin and muscles of blood vessels. |
| 3. In certain areas the muscles are characterized by appearance of spontaneous activtiy, so called. | 3. Each muscle fiber of multiunit smooth muscle has its own nerve supply. |
| 4. Rhythmic contraction and relaxation of these muscles is independent of their innervation. Innervation has role only in modulating its activity. | 4. These muscles are sensitive to chemical mediators at the nerve endings (ACh or NE) in response to which muscle contracts. Single stimulus to the nerve causes repeated firing of action potential which produces irregular tetanic contractions rather than a single muscle twitch as seen in skeletal muscle. |
| 5. Active tension is produced when the muscle is stretched. | 5. No response by the muscle to stretch. |

**Table 10.7: Skeletal muscle, cardiac and smooth muscles compared**

| *Characteristics* | *Skeletal muscle* | *Cardiac muscle* | *Smooth muscle* |
|---|---|---|---|
| 1. Distribution | Fixed to skeleton | Heart only | Two types: Single and multi |
| 2. Structure | Striated; multi-nucleated; non-syncytial | Striated and branched; single nucleus; syncytial | Unstriated; single nucleus; both synctial and non-syncytial |
| 3. Sarcoplasmic reticulum | Well developed | Well developed | Poorly developed |
| 4. Sarcotubular system | Present at A-I junction | Present at Z-lines | Present but not so characteristic |
| 5. Nerve supply | Via somatic nerve | Via 2 branches of ANS | Via two branches of ANS |
| 6. Control | Voluntary | Involuntary | involuntary |
| 7. Blood supply | 3–4 ml/100 gm | 80 ml/100 gm/min | 1.4 ml/100 gm/min |
| 8. RMP | -90 mV | -80 mV | -55 mV unstable |
| 9. Action potential | | | |
| i. Duration | 30-40 msec | 250 msec at HR 75 bpm | 50 msec |
| ii. Amplitude | 120 mV | 100 mV | 60 mV |
| 10. Absolute refractory period | 1–3 msec | 180–200 msec | Not defined |
| 11. Phenomenon of tetanus | Present | Not seen | Seen |
| 12. Muscle twitch duration | 7.5 msec (fast muscle)<br>100 msec (slow muscle) | 1 1/2 times the total duration of action potential | 100 msec |
| 13. Excitation contraction coupling | Rapid process | More rapid process | Very slow process |
| 14. All or none law | Application for single muscle fiber | True for whole of artria or ventricles | True for single muscle fiber |
| 15. Length tension relationship | Maximum active tension at the optimal length | Similar to skeletal muscle | Shows property of plasticity |
| 16. Phenomenon of fatigue | Possible | None | Possible |

*Chapter*

# 11

# Central Nervous System

Nervous system is divided into central nervous system and peripheral nervous system. The central nervous system consists of brain and spinal cord. Peripheral nervous consists of the nerves extending outside the CNS. It is divided into somatic and autonomic nervous system.

## Brain

The brain has three parts:

1. Forebrain (Prosencephalon) comprises:
   i. Telencephalon-consists of cerebrum and their interconnections.
   ii. Diencephalon-thalamus plus hypothalamus.
2. Midbrain (Mesencephalon)
3. Hindbrain (Rhombencephalon) comprises:
   i. Pons
   ii. Medulla oblongata
   iii. Cerebellum.

## Spinal Cord

A cross-section of spinal cord (Fig. 11.1) shows the following structures: (a) Anterior median fissure, (b) Posterior median fissure, (c) Central canal, (d) Anterior horn, (e) Posterior horn, (f) Anterior gray commissure, (g) Posterior gray commissure, (h) Anterior white column, (i) Posterior white column, (j) Lateral white column.

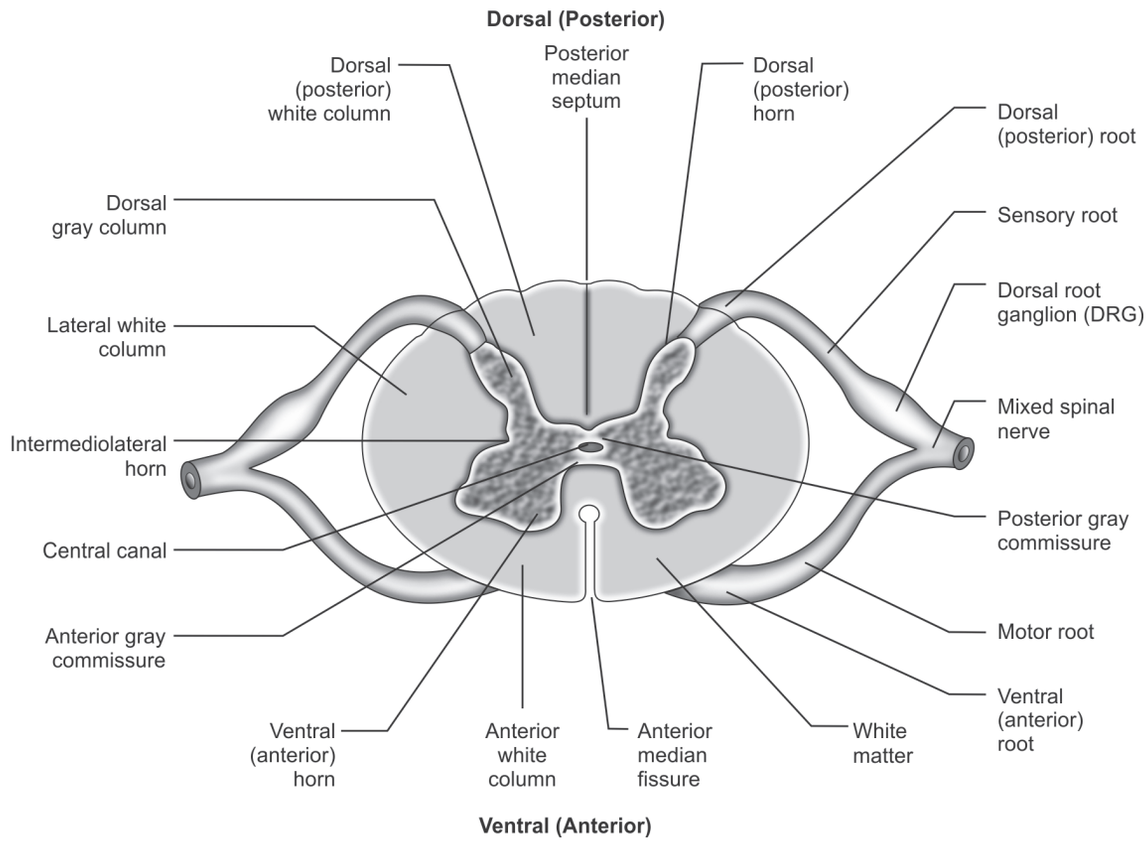



**Fig. 11.1:** Cross-section of spinal cord

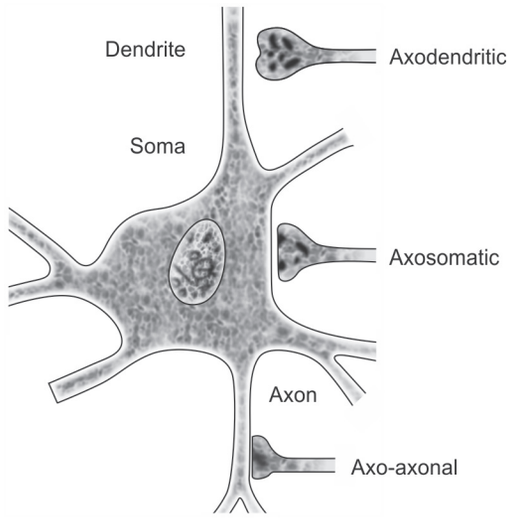



**Fig. 11.2:** Types of synapses

## SYNAPSE

Information about external environment is sensed by receptors which acts as transducer. They convert sensations to action potential which travel via nerve fibers to the center. Hence, there is a series of nerve fiber to the center. The junction between different neuron is known as synapse. It may be a junction between:

- Two neurons
- Neuron and a muscle
- Neuron with different glands of the body.

### *Types of Synapse (Fig. 11.2)*

Axodendritic-axon of one neuron with dendrite of other.
Axosomatic-axon of one neuron with soma of other.
Axo-axonal-axon with axon.

### *Physiological Classification of Synapse (Table 11.1)*

- Chemical Synapse
- Electrical Synapse

### Electrical Events at Synapses

Single stimulus applied to the sensory nerves, does not lead to the formation of a propagated action potential. In a postsynaptic neuron, rather it produces a transient partial depolarization or a transient hyperpolarization.

### *Excitatory Postsynaptic Potential*

The combination of chemical transmitter (like glutamate and aspartate) with the receptor makes the postsynaptic membrane partially depolarized, i.e. there is a drop of potential across the membrane (from–80 mV to –65 mV). This difference (+15 mV) is called excitatory postsynaptic potential (EPSP). The initial depolarizing response produced by a single stimulus to the sensory input begins about 0.5 msec after the afferent impulse enters the spinal cord. It reaches its peak 1–1.5 msec later, and then declines exponentially over the next 4 msec if it is not sufficient to cause generation of a spike. During this period the excitability of the neuron to other stimuli is increased, and consequently the potential is called EPSP. Excitatory postsynaptic potential (EPSP) makes the postsynaptic membrane hypopolarized and if sufficiently strong, causes an action potential to develop in the postsynaptic membrane.

#### *Ionic Basis of Development of EPSP*

AP come → Synaptic transmitter released → Synaptic transmitter combines with the receptors of postsynaptic membrane and this combining causes opening of $Na^+$ $Ca^{2+}$ ion

**Table 11.1: Difference between chemical and electrical synapse**

| *Chemical synapses* | *Electrical synapses* |
|---|---|
| 1. Transmission of impulses from pre to postsynaptic site occurs due to release of chemical mediators | 1. Gap junctions which are formed by the close approximation of pre and postsynaptic membranes act as low resistance bridges through which ions pass easily |
| 2. Seen at most of the synaptic junctions in the nervous system. Unidirectional transmission of signals, i.e. from presynaptic to postsynaptic neuron | 2. Seen at some of the synaptic junctions in the nervous system and can transmit signals in either direction, e.g. Lateral vestibular nucleus, cerebral cortex, hippocampus |
| 3. Presence of synaptic cleft | 3. Synaptic cleft is replaced by low resistance bridges |
| 4. Synaptic delay present | 4. Synaptic delay absent due to low resistance bridges |
| 5. Sensitive to hypoxia | 5. Insensitive to hypoxia |
| 6. Infinite processing of information possible as it allows for large number of synapses per neuron and a large variety of neurotransmitters. This is of immense help in the processing of learning and memory | 6. Transmission across it is rapid and efficient as there are not too many synapses on the same neuron |

channels in the postsynaptic membrane → entry of $Na^+$ and other cations inside the cell from the ECF → hypopolarization and development of EPSP in the postsynaptic membrane. EPSP can also be produced by agents that close $K^+$ channels.

Excitatory postsynaptic potential (EPSP) due to activity in 1 synaptic knob is small, but EPSP produced by each of the active knobs summate. This summation may be spatial or temporal summation.

1. *Spatial summation (Fig. 11.3):* On stimulating two afferent nerve fibers simultaneously, both of which make synaptic connections with the motor neuron, their EPSP's get summated to the critical level and thus may produce a 'spike' discharge from the motor neuron. This is called spatial summation. In other words activity in one synaptic knob facilitates activity in another to approach the firing level.
2. *Temporal summation:* If we stimulate an afferent nerve fiber for the 2nd time before the decay of the 1st stimulation, neither of which alone can generate a 'spike' from the motor neuron; however, each produces some EPSP which get summated to the critical level necessary for the initiation of a 'spike' potential. This is called temporal summation (Fig. 11.4).

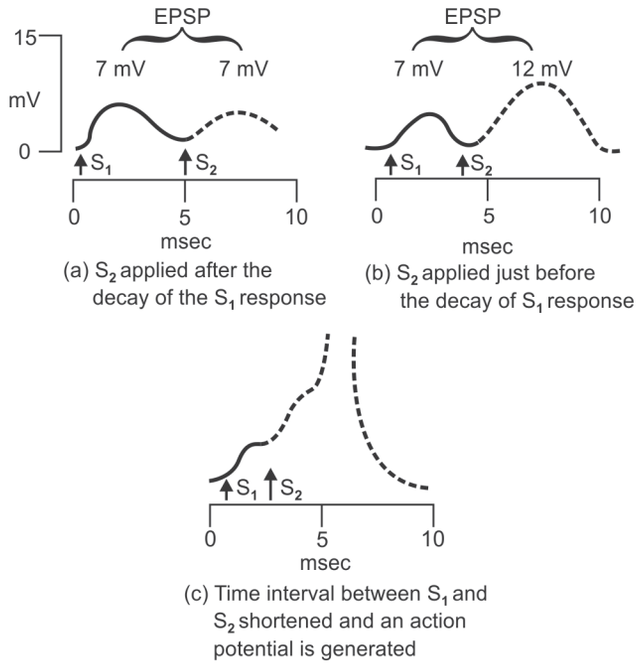



**Fig. 11.4:** Temporal summation

### *Inhibitory Postsynaptic Potential*

Sometimes the combination of chemical transmitter (like GABA, Glycine in brainstem and spinal cord) with the receptor makes the postsynaptic membrane hyperpolarized (For example, the RMP of –80 mV becomes –90 mV). This difference (–10 mV in this case) is called inhibitory postsynaptic potential (IPSP). Hyperpolarization begins at 1–1.5 msec after the entry of afferent impulse into the spinal cord and rises to peak in 1–5 -2 msec after its onset and declines exponentially with a time constant (time to decay to 1/e, or 1/2.718 of maximum) of about 3 msec. During this potential, the excitability of the neuron to other stimuli is decreased; consequently, it is called an IPSP.

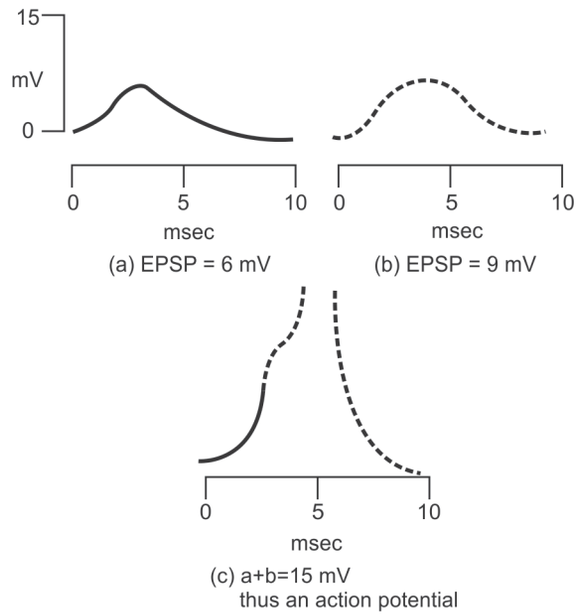



**Fig. 11.3:** Spatial summation

### *Ionic Basis of Development of IPSP*

Inhibitory postsynaptic potential (Fig. 11.5) is due to inhibitory chemical transmitter liberated on the subsynaptic membrane, therefore it becomes permeable to $K^+$ and $Cl^-$ but retains a high degree of impermeability to $Na^+$. This results in hyperpolarization of the whole postsynaptic membrane. IPSPs can also be produced by opening of $K^+$ channels, with movement of $K^+$ out of the postsynaptic cell. In addition, they can be produced by closure of $Na^+$ or $Ca^{2+}$ channels.

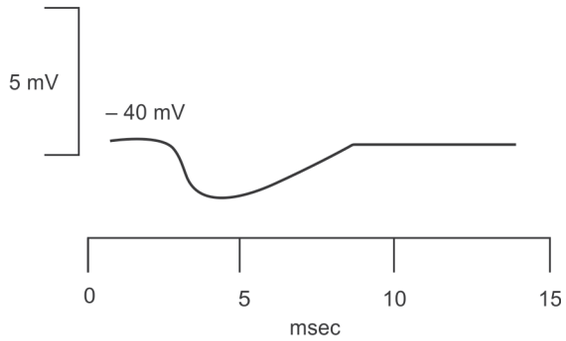



**Fig. 11.5:** Inhibitory postsynaptic potential

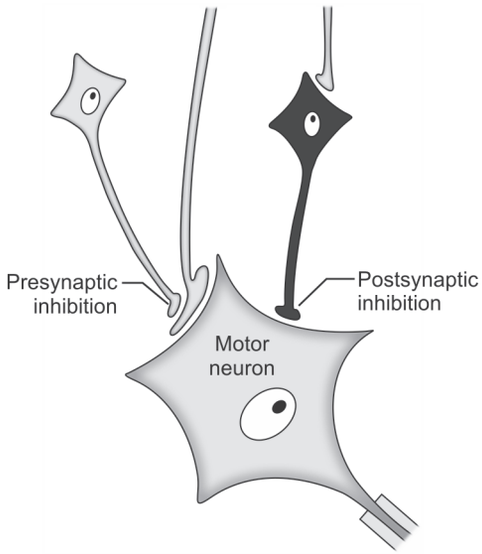



**Fig. 11.6:** Presynaptic and postsynaptic inhibition

## Synaptic Inhibition

It is of two types: Postsynaptic and presynaptic (Fig. 11.6).

### *Postsynaptic Inhibition*

It depends upon the delivery of an inhibitory chemical by the incoming axons which hyperpolarize the subsynaptic membrane. It is subdivided into direct and indirect inhibition:

a. **Direct inhibition (by development of IPSP):** Afferent fibers from muscle spindle (stretch receptors) in skeletal muscle are known to pass directly to the spinal motor neuron of the motor unit supplying the same muscle. Impulses in this afferent supply cause EPSP which summate to produce propagated response in postsynaptic motor neurons. At the same time, IPSP's are produced in motor neurons supplying the antagonist muscles. This later response is mediated by branches of afferent fibers that end on golgi bottle neurons. These interneurons, in turn, secrete the inhibitory transmitter glycine at synapses on the proximal dendrites or cell bodies of the motor neurons that supply the antagonist (Fig. 11.7). Therefore, activity in the afferent fibers from the muscle spindles excites the motor neurons supplying the muscle from which the impulses come and inhibits those supplying its antagonists **(reciprocal innervation)**.

b. **Indirect inhibition** (due to the effect of previous postsynaptic neuron discharge), e.g.
   - Postsynaptic cell can be refractory to excitation because it has just fired and is in its refractory period.
   - During after hyperpolarization.
   - Renshaw cell inhibition or negative feedback inhibition

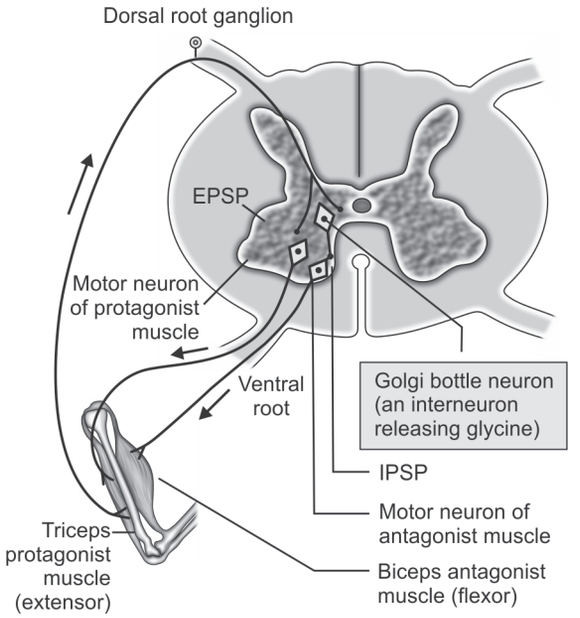



**Fig. 11.7:** Postsynaptic inhibition in the spinal cord: An example of "Direct inhibition"

### *Renshaw Cell Inhibition*

In this inhibition, motor nerve gives off some collateral branches as they traverse the spinal cord towards the ventral root and these collaterals make excitory synaptic connections with interneurons, called Renshaw cell situated in the

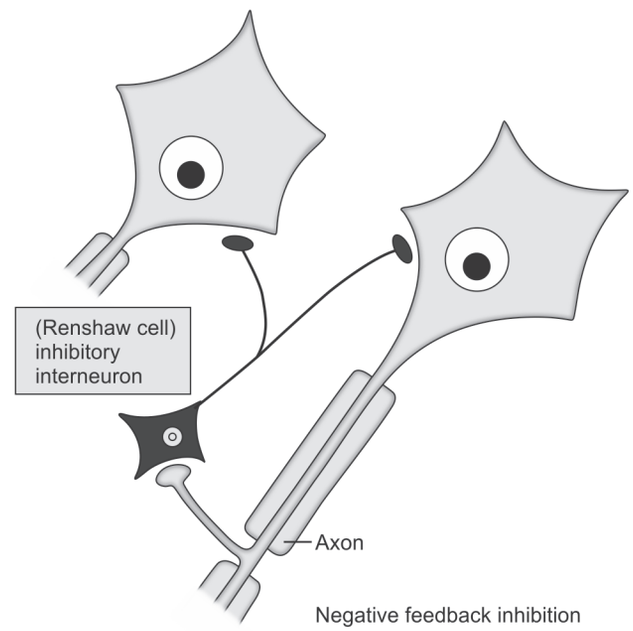



**Fig. 11.8:** Renshaw cell inhibition/Negative feedback inhibition

ventromedial part of ventral horn (Fig. 11.8). These Renshaw cell in turn send axons which make inhibitory synaptic connections with the motor neurons. Renshaw cell are stimulated by ACh.

### *Presynaptic Inhibition*

This type of inhibition occurs at the presynaptic terminals before the signal ever reaches the synapse. Presynaptic inhibition occurs because of failure of the release of excitatory neurotransmitter substance from the presynaptic axon terminal. This occurs in synapses where an inhibitory neuron (C in Fig. 11.9) synapses with the afferent fibers of an excitatory neuron (A in Fig. 11.9) before the later synapses with the efferent neuron (B in Fig. 11.9). In other words the presynaptic inhibition occurs because of axo-axonal synapses.

Activation of presynaptic receptors reduces the opening of $Ca^{2+}$ channels directly or increases $Cl^-$ and or $K^+$ conductance (which indirectly reduces $Ca^{2+}$ entry), and this decrease the size of the action potential reaching the excitatory ending. So the amount of excitatory transmitter released is reduced. The inhibitory transmitter at the axo-axonal synapse is GABA. Acting via GABA A receptors, it increases $Cl^-$ conductance, whereas GABA B receptors via G protein, produces an increase in $K^+$ conductance. Other transmitters also mediate presynaptic inhibition by G protein-mediated effects on $Ca^{2+}$ channels and $K^+$ channels.

***Note***

1. Presynaptic facilitation is produced when the action potential is prolonged and the $Ca^{2+}$ channels are open for a longer period. Therefore, repolarization gets delayed, allowing depolarization to continue. It is mediated by serotonin (Serotonin released at an axo-axonal ending increases intraneuronal cAMP levels, and the resulting phosphorylation of one group of $K^+$ channels closes the channels, slowing repolarization and prolonging the action potential).
2. *Feed forward inhibition:* It is seen in cerebellum. In this type of inhibition a neuron is connected through two pathways: One excitatory and other inhibitory. For example, in cerebellum the stimulation of Basket cells (BC in Fig. 11.10) produces IPSPs in the Purkinje cells (PC in Fig. 11.10). However, the basket cells and the Purkinje cells are excited by the same parallel-fiber excitatory input. This arrangement is called feed forwad inhibition. and helps to prevent the duration of the excitation produced by any given afferent impulse.

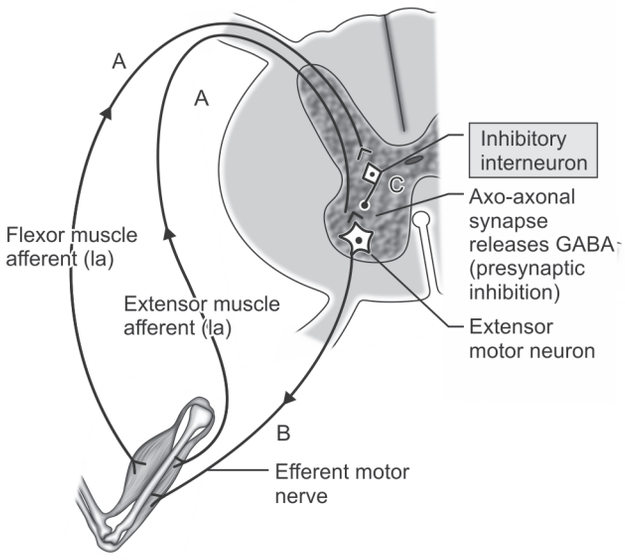



**Fig. 11.9:** Presynaptic inhibition

## Properties of Synapse

1. *Convergence and Divergence:* Many presynaptic neurons meet on a common focus on any single postsynaptic membrane called convergence. For example in spinal motor neuron, some inputs come directly from the dorsal root, some from the long descending spinal tracts, and many from interneurons.

   The axon of most presynaptic neurons divide into many branches that separate out in different direction to end on many postsynaptic neurons called divergence.
2. *One way conduction:* Synapses permits conduction of impulses in one direction only, i.e. from the presynaptic to postsynaptic neuron. This is because the chemical mediator at the synaptic junction is located in the synaptic knob of the presynaptic fibers but not in the postsynaptic membrane.

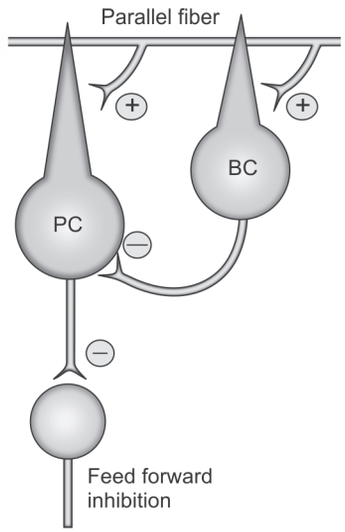



**Fig. 11.10:** Feed forward inhibition

3. *Synaptic delay:* When an impulse reaches the presynaptic terminals, there is a gap of about 0.5 msec before a response is obtained in the postsynaptic neuron called synaptic delay. This is due to the time it takes for the synaptic mediator to be released and to act on the postsynaptic membrane.

   ***Significance***

   a. Conduction along a chain of neurons is slow if there are many synapse in the chain.
   b. It is possible to determine whether a given synapse is mono or polysynaptic.

4. *Synaptic Fatigue/Habituation:* Repeated stimulation of presynaptic neuron lead to gradual decrease and finally disappearance of the postsynaptic response.
   For example epilepsy
5. *Summation (Fig. 11.11)*
   Hypothetic nerve neuron A and B converge on X.B diverges on X and Y.A stimulus applied to A or B will set-up an EPSP in X.
   - If A and B are stimulated at the same time, two areas of depolarization will be produced in X and their action will sum up **called spatial summation.**
   - If neuron B is stimulated repeatedly, X and Y will discharge called **temporal summation.**
6. *Occlusion (Fig. 11.12):* When two afferent nerves A (suppose it is 5 units) and B (5 units) to a skeletal muscle are simultaneously stimulated, it is sometimes seen that the tension developed by the muscle under observation is less than the sum of tension produced by each afferent nerve stimulated separately. This phenomenon is called occlusion. This is because some of the motor neurons which are common to both, are excited maximally when either A or B is stimulated separately; they give no greater response when A or B are stimulated together. This decrease in response is due to presynaptic fibers sharing postsynaptic neurons (refer the figure given for summation). Thus, occlusion is due to afferent fibers overlapping in their central distribution.

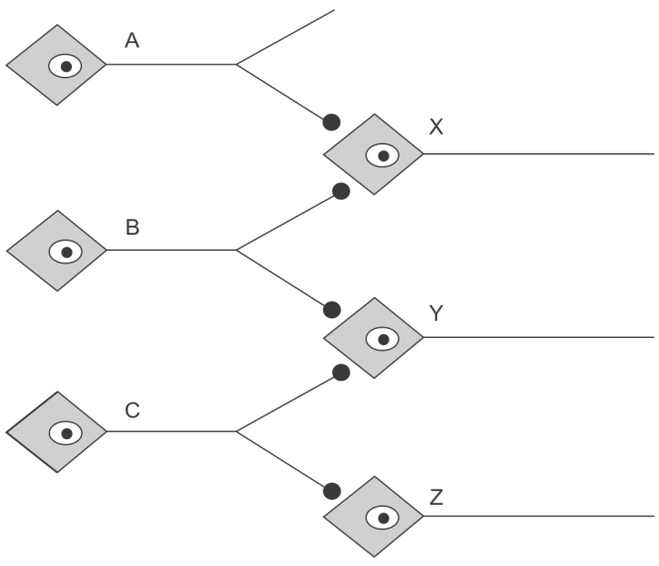



**Fig. 11.11:** Summation

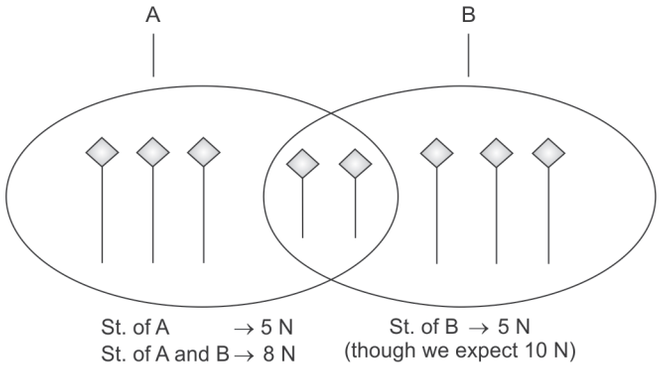



**Fig. 11.12:** Occlusion

7. *Subliminal fringe:* Subliminal means below the threshold, and fringe means border, thus the postsynaptic neurons are said to be in the subliminal fringe if they are not discharged by activity in the presynaptic neurons but do have their excitability increased.

   When two afferent excitatory nerves A (suppose it is 3 units) and B (3 units) to a skeletal muscle are stimulated at the same time, two areas of depolarization will be produced, and sometimes the tension developed by the muscle is greater than the sum of tension produced by each afferent nerve stimulated separately (Fig. 11.13). This is because, effect of each depolarization while fully activating a certain number of motor neurons also acts on a further number subliminally; and that some of these subliminally influenced motor neurons are common to 'A' and 'B'. As a result, subliminal excitation can thus sum up to produce threshold stimulation. This is another example of spatial summation.

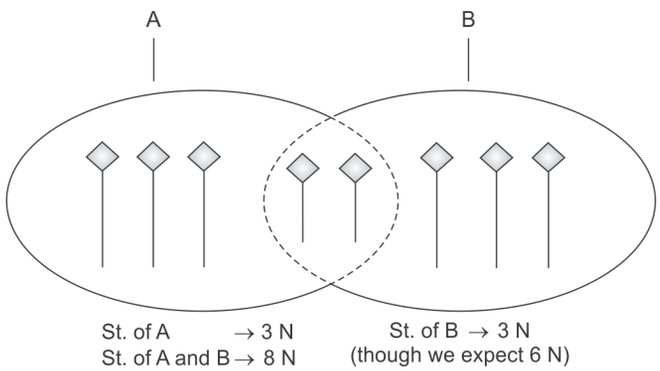



**Fig. 11.13:** Subliminal fringe

8. *Synaptic plasticity:* Plasticity means the capability of being easily moulded or changed. Synaptic conduction thus can be increased (strengthened) or decreased (weakened) on the basis of past experience. These changes can be presynaptic or postsynaptic and play an important role in learning and memory.

### Forms of Synaptic Plasticity

a. *Post-tetanic potentiation:* Here, a brief tetanizing stimuli in the presynaptic neuron results in increased production of postsynaptic potentials lasting up to 60 sec. It occurs due to increased $Ca^{2+}$ in the presynaptic neuron (Fig. 11.14). Hence, the response is potentiated.
b. *Long-term potentiation:* If post-tetanic potentiation gets much more prolonged and lasts for days, it is called long-term potentiation. It is due to increase in intracellular $Ca^{2+}$ in the postsynaptic neuron rather than presynaptic. It occurs in many parts of the nervous system but has been studied in greatest detail in the hippocampus.
c. *Long-term depression:* It is opposite to long-term potentiation (LTP). It resembles LTP in many ways, but it is characterized by a decrease in synaptic strength. It is produced by slower stimulation of presynaptic neurons and is associated with a smaller rise in intracellular $Ca^{2+}$ than occurs in LTP. This phenomenon commonly occurs in the hippocampus and the cerebellum.
d. *Habituation:* When a same stimulus occurs again and again, the response to stimulus decreases referred to as habituation.
e. *Sensitization:* It is the prolonged occurrence of increased postsynaptic responses after a stimulus (to which an animal is habituated ) is paired once or several times with a noxious stimulus. It is due to presynaptic facilitation. Sensitization may occur as a transient response, or if it is reinforced by additional pairings of the noxious stimulus and the initial stimulus. It is due to a $Ca^{2+}$ mediated change in adenylyl cyclase that leads to a greater production of cAMP.

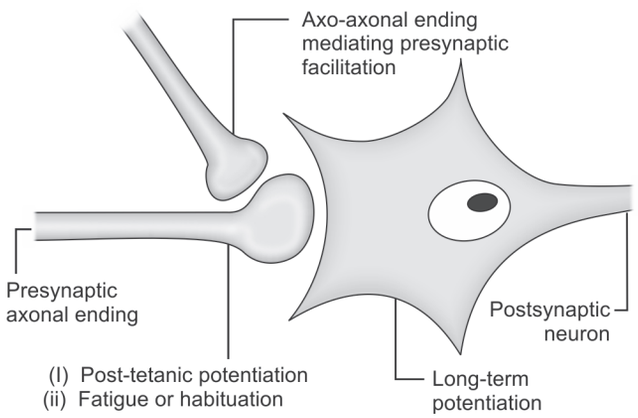



**Fig. 11.14:** Synaptic plasticity

***Note***

*Effect of pH*

*Alkalosis:* When pH is increased the neuronal excitability is markedly elevated.

*Acidosis:* When pH is decreased the neuronal excitability is decreased. For example in diabetic ketoacidosis neuronal excitability decreases.

## RECEPTORS

Receptors (Fig. 11.15) are transducers that converts various forms of energy into action potential and nerve impulses. Sensory system starts with receptors. Information about various internal and external environment reaches nervous system via various receptors. Sensory receptors may be a part of a neuron or a specialized cell that can generate

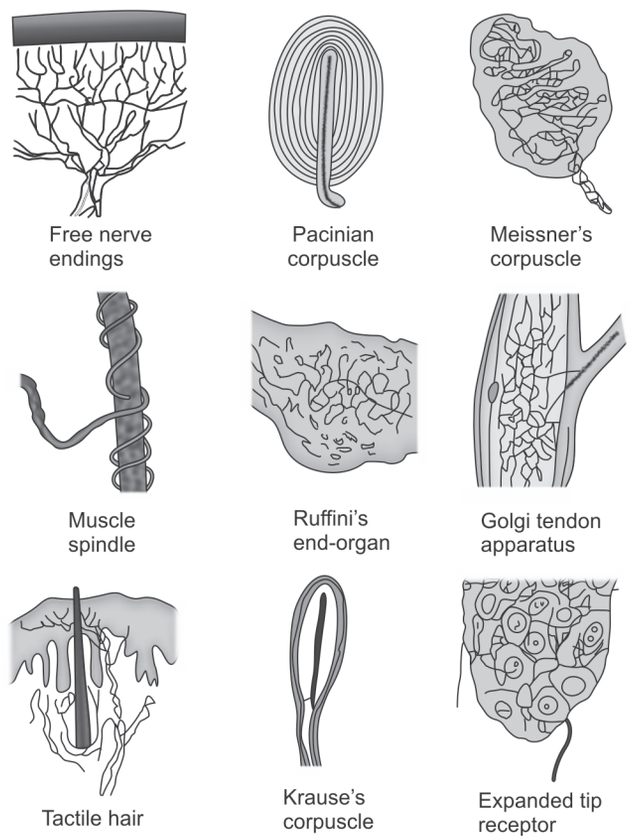



**Fig. 11.15:** Cutaneous receptors

action potential in afferent neuron. Receptors along with the surrounding non neural cells is called sense organs.
There are five basic types of receptors:

1. *Mechanoreceptors:* Mechanical compression and stretching of receptors are detected. For example, tactile receptors, pacinian corpuscles, muscle spindles, Golgi tendon organ, proprioceptors.
2. *Thermoreceptors:* Detect changes in warm and cold temperature.
3. *Nociceptors:* Detect damages occuring in tissues like pain.
4. *Electromagnetic receptors:* For example, rods and cones.
5. *Chemoreceptors:* For example, taste and smell, carotid body and aortic body, chemoreceptors in hypothalamus, osmoreceptors in hypothalamus.

## Properties of Receptors

1. *Adequate stimulus:* Receptors in each of the sense organs are adapted to respond to one particular form of energy (stimulus) at a much lower threshold than other receptors respond to this form of energy which is called adequate stimulus. For example, touch for tactile receptors, light for rods and cones.
2. *Receptor/generator potential:* Whatever be the strength of stimulus that excites the receptor, its immediate effect is to change the membrane electrical potential of the receptor. The receptor converts mechanical energy into electrical response called sensory transduction.

   Small depolarizing potential developed in receptors is called receptor/generator potential. It is a nonpropagated local graded potential, i.e. magnitude is proportionate to the strength of stimulus (does not obey all or none law). It depolarizes the nerve at 1st node of Ranvier. Once the firing level is reached, an action potential is developed and is propagated. If the receptor potential is great enough, the neuron fires again and again as soon as it repoarizes and it continues to fire as long as the generator potential is at the threshold level of excitation. Thus, the node converts graded response of receptor potential into action potential. The frequency of action potential in the sensory nerve is proportionate to the strength of stimulus.

   **Mechanism of Generation**

   The basic cause of receptor potential is change in membrane permeability. This is explained below by taking the case of pacinian corpuscle. In pacinian corpuscle the central fibers are surrounded by capsule of multiple layer of connective tissue. Compression anywhere in capsule deform the membrane of nerve fiber. Tip of nerve which is inside the capsule is demyelinated. 1st node of Ranvier is inside the capsule.

   **Ionic Basis**

   Compression on the capsule → nerve endings deformed → sodium channels open → depolarization → receptor potential generated → action potential at 1st node of ranvier → propagated along sensory nerve fibers.
3. *Adaptation:* When a sustained stimulus of constant strength is applied, the frequency of action potential in its sensory nerve declines gradually. Based on degree, there are two types of adaptations:
   Rapidly adapting. For example, touch receptors.
   Slowly adapting. For example, pain receptors, chemoreceptors, baroreceptors, stretch receptors.
4. *Intensity discrimination/Sensory coding:* Information about intensity of stimulus (e.g. whether touch is fine or crude) to brain is transmitted by two mechanisms:
   a. By variation in frequency of action potential generated in the sensory nerve. This depends on the magnitude of receptor potential. As receptor potential increases, frequency of action potential increases.
   b. By variation in number of receptors stimulated.
      According to **Weber Fechner law**, magnitude of sensation (S) felt is proportional to the logarithm of intensity (I) of stimulus.
      $S = k \log I + C$ , where k and C are constants.
5. *Labelled line principle:* In the normal course, a touch or pain or temperature receptor is connected to a specific series of neurons which carry the message up to the cerebral cortex where it is interpreted. It is interesting to question whether the perceived modality of a stimulus depends on the receptor, or on the pathway through which it travels. But the modality actually depends upon the pathway. To understand better let as consider an example (though impractical), if the retina where connected to the auditory nerve, stimulation of the retina by light would evoke a sensation of sound. That is, we would be able to 'hear a torch'. This concept of the modality being dependent on the pathway has been termed as the labelled line principle. That is the pathways (or lines) are labelled as touch lines, temperature lines, etc. Thus, a labelled line sensory channel consists of a set of neurons devoted to carry particular sensory modality.
6. *Muller's doctrine of specific nerve energy:* Nerve fibers transmit only nerve impulse or action potential, but we experience different sensations. For example, the action potential produced in a nerve fiber from a thermoreceptor is identical to that produced in a tactile receptor. There are separate pathway for each sensation. Each nerve tract terminate at a specific point in CNS. The type of sensation felt when nerve fiber is stimulated is determined by the point in the nervous system (cortex), where the fibers



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ends. When the nerve pathway from a particular sense organ is stimulated, the sensation is produced for which the receptor is specialized, no mattter how or where along the pathway it is stimulated. This principle is called Muller's doctrine of specific nerve energy. For example if the sensory nerve from a pacinian corpuscle in the hand is stimulated by pressure at the elbow or by irritation from a tumor in the brachial plexus,the sensation evoked is touch.

7. *Law of projection:* If we stimulate anywhere in the pathway, the sensation produced is projected to the area where receptors are located. This explains the phantom limb phenomenon:

### *Phantom Limb*

If a person's limb is amputated, ends of nerve cut at the time of amputation form nerve tangles or neuromas. These are hyper sensitive. These neuromas are stimulated with minimum stimulus or discharge spontaneously. This generates impulses in nerve fiber that previously came from the receptors in the removed limb and the sensation produced are projected to where the receptors used to be located.

## REFLEXES

Reflex is an involuntary (automatic) response to a stimulus. It depends on integrity of reflex pathway, i.e. the reflex arc. Here, a sensory impulse is automatically converted into a motor effect through the involvement of central nervous system. When a person walks bare footed and he steps over a thorn he withdraws his affected limb while extends his other limb (to support the body weight), the whole action is reflex and does not require the presence of will.

### Reflex Arc

It consist of a receptor, an afferent neuron, an efferent neuron and an effector organ (Fig. 11.16). The number of synapses (connection between afferent and efferent neurons) vary from one to many hundred. These synapses are located in the brain or spinal cord.

Activity in the reflex arc starts in a sensory receptor with a receptor potential, which is a nonpropagated graded response whose magnitude is proportionate to the strength of the stimulus. This generates all-or-none action potentials

**Table 11.2: Comparison between end-plate potential, postsynaptic potential, receptor potential and action potential**

| | *End-plate potential (EPP)* | *Postsynaptic potential (PSP)* | *Receptor potential (RP)* | *Action potential (AP)* |
|---|---|---|---|---|
| Site | End-plate (specialized region on muscle cell membrane) | Postsynaptic membrane | Receptor nerve ending | Axons |
| Origin | Opening of chemically gated channels by neurotransmitters | Opening of chemically gated channels by neurotransmitters | Opening of ionic channels by adequate stimulus (e.g. touch or temperature) | Suprathreshold depolarization by EPP, PSP, RP or AP in nearby segment of axon |
| Amplitude | Small, graded | Small, graded | Small, graded | Large, all or none |
| Determinants of amplitude | Amount of neurotransmitter | Amount of neurotransmitter | Stimulus intensity | Amplitude fixed for a given set of conditions, can vary if the condition change |
| Nature of signal | Hypopolarization | Hypopolarization (EPSP) or Hyperpolarization (IPSP) | Hypopolarization (Exception-Hyperpolarization occurs in visual receptors) | Hypopolarization |
| Duration | Variable, relatively long | Variable, relatively long | Variable, relatively long | All or none, short |
| Spread | Non-propagated, spread decreases with time and along distance | Non-propagated spread decreases with time and along distance | Non-propagated, spread decreases with time and along distance | Propagated with decrement |
| Nature of phenomenon | Physical phenomenon dependent on cable properties of cell membrane | Physical phenomenon dependent on cable properties of cell membrane | Physical phenomenon dependent on cable properties of cell membrane | Uniquely biological phenomenon |

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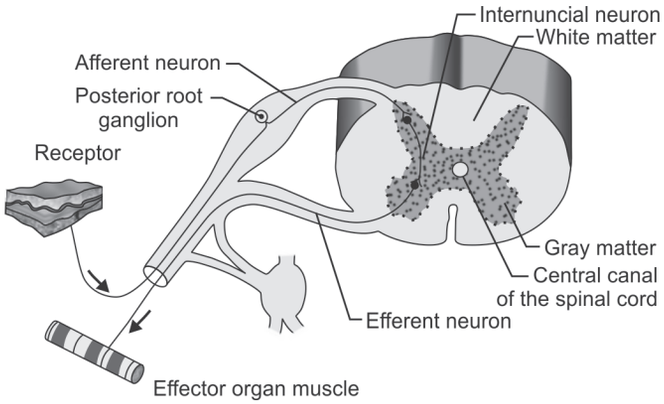


**Fig. 11.16:** Reflex arc

in the afferent nerve, the number of action potentials being proportionate to the size of the generator potential. In the CNS, the responses are again graded in terms of EPSPs and IPSPs at the synaptic junctions. All-or-none responses are generated in the efferent nerve. When these reach the effector, they again set up a graded response (end-plate potential). When the effector is smooth muscle, responses summate to produce action potentials in the smooth muscle, but when the effector is skeletal muscle, the graded response is always adequate to produce action potentials that bring about muscle contraction (Fig. 11.17).

From above it is clear that in the portions of the arc specialized for transmission (afferent and efferent axons, muscle membrane), the responses are all-or-none action potentials. It should be emphasized that the connection between the afferent and efferent neurons is usually in the CNS, and activity in the reflex arc is modified by the multiple inputs converging on the efferent neurons.

***Note:*** The afferent neurons enter via the dorsal roots or cranial nerves. The efferent nerve fibers leave via the ventral root or corresponding motor cranial nerves. The principle that in the spinal cord , the dorsal roots are sensory and the ventral roots are motor is known as the Bell-Magendie law.

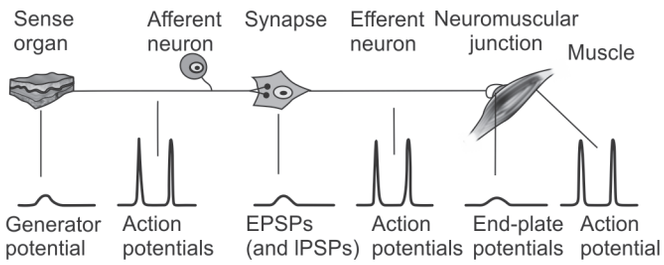


**Fig. 11.17:** Relative strength of various potentials

## Classification of Reflexes

1. *Monosynaptic reflexes:* Reflexes in which only one synapse is present between the afferent and efferent neurons. For example, All stretch reflexes (biceps, triceps, knee jerks).
2. *Polysynaptic reflexes:* Reflexes in which one or more interneurons are present between the afferent and efferent neurons. For example, Withdrawal reflexes, gross flexor reflex, gross extensor reflex.

### *Monosynaptic Reflexes (Stretch Reflexes)*

When a skeletal muscle with an intact nerve supply is stretched, it contracts. This response is called the stretch reflex.

- *Stimulus:* Stretch to the muscle
- *Receptor:* Muscle spindle
- *Neurotransmitter:* Glutamic acid (at the central synapse)
  For example, Knee-jerk reflex: When the patellar tendon is tapped by a patellar hammer, it stretches the quadriceps muscle, the stretched muscle contracts reflexly, elevating the leg.
- *Reaction time:* The time between the application of the stimulus and the response is called the reaction time. For example, For knee jerk it is 19–24 msec.
- *Central delay:* It is the time taken for the reflex activity to traverse the spinal cord. The central delay for the knee jerk is 0.6–0.9 msec.

Since, the minimum synaptic delay is 0.5 sec, therefore only one synapse could have been traversed for this reflex activity, stretch reflexes are thus called monosynaptic reflexes.

### *Muscle Spindle*

Muscle contains two types of fibers:

1. Extrafusal fibers
2. Intrafusal fibers

1. *Extrafusal fibers:* They are regular contractile units of the muscle.
2. *Intrafusal fibers:* They are muscle fibers in the muscle spindle which is the sense organ for stretch reflex. Each muscle spindle consists of 10 muscle fibers. These fibers are enclosed in a connective tissue capsule. These fibers are more embryonic in character. The fibers in the spindle have less distinct striations than rest of the fibers in spindle. The ends of the capsule of the spindle are attached to the tendons at either end of the muscle (or to sides of extrafusal fibers). Only the ends of intrafusal fibers are contractile. There are two types of intrafusal fibers in mammalian muscle spindles.
   a. Nuclear bag fibers
   b. Nuclear chain fibers.



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### Nuclear Bag Fibers

They contain many nuclei in a dilated central area and so called nuclear bag fibers. There are two nuclear bag fibers per muscle spindle. Nuclear bag fibers are of two types:

a. Nuclear bag fiber-1: With low level of myosin ATPase activity
b. Nuclear bag fiber-2: With high level of myosin ATPase activity.

### Nuclear Chain Fibers

They are thinner and shorter and lacks a definite bag. There are four or more nuclear chain fibers per muscle spindle. Their ends connect to sides of nuclear bag fibers.

### Sensory Innervation

Sensory innervations is through group Ia and group II sensory fibers. Sensory nerve (afferent) endings in each spindle are of two types:

i. *Primary (annulospiral) endings:* They are the terminations of rapidly conducting group Ia afferent fibers. One branch of the Ia fibers innervates nuclear bag fiber 1, another branch innervate nuclear bag fiber 2 and nuclear chain fibers.These sensory fibers wrap around the center of nuclear bag and nuclear chain fibers.
ii. *Secondary (flower spray ending):* They are the terminations of group II sensory fibers and are located nearer the ends of the intrafusal fibers but only on nuclear chain fibers.

### Motor Innervation

Muscle spindle (Fig. 11.18) is the only organ receiviving motor innervation. Motor innervation comes from:

i. γ efferents of Leksell (small motor neurons)
They go exclusively to muscle spindles. The ending of γ efferent fibers are of two types:
   a. Plate ending on nuclear bag fibers ($\gamma_1$).
   b. Trail ending on nuclear chain fibers ($\gamma_2$).

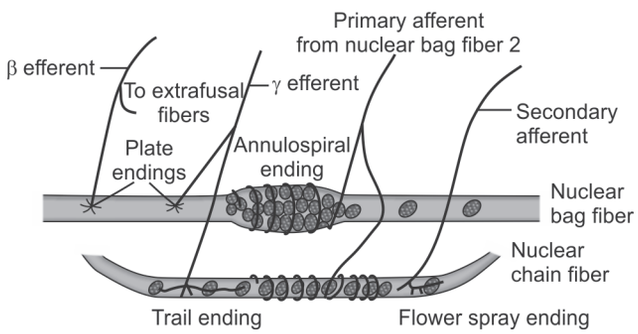


**Fig. 11.18:** Muscle spindle and its neural connections

ii. β motor neurons (larger motor neurons)
They innervate both intrafusal and extrafusal fibers.

### Response of Muscle Spindle to Stretch

Functionally muscle spindle shows two types of responses:

1. *Dynamic (by nuclear bag fibers):* Here primary sensory nerve ending discharge impulse at rapid rate when the muscle is rapidly stretched. They fire less rapidly if stretch is continued. The discharge of impulses start only if there is change in the degree of stretching of muscle. Thus, the response depends upon the rate of change in the length of the muscle.
2. *Static (by nuclear chain fibers):* When stretch is continuing, static responses comes into play. Thus muscle spindle gives response to change in the length of the muscle as well as rate of change in length.

### Mechanism of Activation of Muscle Spindle

a. Intrafusal fibers are parallel to extrafusal fibers. When the extrafusal fibers (muscle fibers) are passively stretched, stretch is transmitted to the intrafusal fibers → stimulation of Ia fibers → stimulation of α motor neuron → contraction of extrafusal fibers (stretch reflex) → shortening of muscle belly.
b. Stimulation of γ efferents produces contraction of intrafusal fibers → stretches nuclear bag portion of spindles → stimulation of Ia sensory fibers → stimulation of α motor neuron → contraction of extrafusal fibers (stretch reflex) → shortening of muscle belly.

Thus, the muscle can be made to contract via stimulation of α motor neuron that innervate the extrafusal fibers directly or stimulation of γ motor neurons that initiate contraction indirectly via stretch reflex. Stretching causes contraction of extrafusal fibers and shortening of muscle. Thus, spindle discharge decreases. The spindle and its contraction constitute a feedback circuit thus maintaining the length of the muscle.

### Functions

1. *Maintenance of our posture:* Maintaining posture (e.g. standing) or changing the posture are effected by appropriate adjustment of γ motor activities of different groups of muscles.
2. Role of muscle spindle in voluntary motor activity.
Normally for initiation of skeletal muscular contraction, stimulation of α motor neurons are neccessary. Along with α motor neuron firing, the γ motor neuron also fire concomitantly, so that a skeletal muscle contraction can be made effective (α - γ linkage).

Imagine what would have happened if this do not occur: Stimulation of the α motor neuron → initiation of

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contraction of extrafusal fibers; but this contraction will cause (as there is now a shortening of the extrafusal fibers), relieving of stretch of the nuclear bag region, causing the Ia afferents to stop its discharge. This in turn will lead to lengthening of the extrafusal fibers, i.e. cancellation of the α motor stimulation effect. The concomitant firing of the γ efferent prevents this.

3. *Damping function:* An important function of stretch reflex is its ability to prevent oscillation or jerkiness of body movements. This effect can also be called as signal averaging function of muscle spindle.
4. It plays a role in the maintenance of muscle tone.

## Inhibition of Stretch Reflexes

Because of it's monosynaptic pathway, the inhibition of stretch reflexes is produced by pathways that end with inhibition of α-motor neurons. This is brought out by two mechanisms:

1. Reciprocal innervations
2. Inverse stretch reflex.

### *Reciprocal Innervation*

When stretch reflex occurs, the muscle that antagonizes the action of the muscle involved relaxes, i.e. when the agonist contracts the antagonist is relaxed (Fig. 11.19). This is due to reciprocal innervation.

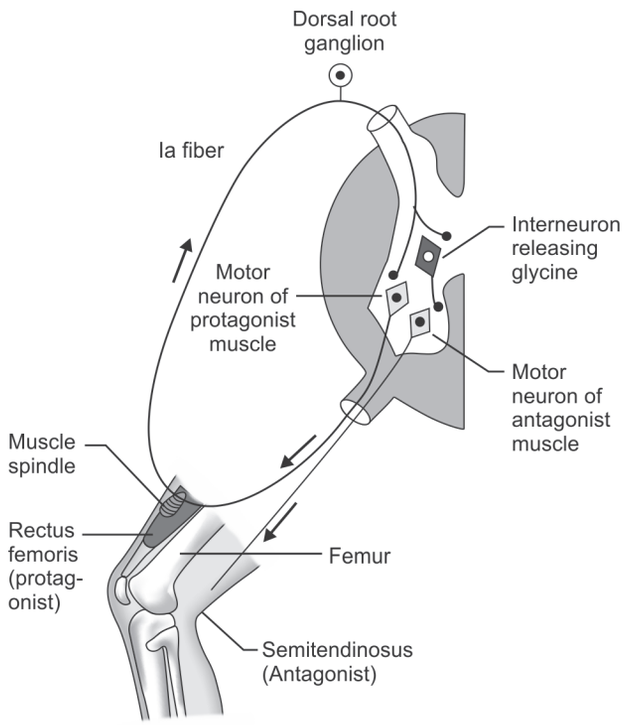


**Fig. 11.19:** Reciprocal innervation

- Receptor-Muscle spindle
- Afferent nerve-Ia
- Center-Spinal cord.
- Efferent nerve-α motor neuron to antagonist muscle.

In the spinal cord a collateral branch from Ia fibers arises. It synapses with an inhibitory interneuron (Golgi bottle neuron) that synapses directly on motor neuron supplying the antagonist muscle. The pathway mediating this effect is bisynaptic, i.e. two synapses are involved. This is an example of postsynaptic inhibition.

#### *Significance*

Reciprocal innervation ensures that the movement of the 'agonist' muscle is not obstructed by contraction of the 'antagonist' muscles.

### *Inverse Stretch Reflex/Autogenic Inhibition*

As the strength of the stretch increases , the reflex contraction also increases. But after a certain extent, as the strength of stretch increases contraction ends and muscle relaxes. This relaxation in response to strong stretch is called inverse stretch reflex.

- Receptor-Golgi tendon organ.
- Afferent-Ib myelinated nerve fibers
- Center-Spinal cord, the Ib fibers end on inhibitory interneurons that inturn end directly on the motor neurons.
- Efferent -α motor neurons to muscle fiber.

#### *Golgi Tendon Organ*

This organ consists of a net-like collection of knobby nerve endings among the fascicles of a tendon (Fig. 11.20). There are 3–25 muscle fibers per Golgi tendon organ.

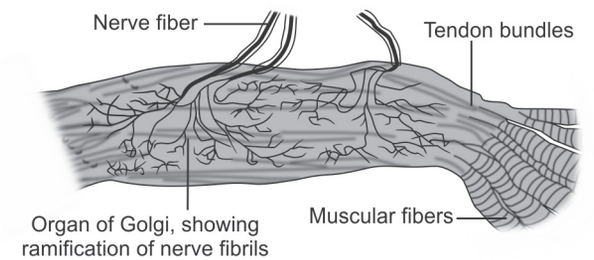


**Fig. 11.20:** Golgi tendon organ

#### *Effect*

- Stimulation of these Ib fibers leads to the production of IPSP on motor neurons that supply the same muscle, from which the fibers arise (Fig. 11.21).
- Since, Golgi tendon organ are in series with the muscle fibers, they are stimulated by both passive stretch and



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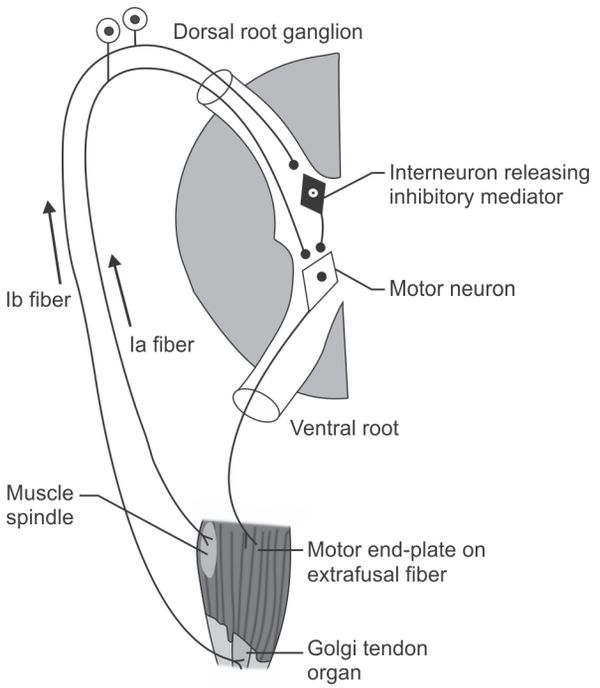


**Fig. 11.21:** Pathway responsible for stretch and inverse stretch reflex

active contraction of muscle. The threshold of Golgi tendon organ is low.

### *Significance of Inverse Stretch Reflex*

1. It is a protective reflex and prevents the tearing of muscle by extreme stretch.
2. It is important in maintaining tension during normal muscle activity.
3. Clasp-knife effect/Lengthening reaction.

It is the response of a spastic muscle (high resting tone) to stretching or lengthening due to operation of stretch reflex and inverse stretch reflex. When muscles are hypertonic, moderate stretch produces reflex contraction of the muscle (due to stretch reflex), while strong stretch produces muscle relaxation (due to inverse stretch reflex).

For example, if triceps muscle becomes spastic due to any cause, passive flexion of the elbow, meets immediate resistance due to initiation of the stretch reflex in the triceps muscle. Further stretch activates inverse stretch reflex, as a result the resistance to flexion suddenly collapses and arm flexes. However, continued passive flexion stretches the muscle again, and the sequence may be repeated. This sequence of resistance followed by relaxation when a limb is moved passively is known as the clasp-knife effect because of it's resemblance to the closing of a pocket knife. It is known as the lengthening reaction because it is the response of a spastic muscle to lengthening.

## Polysynaptic Reflexes (Withdrawal Reflexes)

When more than one synapse is involved in the reflex pathway, it is called polysynaptic reflexes (Fig. 11.22). The reflex path branches in a complex fashion. Because of the difference in the number of synapses, the synaptic delay varies. The activity in the branches with fewer synapses reaches the motor neurons first followed by the activity in the longer pathways. This will lead to prolonged response in motor pathways.

Some of the branched pathways turn back on themselves, permitting activity to reverberate until it becomes unable to cause a propagated trans-synaptic response. Such circuits are called reverberating circuits. These are common in brain and spinal cord, e.g. Withdrawal reflex.

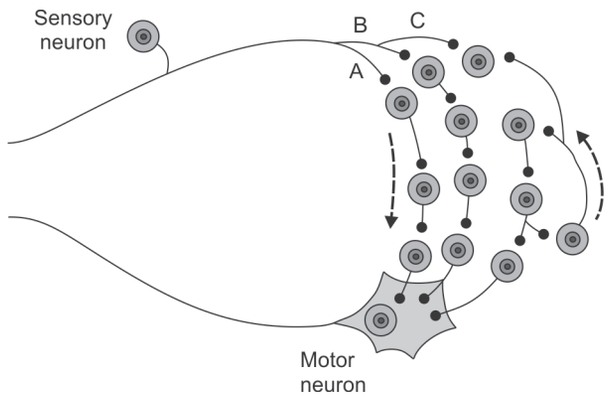


**Fig. 11.22:** Polysynaptic connections between afferent and efferent neurons in the spinal cord. The dorsal root fiber activates pathway A, pathway B and pathway C. Note that one of the interneurons in pathway C connects to a neuron that doubles back to other interneurons, forming reverberating circuits

### *Withdrawal Reflex*

It is a typical polysynaptic reflex.

- *Stimulus:* It occurs in response to a noxius and usually painful stimulation of the skin, subcutaneous tissue or muscle.
- *Response:* Contraction of the flexor and inhibition of extensor.
- *Effect:* The part stimulated is flexed and withdrawn from the stimulus (flexor response).

  If stimulus is still stronger, the response includes flexion and withdrawal of that limb and extension of opposite limb. This is called crossed extensor response (Fig. 11.23).

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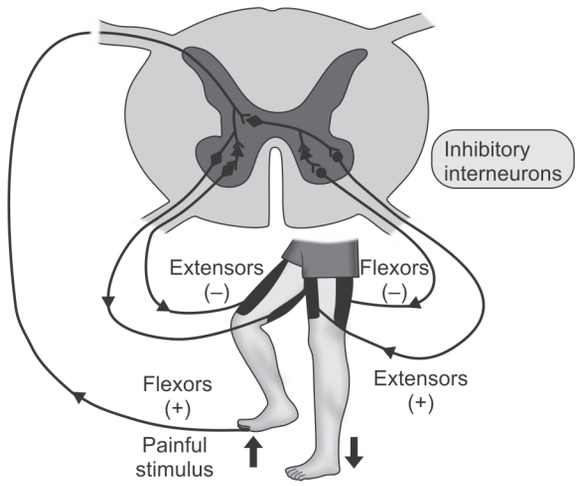


**Fig. 11.23:** Withdrawal reflex

### *Mechanism*

If the strength of stimulus is more, the excitatory impulse spread up and down the spinal cord to more and more motor units, a phenomenon called irradiation of stimulus and the increase in the total motor units is called recruitment of motor units.

### *Importance*

It is a protective reflex. Flexion of the stimulated limb gets it away from the source of irritation and extension of the other limb supports the body. The pattern assumed by all the 4 limbs puts the animal in a position to run away from the offending stimulus.

### *Characteristic Features*

1. Withdrawal reflexes are prepotent, i.e. they prevent the spinal pathways from any other reflex activity taking place at the moment.
2. A weak stimulus causes quick flexion movement whereas a strong stimulus causes prolonged flexion and sometimes a series of flexion movements. The prolonged response is due to prolonged repeated firing of motor neurons. The repeated firing is called after discharge, which is due to continued bombardment of motor neurons by impulses arriving by complicated and circuitous polysynaptic paths (reverberating circuits).
3. *Local sign:* It refers to the ability of the reflex to confine the withdrawal exactly to the portion of the body affected by the noxious stimulus. For example, if the medial surface of the limb is stimulated, the response will include some abduction with flexion, whereas stimulation of the lateral surface will produce some adduction with flexion. This dependence of the exact response on the location of the stimulus is called local sign.

## General Properties of Reflexes

1. *Adequate stimulus:* The stimulus that produces a reflex is very precise, as the receptors respond maximally only when an appropriate specific stimulus is applied. It is called adequate stimulus for the particular reflex.
2. *Final common pathway:* The alpha motor neurons that innervate the extrafusal fibers are the final common pathway over which the neural control system coordinates the activity of skeletal muscle fibers. It serves both as the integrating center and efferent pathway.
3. *Central excitatory and inhibitory states:* The spinal cord shows prolonged changes in excitability because of activity in reverberating circuits or prolonged effects of synaptic mediators. The prolonged state in which excitatory influences exceed inhibitory influences is called central excitatory state and conversely if inhibitory state dominates, it is called central inhibitory state. For example, after complete transection of the spinal cord, when reflex movements return, a mild noxious stimulus on the lower limb may cause withdrawal reflex and autonomic changes like urination, defecation, sweating and fluctuations in BP. This is referred to as **Mass reflex.**
4. *Habituation and sensitization of reflex responses:* Though the reflexes are fixed they can still be modified by experience. If stimulus is benign and repeated at frequent intervals, the response declines and disappears. This phenomenon is called habituation. It is due to synaptic fatigue which is due to exhausation of chemical transmitter, as its synthesis is not as rapid as its release. The decrease in release of NT can also be due to gradual inactivation of $Ca^{2+}$ channels at presynaptic terminal. This decreases intracellular $Ca^{2+}$ and release of NT.

# SENSORY SYSTEM

## Sensory Cortex

Both the lemniscal and anterolateral systems ultimately convey impulses to the sensory cortex.

### *Primary Sensory Area (S1)*

1st somatic sensory area, located in postcentral gyrus containing the Brodmann's area 3, 1, 2.

- Area 3-respond to light touch
- Area 1 and 2 respond to deep stimuli such as pressure and joint movement.

It is supplied by afferents from both side of face and opposite side of the body.



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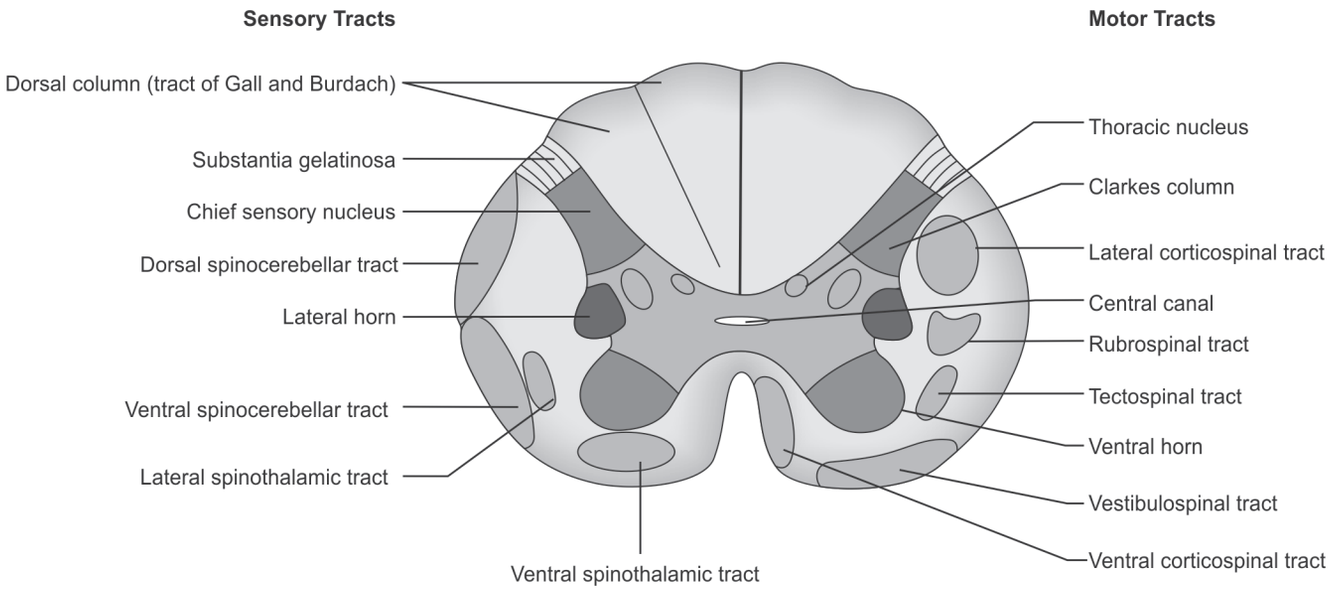


**Fig. 11.24:** Cross-section of spinal cord showing location of major sensory and motor tract

### *Sensory Homunculus*

The different areas of body have a topographical representation in the postcentral gyrus. The representation is such that the body appears upside down. Thus, foot area occupies the most medial part of the gyrus, (which is on the medial side of the cerebral hemisphere) and face area is situated in lateral part of the gyrus. Tongue occupies a position further down than that of the face. However, the parts of the face are not represented in an inverted manner (Fig. 11.25).

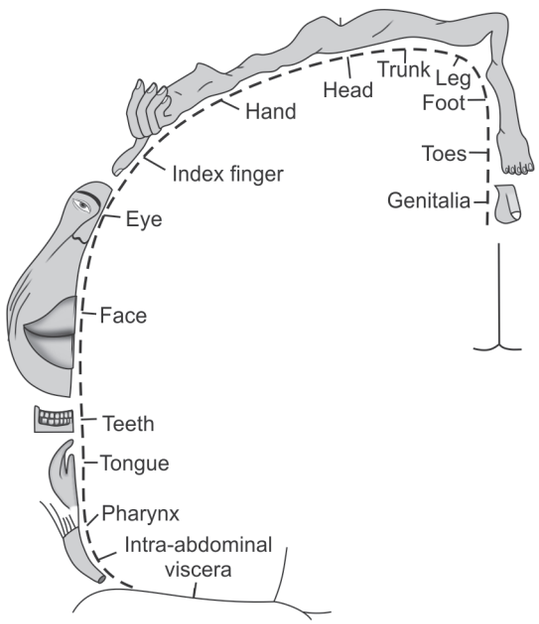


**Fig. 11.25:** Sensory homunculus

Areas of the body, which are very sensitive (that is, where the population of receptors is very high), occupy a bigger space irrespective of the actual size of the organ. The sensory homunculus represents the opposite half of the body as both the lemniscal and anterolateral system have crossed the midline to end on the opposite half of the cortex.

### *Functions of S1*

Widespread bilateral excision of somatosensory area I causes loss of the following types of sensory judgment:

1. The person is unable to localize discretely the different sensations in the different parts of the body. However, he or she can localize these sensations crudely, such as to a particular hand, to a major level of the body trunk, or to one of the legs. Thus, it is clear that the brainstem, thalamus, or parts of the cerebral cortex not normally considered to be concerned with somatic sensations can perform some degree of localization.
2. The person is unable to judge critical degrees of pressure against the body.
3. The person is unable to judge the weights of objects.
4. The person is unable to judge shapes or forms of objects. This is called astereognosis.
5. The person is unable to judge texture of materials because this type of judgment depends on highly critical sensations caused by movement of the fingers over the surface to be judged.

***Note:*** In specific absence of only somatosensory area I, appreciation of pain and temperature sense is preserved both in

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quality and intensity. But the sensations are poorly localized, indicating that pain and temperature localization depends greatly on the topographical map of the body in somatosensory area I to localize the source.

### *Secondary Sensory Area (S2)*

Located in parietal cortex in lateral cerebral sulcus, removal of it produces deficits in discrimination power.

## Ascending (Sensory) Tracts

1. Tracts in dorsal white column (Medial lemniscal system/ Tract of Gall and Burdach).
   a. Fasciculus gracilis
   b. Fasciculus cuneatus.
2. Tracts in lateral white column
   a. Lateral spinothalamic tract
   b. Dorsal spinocerebellar tract
   c. Ventral spinocerebellar tract.
3. Tract in ventral white column
   a. Ventral spinothalamic tract.

Always for any sensory pathway there are three order neurons:

i. 1st order neuron-from receptors to spinal cord or to medulla (in case of dorsal column pathway).
ii. 2nd order neuron from the spinal cord or at the level of medulla to thalamus.
iii. 3rd order neuron from thalamus to sensory cortex.

### *Tracts in Dorsal White Column*

It conveys the following information from various part of the body (Fig. 11.26)—fine touch, tactile localization and two point discrimination, pressure, vibration, proprioception, kinesthetic sensation and some unconscious kinesthetic impulses to cerebellum (via external arcuate fibers), some superficial reflexes.

#### *Fine Touch Pathway*

Receptors (for both fine and crude touch)—Meissner's corpuscle, Merkle's corpuscle, Pacinian corpuscle.

***1st Order Neuron***

Impulse is carried from receptors to spinal cord (to fasciculus gracilis and cuneatus) by A β fiber. Some touch impulses are also conducted via C fibers. They do not relay there. Fasciculus gracilis receives afferents from lower half (lumbar and sacral segments) (Fig. 11.27). Fasciculus cuneatus receives afferents from upper half (cervical and thoracic segments). Above the midthoracic region the fibers from spinal cord are represented as sacral to cervical segment from medial to lateral in the spinal cord.

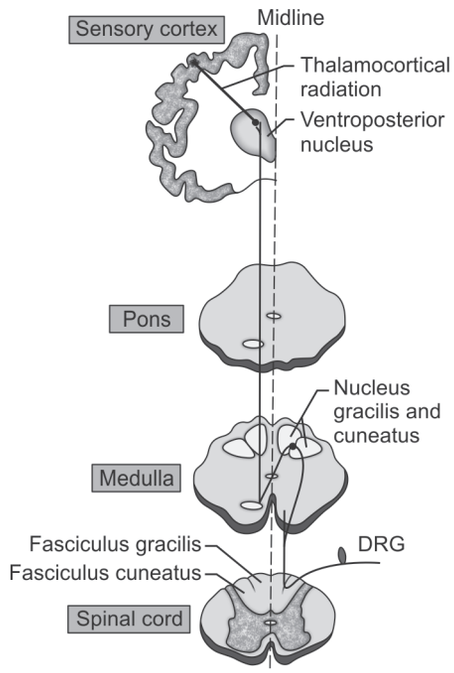


**Fig. 11.26:** Dorsal or posterior column pathway

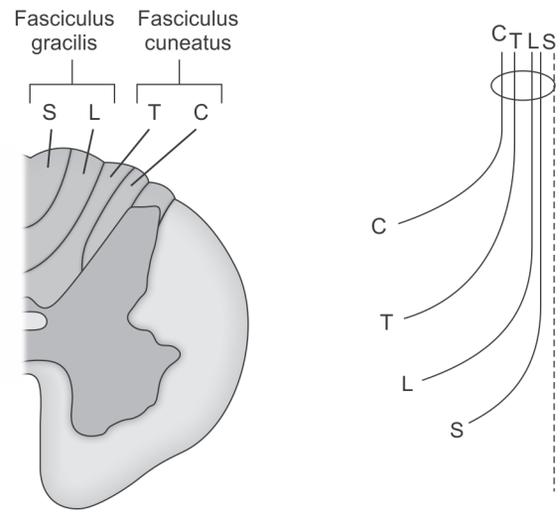


**Fig. 11.27:** Arrangement of cervical, thoracic, lumbar and sacral fibers in the spinal cord: At Midthoracic level

Majority of fibers end in medulla in nucleus gracilis and nucleus cuneatus respectively (1st relay station).

***2nd Order Neuron***

2nd order neuron arise from nucleus gracilis and nucleus cuneatus. They are divided into two groups:

1. External arcuate fibers-dorsal and ventral group
   - Dorsal fibers via inferior cerebellar peduncle of same side to end in cerebellum
   - Ventral fibers via opposite side to cerebellum.



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2. Internal arcuate fiber-cross to opposite side and pass through midbrain in the medial lemniscus to end in specific relay nuclei of thalamus (ventroposterior nuclei) this forms the 2nd relay station.

***3rd Order Neuron***

Axons of 3rd order neurons pass via posterior limb of internal capsule to end in the sensory cortex.

## Lateral Spinothalamic Tract

It carries fibers of all types of pain, temperature, itch and tickle sensation.

### *Pathway of Pain*

Receptors-Free nerve endings.

***1st Order Neuron***

Impulse is carried from receptors to spinal cord by:

a. A δ (fast pain): The neurotransmitter is glutamate.
b. C-slow pain: The neurotransmitter is substance P.

On entering the spinal cord pain signal take two pathway to the brain, through:

i. *Neospinothalamic pathway for fast pain:* A δ terminate mainly in lamina 1 of dorsal horn cells.
ii. *Paleospinothalamic pathway for slow pain:* C fiber terminates on lamina 2 and 3 (lamina 2 and 3 together called as substantia gelatinosa).

***2nd Order Neuron***

2nd order neurons arise at the level of spinal cord. Most of axons of 2nd order neurons cross in anterior white commissure obliquely to opposite side of the same segment. They ascend in the lateral spinothalamic tract. Fibers from neospinothalamic tract end in the ventroposterior nuclei of thalamus. Fibers from paleospinothalamic pathway end in intralaminar and ventrolateral nuclei of thalamus (Fig. 11.28).

On their way to thalamus these fibers send collaterals to reticular formation, periaqueductal gray, tectum. Paleospinothalamic fibers give off much more collaterals than the neospinothalamic tract (only 1/10th to 1/4th of the fibers pass to the thalamus).

Axons from the sacral and lumbar segments of body are pushed laterally by axons crossing midline at successive higher levels. Therefore the fibers are represented as cervical to sacral segments from medial to lateral in the spinal cord.

A lesion in cervical region situated close but outside the spinal cord (e.g. tumor) will cause loss of pain sensation in the sacral or lumbar segments as they are most superficial. But sensation of cervical region persists (Fig. 11.29).

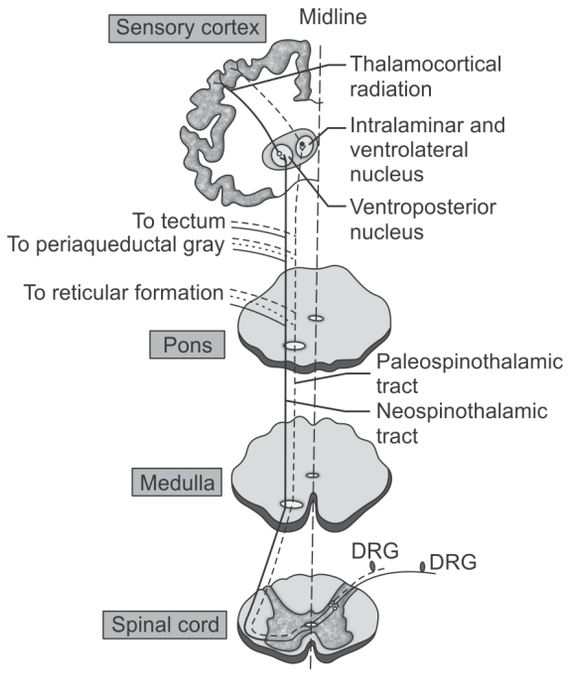


**Fig. 11.28:** Lateral spinothalamic pathway

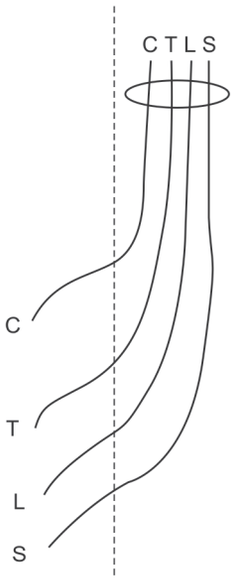


**Fig. 11.29:** Sacral and lumbar segment pushed laterally by axons crossing midline at successive higher level

***3rd Order Neuron***

In thalamus 3rd order neuron starts and ends in sensory cortex.

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### Ventral (Anterior) Spinothalamic Tract

It conveys crude touch.

#### Crude Touch Pathway

***1st Order Neuron***

Impulse is carried from receptors to spinal cord by A β fibers. Some touch impulses are also conducted via C fibers. After entering the spinal cord the fibers end round the cells which are situated at the median part in the dorsal horn (1st relay station), from where 2nd order neuron arises (Fig. 11.30).

***2nd Order Neuron***

2nd order neuron cross in anterior white commissure obliquely to opposite side of same segment to end in ventroposterior nucleus of thalamus. Small number of axons of 2nd order neurons are uncrossed and may ascend homolaterally as anterior spinothalamic tract.

While ascending, the ventral spinothalamic tract runs in parallel with the lateral spinothalamic tract and together constitutes the spinal lemniscus or anterolateral system of ascending fibers. At higher brainstem level, this tract sends several collaterals into the reticular formation and tegmentum.

***3rd Order Neuron***

In thalamus 3rd order neurons starts and ends in sensory cortex.

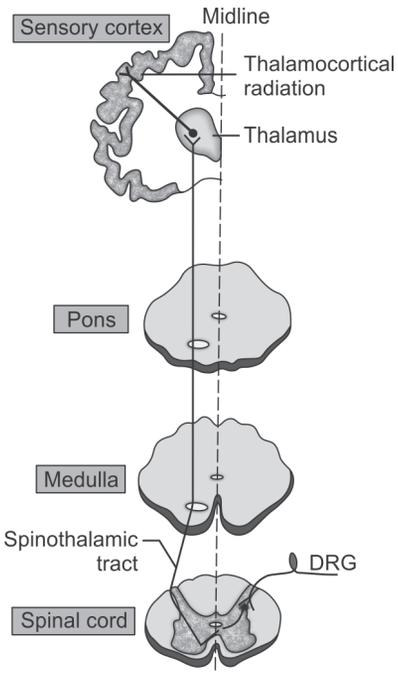


**Fig. 11.30:** Ventral (anterior) spinothalamic tract

### Dorsal (Posterior) Spinocerebellar Tract

*Functions:* It carries 'unconscious' kinesthetic impulses to the cerebellum which are essential for the regulation of body posture.

***1st Order Neuron***

The 1st order neuron arises from the muscle spindle, joints and the skin. It enters the spinal cord via the DRG and makes a short ascent in the dorsal funiculus of the same side, then terminate in the Clarke's column of cells (nucleus dorsalis).

***2nd Order Neuron***

2nd order neuron arises from the Clarke's column and it proceeds up through the dorsal spinocerebellar tract of the same side and reaches medulla. In medulla, fibers enter the inferior cerebellar peduncle of the same side and end in 'vermis of cerebellum' from where the 3rd order neurons arise (Fig. 11.31).

***3rd Order Neurons***

3rd order neurons arise from the vermis of cerebellum and its axons passes to the anterior and posterior lobes of the cerebellar cortex.

### Ventral (Anterior) Spinocerebellar Tract

*Functions:* Same as that of dorsal (posterior) spinocerebellar tract.

***1st Order Neuron***

The 1st order neuron arises from the muscle spindle, joints and the skin. It enters the spinal cord via the DRG and terminate in the Clarke's column of cells (nucleus dorsalis).

***2nd Order Neuron***

2nd order neuron arises from the Clarke's column of cells. Most of the 2nd order neuron cross to the opposite side (some remain uncrossed) and it proceeds up via the ventral spinocerebellar tract of the same side and extends up to the level of red nucleus (in midbrain). At red nucleus, fibers turn sharply backwards and downwards and then enter the superior cerebellar peduncle of same side and end in 'vermis of cerebellum' from where the 3rd order neurons arise (Fig. 11.31).

***3rd Order Neurons***

3rd order neurons arise from the vermis of cerebellum and goes to the anterior lobe of the cerebellar cortex.

## Sensation from Face

Sensation from face are carried by sensory root of trigeminal nerve. Peripheral processes of neurons in the trigeminal



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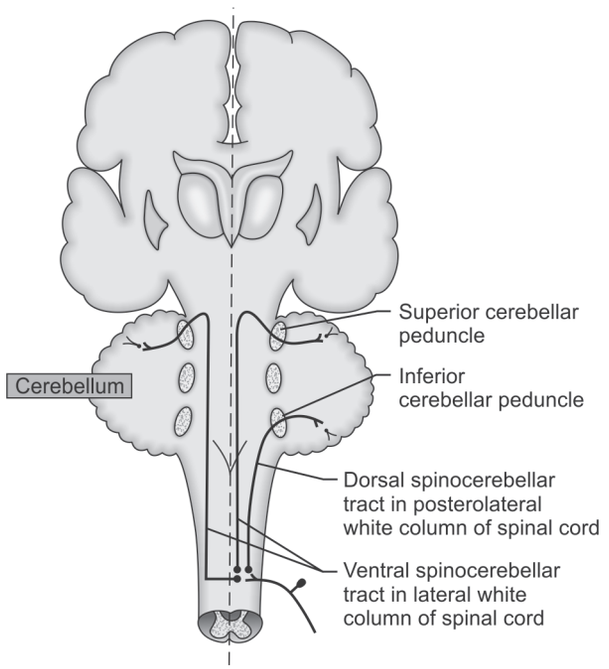



**Fig. 11.31:** Ventral (anterior) spinocerebellar tract

ganglion pass through the ophthalmic, maxillary, mandibular divisions of trigeminal nerve. Trigeminal sensory nucleus has three components (Fig. 11.32).

a. Principal/chief/main sensory nucleus—located in pons.
b. Spinal nucleus—extend down to upper spinal cord.
c. Mesencephalic nucleus—extend from pons into midbrain.

*1st order neuron:* Located in trigeminal ganglion.

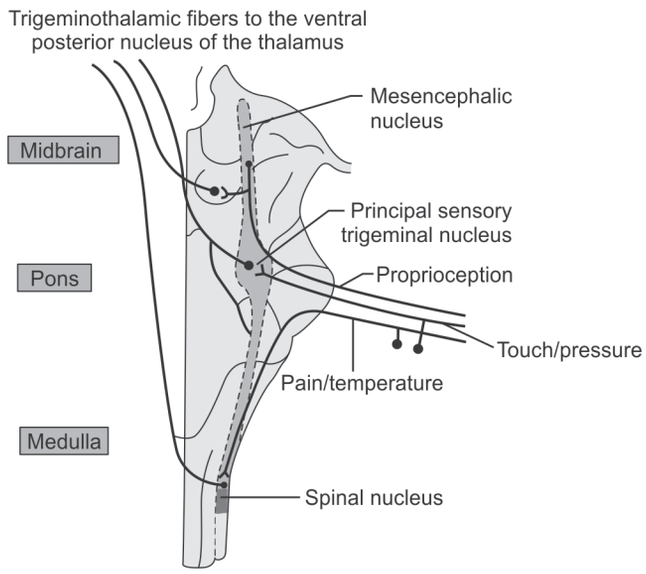



**Fig. 11.32:** Sensory supply of face

*2nd order neuron:* Located in the 3 components of the sensory trigeminal nucleus.

*3rd order neuron:* Located in VPM nucleus of thalamus.

Fibers conveying touch, tactile sensations, pressure terminate in the principal nucleus. Fibers arising from the principal sensory cross to the opposite side and ascend up to terminate in ventroposterior nucleus of thalamus. From here, the fibers are send to the sensory cortex.

Fibers carrying pain and temperature from face, after reaching trigeminal ganglion descend from the pons through the medulla and spinal cord to end in the spinal nucleus. Fibers from the spinal nucleus cross to opposite side, ascend up in the spinal cord and medulla to the ventroposterior nucleus of thalamus. From here the fibers are send to the sensory cortex.

Proprioceptive impulses from the muscles of mastication and from the facial and extraocular muscles enter the pons and ascend to the mesencephalic nucleus. They are the only primary afferents to have their cell bodies located within the CNS. From the mesencephalic nucleus fibers leave, cross to opposite side to terminate in the ventroposterior nucleus of thalamus. From the ventroposterior nucleus of thalamus, the fibers are send to the sensory cortex.

## Pain Sensation

Pain refers to an unpleasant sensory and emotional experience associated with actual or potential tissue damage.

### *Visceral Pain*

Pain sensation from visceral organs can arise due to conditions like ischemia (e.g. cardiac pain), obstruction of hollow viscous, inflammation, distention, severe vasodilatation, etc.

### *Characteristic Features of Visceral Pain*

1. It is referred.
2. It is poorly localized.
3. Accompanied by autonomic symptoms like nausea, vomiting and fall of BP.
4. Pain of hollow viscous is often felt as colic, i.e. it comes and goes to reappear again.
5. Visceral pain initiates reflex spasm (contraction) of skeletal muscle in the abdominal wall and makes it rigid. Clinically this reflex spasm is called **guarding.** It is a protective reflex.

### ***Referred Pain***

Irritation of a viscus frequently produces pain that is felt not in the viscus, but in some somatic structure that may be

considerable distance away. Such a pain is said to be referred pain. For example:

a. Cardiac pain is referred to inner aspect of left arm.
b. Pain in tip of shoulder caused by irritation of central portion of diaphragm.
c. Pain in testicle due to distention of ureter.

When visceral pain is both local and referred, it seems to spread from local to distant site-radiating pain. For, example, in appendicitis pain starts in the right iliac fossa and radiates towards center of abdomen.

### *Basis*

Pain is referred, usually to a structure that developed from the same embryonic segment or dermatome. This principle is called dermatomal rule. For example, heart and the arm have the same segmental origin, testicle has migrated with its nerve supply from the primitive urogenital ridge from which kidney and ureter developed.

### *Theories of Referred Pain*

1. *Convergence theory:* It holds that somatic and visceral afferents converge on the same spinothalamic neurons (Fig. 11.33).
2. *Facilitation theory:* The afferent impulses from visceral structures produce subliminal fringe effects that lower the threshold of spinothalamic neurons. Therefore, any slight activity in the pathways transmitting pain impulses from somatic regions and which normally would die out with in the spinal cord is facilitated (Fig. 11.34).

## Modulation of Pain

Noxious stimuli of comparable intensity may produce varying degrees of pain in same individual under different circumstances. For example, injury acquired by an individual in sports field is less painful than comparable injury in road accidents. This is due to modulation of pain. Modulation of pain occurs at spinal and supraspinal level.

### *Spinal Level*

#### *Gate Control Theory*

According to this theory, the dorsal column acts as gate for the transmission of pain sensation. It has been observed that the activation of large myelinated touch fibers reduces pain. Touch fibers give collateral (directly or through interneurons) in the substantia gelatinosa of the dorsal horn of the spinal cord. These collaterals inhibit the pain fiber presynaptically. So pain is not transmitted to higher centers.

Thus, the dorsal horn is the GATE through which the pain impulses reach the lateral spinothalamic system. Stimulation of large fibers (touch) closes the gate and pain impulses cannot ascend upwards. When a touch stimulus is applied to the same area subjected to a noxious stimulus, touch fiber give a collateral to substantia gelatinosa of the dorsal horn of spinal cord.

### *Supraspinal Level*

#### *Endogenous Pain Inhibiting System*

The capability of brain to suppress the input of pain signals to the nervous system by activating a pain control system is called endogenous pain inhibiting system. So it is built in mechanical analgesic system consists of periaqueductal gray mater and periventricular areas of midbrain surrounding aqueduct of Sylvius. These fibers terminate on raphe magnus nucleus and nucleus reticularis paragiganto cellularis in medulla (Fig. 11.35).

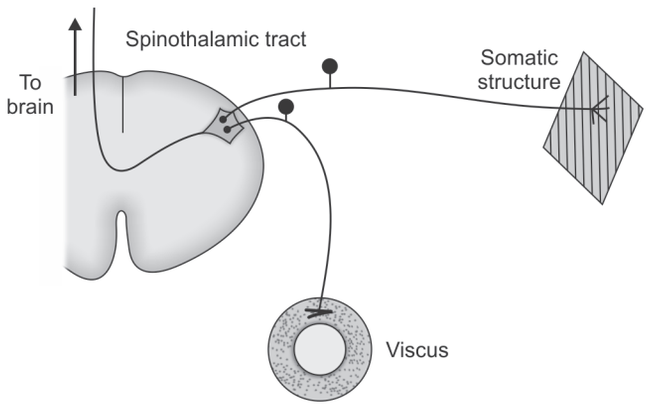



**Fig. 11.33:** Convergence theory

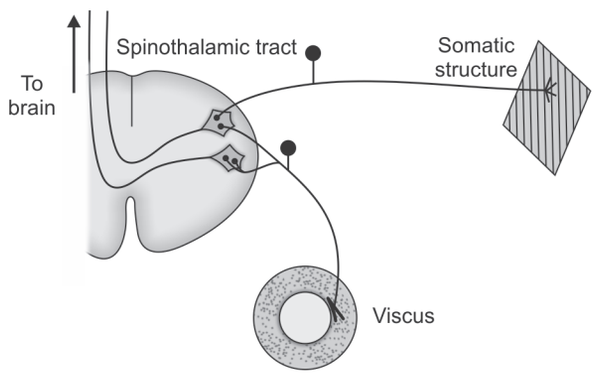



**Fig. 11.34:** Facilitation theory

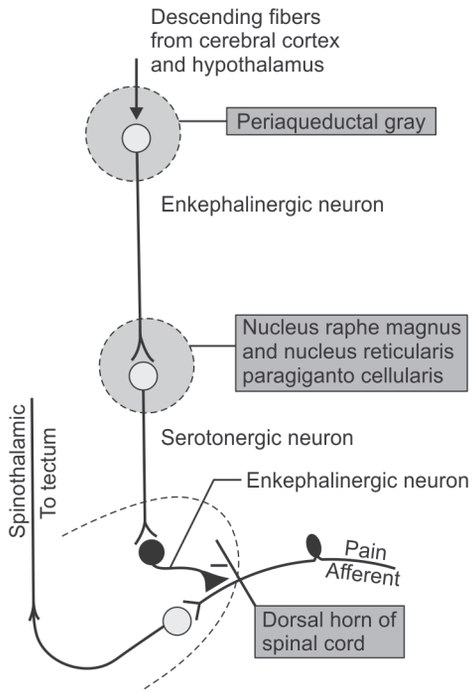



**Fig. 11.35:** Endogenous pain inhibiting pathway

***Periaqueductal Gray Area in the Midbrain***

It inhibits pain by stimulating the raphe magnus nucleus. Neurons of periaqueductal gray (PAG) have opioid receptors on the surface membranes. When opioid receptors are stimulated by exogenously administrated opiod compounds (analgesics) or by endogenous opioid neurotransmitters (enkephalins), the pain suppression mechanism is activated leading to reduced pain.

***Raphe Magnus Nucleus***

The seratonergic neurons of the raphe magnus nucleus (RMN) and nucleus reticularis paragiganto cellularis (NRPC) descend and end on interneurons in posterior horn of spinal cord. These neurons secrete serotonin (Serotonin stimulate interneurons in spinal cord). These interneurons produce neurotransmitter enkephalin. The interneurons synapse with A δ and C fibers of first order.

Substance P is released during the stimulation of afferent A δ and C fibers. These afferent neurons possess opiate receptors on the membrane surface. Opiate peptides like enkaphalins and endorphins produced endogenously binds to these receptors and decrease the release of substance P. Thus the transmission of pain is inhibited. These cause mainly presynaptic inhibition on pain pathway.

***Note***

- Fibers from the limbic system supply the PAG. This explains why a soldier wounded in the battle field feel no pain during the heat of battle.
- Collaterals from spinothalamic tract stimulate descending inhibitory pathway.

### *Revised Gate Control Theory*

Pain modulation theory is revised to form revised gate control theory. According to this, the touch fibers while ascending to the thalamus give off collateral fibers to reticular formation, nucleus raphe magnus and nucleus reticularis paragiganto cellularis. These collaterals activates descending fibers (from NRM and NRPC) which inhibit pain pathway.

**Clinical Application**

1. Gate control theory explains the relief of pain by rubbing skin near painful areas and relief of pain by balm and by counter irritants.
2. In acupuncture, introduction of sharp needles in selected spots cause local pain and it activates endogenous pain inhibiting system and give relief to pain anywhere in the body.

## MOTOR SYSTEM

### Motor Cortex

#### *Primary Motor Area (Area 4)*

Located in the precentral gyrus. Area of cortex representing a part of body is not proportional to the size of the part, but rather to intricacy of movements in the region. Thus relatively large areas of cortex are responsible for movements in the hands or in the lips. In the precentral gyrus, the body is represented in the upside manner-Motor homunculus.

#### *Motor Homunculus*

The various parts of the body are topographically represented in the precentral gyrus based on the motor projections from the motor cortex. The feet is represented at the top of the gyrus and the face at the bottom. The facial area is represented bilaterally, but the rest of the representation is generally unilateral. Stimulation of different areas produce response on muscles of opposite half of the body. The cortical representation of each body parts is proportionate in size to the skill with which the part is used in fine, voluntary movement. The area involved in speech (lowermost part of face) and hand movements (fingers) are especially large in the cortex (Fig. 11.36).

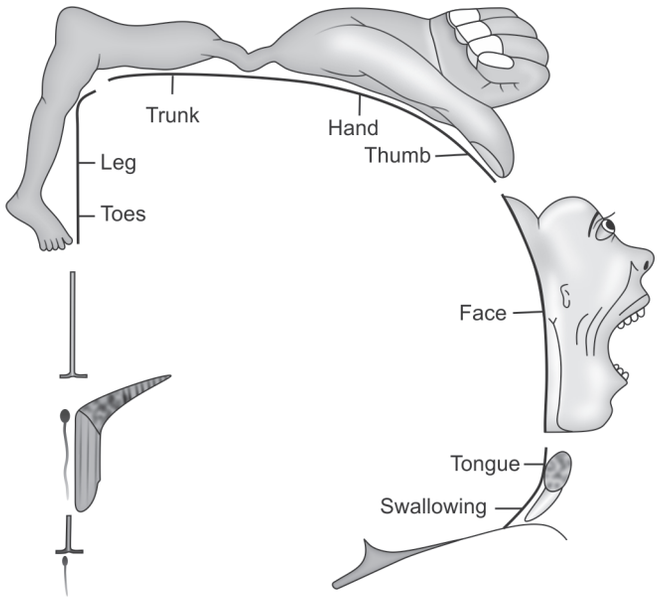



**Fig. 11.36:** Motor homunculus

Additional motor areas are primarily:

a. *Premotor area (area 6):* Lies anterior to the precentral gyrus. Its functions are programming of motor activity and postural support for wide variety of detailed movement.
b. *Supplementary motor area:* Primarily involved in voluntary movement which are complex and involve planning.
c. Frontal eye field (area 8)
d. Occipital eye field (area 19)

## Pyramidal Tract

This is the longest tract starting from the motor cortex and reaching the last segment of the spinal cord. The pyramidal (PT) fibers pass from the motor area to the spinal ventral horn cells and to motor nuclei of opposite side (Fig. 11.37).

1. The pyramidal tract fiber to the spinal ventral horn cells constitute the ***corticospinal tract***.
2. The pyramidal fiber to the motor cranial nuclei (3 and 4 in the midbrain, 5, 6, 7 in the pons, 9 to 12 in medulla) constitute the ***corticobulbar tract***.

### *Origin*

- 30% from motor cortex, area 4 in precentral gyrus
- 30% from premotor cortex, area 6
- 40% from somatosensory area 1 and 2.

### *Course of Pyramidal Tract*

The pyramidal tract fibers arise from Betz cells of cerebral cortex. They converge towards the brainstem as a radiating mass of fibers called corona radiata to reach the internal capsule.

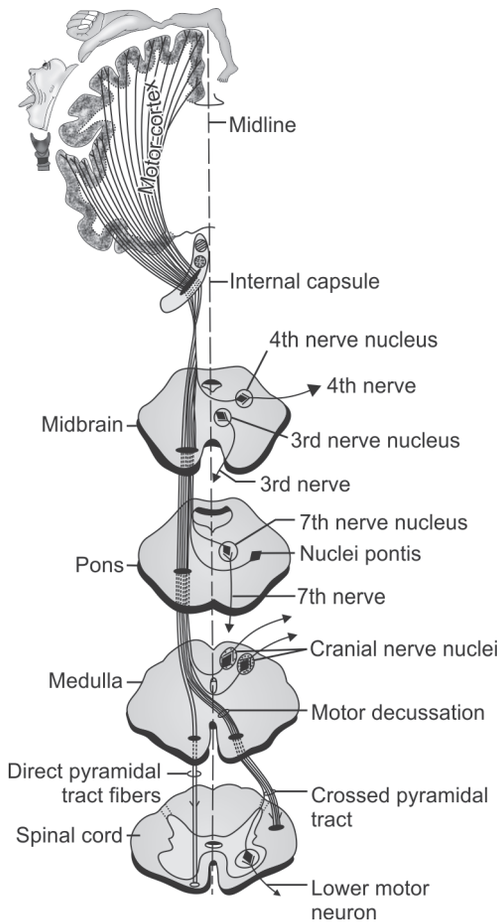



**Fig. 11.37:** Pyramidal tract

#### *In Internal Capsule*

It lie in the bend (genu), and the anterior 2/3 of the posterior limb. In internal capsule the PT fiber get intermingled with extrapyramidal fibers (EPT). Therefore lesion in this region includes both PT and EPT fibers.

#### *In Midbrain*

It lie ventral to the substantia nigra, occupying the middle 3/5 of this region.

#### *In Pons*

They occupy the most ventral aspect in front of trapezium. Here the compactness of bundle is loosened.

#### *In Medulla*

In the medulla scattered fibers are reunited to a compact bundle. This compact bundle now produce an elevation called pyramid.

- In the lower part of medulla 80–85% fiber cross to the opposite side, enters the lateral white column called lateral corticospinal tract(crossed/indirect). It extends throughout the cord.
- About 15–20% fiber do not cross and enter anterior white column near the median fissure called anterior corticospinal tract (uncrossed/direct). Through interneurons they cross the midline, when it reaches the level of muscles it controls. It does not extend beyond the lower cervical or mid thoracic region.

### *Functions of Pyramidal Tract*

1. Lateral corticospinal tracts convey motor impulses to the spinal cord for controlling voluntary movements, specially the fine and precise movements of fingers and hands to carry out skilled work.
2. Anterior corticospinal tract control the muscles of trunk and proximal portion of limb to carry out postural adjustments and gross movements.
3. Corticospinal fibers arising from the somatic sensory area (1 and 2) and parietal lobe association cortex are concerned with sensory-motor coordination.
4. Some corticospinal fibers end at excitatory synapses on $\alpha$ and $\delta$ motor neurons, whereas others end on interneuron that may excite or inhibit the $\alpha$ motor neurons and thus controlling $\alpha$ motor neuronal activity.
5. Corticobulbar fibers are responsible for voluntary control of muscle of larynx, pharynx, palate, upper and lower face, jaw and eye.

## Extrapyramidal System

The part of descending brainstem and spinal pathways which do not pass through the pyramids and are concerned with postural control are referred to as extrapyramidal system. The various extrapyramidal tracts includes:

### *Medial Longitudinal Fasciculus*

It arises from the medial vestibular nucleus, reticular formation, superior colliculus and interstitial nucleus of Cajal. The tract descends uncrossed up to upper cervical region.

*Functions*

- Coordination of reflex ocular movements
- Integration of movements of eyes and neck.

### *Lateral Vestibulospinal Tract*

It arises from lateral vestibular nucleus of same side, runs uncrossed and ends at various levels of spinal cord.

***Functions***

- Maintenance of muscle tone and posture.
- Maintenance of position of head and body during acceleration.

### *Medial Vestibulospinal Tract*

It arises from the medial and inferior vestibular nuclei on both sides, descends uncrossed and ends at various levels of spinal cord.

***Functions***

Maintenance of equilibrium and muscle tone.

### *Reticulospinal Tract*

It arises from the reticular formation of pons and medulla, descends mostly uncrossed and extends up to the thoracic segments.

***Functions***

- Coordination of voluntary and reflex movements
- Control of muscle tone.

### *Rubrospinal Tract*

It arises from the red nucleus, crosses to the opposite side and extends up to the thoracic segments.

***Function***

The tract has a facilitatory influence on flexor muscle tone.

### *Tectospinal Tract*

Fibers arise from superior colliculus in the midbrain, cross to the opposite side in the tegmentum and descend up to the lower cervical region.

***Functions***

This tract indirectly connects retina with spinal motor neuron and coordinates retinal impulses with body movements.

### *Olivospinal Tract*

Fibers arise from inferior olivary nucleus of medulla, crosses to opposite side and descends up to cervical region. It is less developed and less important in mammals.

***Functions***

Control of movements due to proprioception.
Disease or lesion of extrapyramidal tract causes difficulty in initiating the voluntary movements.

## Applied Aspect

### *Upper Motor Neuron Lesions*

It is due to lesion of the upper motor neurons (UMNs), i.e. the corticospinal tract neurons that innervates spinal motor neurons, but they can also include brainstem neurons that controls spinal motor neurons (Fig. 11.38).

### *Lower Motor Neuron Lesions*

It is due to the lesion of the lower motor neurons (LMNs), i.e. the spinal and cranial motor neurons that directly innervate the muscles. For example, in anterior poliomyelitis the anterior horn cells are damaged.

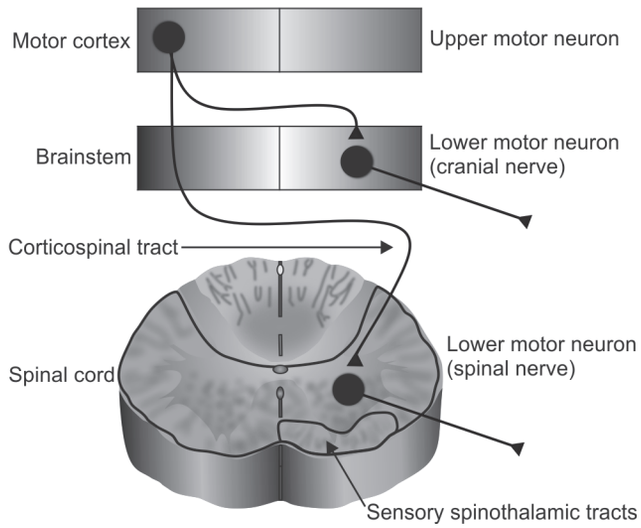



**Fig. 11.38:** Schematic representation of origin and location of upper motor neuron and lower motor neuron

### *Some Popular Clinical Terms*

1. **Hemiplegia:** Paralysis of one half of the body. There are two types of hemiplegia—dense hemiplegia and crossed hemiplegia.
   a. *Dense hemiplegia*: Here the lesion occurs at internal capsule. There is weakness of whole opposite side of the body including face. This is a type of UMN type of lesion affecting the whole opposite of the body.
   b. *Crossed hemiplegia:* Here the site of lesion is in the brainstem. Cranial nerve involvement depends on the level of lesion. There is ipsilateral cranial nerve involvement (LMN type of cranial nerve lesion) and contralateral weakness of body (UMN type).

   The patient walks on a narrow base, has a difficulty in bending his knees and drags his feet along as if they are glued to the floor this is referred as spastic or hemiplegic gait.
2. **Paraplegia:** Paralysis of both the lower limbs.
3. **Monoplegia:** Paralysis of single limb.
4. **Quadriplegia:** Paralysis of all the four limbs.

### *Effects of Lesions at Various Levels of CNS*

Pyramidal system (PS) can be injured by cerebrovascular accidents (CVA). The CVA is the major cause of pyramidal lesions. Two major forms of CVA are: (1) Infarction (2) Hemorrhage. In the brain, an artery can be blocked by thrombosis or embolism. The CVA can damage the pyramidal system at various places like internal capsule, motor cortex and brainstem.

1. When the injury is located at internal capsule then hemiplegia (contralateral side) is the rule. This is because PT fibers are so crowded here that even a slight injury will

**Table 11.3: Pyramidal and extrapyramidal tracts compared**

| *Pyramidal tracts* | *Extrapyramidal tracts* |
|---|---|
| 1. Phylogenetically it is a newer motor system developed recently | 1. It is an old motor system |
| 2. Its axons pass without relay to the spinal segments where they form synapses with either interneurons in the dorsal horn or directly with the motor neuron themselves | 2. Discharges is through several tracts. Polysynaptic and multichannel pathway |
| 3. They have greater influence over motor neurons that control muscles involved in fine movements, particularly those of the fingers and hand | 3. They are involved with coordination of the large muscle groups used in the maintenance of upright posture, in locomotion and in head and body movements when turning towards a specific stimulus |
| 4. Lesions of these tract produces 'spasticity' in the muscles involved | 4. Its lesion produces 'rigidity' of the muscles involved |
| 5. The tract start functioning after the completion of myelination at the second year after birth | 5. The tract starts functioning from before birth |
| 6. Slower rate of conduction | 6. Faster rate of conduction |
| 7. Only facilitatory fibers are present | 7. Both facilitatory and inhibitory fibers present |

**Table 11.4: Difference between rigidity and spasticity**

| *Spasticity* | *Rigidity* |
|---|---|
| 1. Seen following the lesion of pyramidal tract (corticospinal tract), the most common site being the internal capsule | 1. Seen following the lesion of basal ganglia and therefore called extrapyramidal rigidity |
| 2. Involves only one group of the muscle either agonist or antagonist. Antigravity muscles are usually involved | 2. Involves both the agonist as well as the antagonist muscle, therefore more uniform hypertonia and often it is so distributed as to produce a general attitude of flexion of the limbs and trunk |
| 3. A state of increased tone which is described as clasp knife type | 3. Hypertonia described here is of two types:<br>i. Lead pipe rigidity-Passive movement of an extremity meets with a plastic dead feeling resistance as though bending a lead pipe<br>ii. Cogwheel rigidity-Resistance to passive movement of an extremity is regularly or irregularly variable. There will be series of catches during passive movement of the extremity. This is described as like a lever rubbing on the teeth of a cogwheel |
| 4. It is form of spasticity which is stretch sensitive. The degree of increased tone developed during any passive stretch is proportional to the speed of the applied stretch | 4. No similar phenomenon seen here |

cause damage to large number of fibers. In severe lesions, sensory and visual tracts are involved, so hemianesthesia and homonymous hemianopia develop.

2. When there is a damage of area 4, monoplegia (contralateral side) or localized lesion (e.g. in the face) is the general rule. This is because the PT fibers are very scattered here. Therefore to cause hemiplegia, lesion in area 4 has to be very extensive. Morever in cortical lesions, there will be other signs, e.g. convulsive seizures, astereognosis, aphasia, etc.
3. Brainstem lesions can be often diagnosed by reference to the gross anatomy. For example:
   a. In lesions of midbrain, there will be signs of 3rd nerve paralysis on the side of lesion and spastic hemiplegia on the other (contralateral) side (Weber's syndrome).
   b. When the lesion is lower down in the brainstem, there will be, symptoms depending on the exact site of injury. There will be signs of injury of 7th, 9th, 10th or even hypoglossal (12th) nerve injury on the side of lesion and spastic hemiplegia on the contralateral side.
4. Upper level of spinal cord—quadriplegia + respiratory paralysis.
5. Thoracic and lumbar—paraplegia; respiration remains normal.

***Note***

1. Cerebrovascular accident induced damage of PS is called stroke or apoplexy. Onset of stroke is usually sudden. In the initial phase there will be usually signs of shock. After a few days, provided the patient survives, the shock passes off and the stage of chronic pyramidal lesion appears.
2. Babinski's response is obtained by stroking (to pass gently in one direction) outer edge of the sole of the foot with firm tactile stimulus. The direction of stroke is from the heel towards the little toe and then medially across the metatarsus. In normal healthy individuals, it produces a downward movement (plantar flexion) of the great toe and the small toes (Babinski sign-negative). This is due to contraction of flexor hallucis longus. Babinski plantar response appears with the development of the pyramidal tracts and its presence indicates the development of these tracts. Normally it is a flexor response.
3. Babinski sign is positive in UMN lesion. Here on stroking the outer edge of the sole of the foot with firm tactile stimulus produces first an upward movement (dorsiflexion) of the great toe and fanning out (abduction) of the small toes. This is due to contraction of extensor hallucis longus; physiologically it is a withdrawal response.

   Babinski sign if once becomes positive remains positive for rest of the life.

   Causes of positive Babinski sign:

   i. Lesion of pyramidal tracts
   ii. Infants (below 1year) as the pyramidal tracts are not well developed
   iii. During deep sleep
   iv. Cheyne-Stokes respiration due to hypoxia.

### Release Phenomenon

Some features are not normally seen in healthy persons because they are suppressed by the CNS. Some particular damages of CNS cause release of it and the feature, uptill now

**Table 11.5: Differences between lower and upper motor neuron lesion**

| *Lower motor neuron lesion (LMNL)* | *Upper motor neuron lesion (UMNL)* |
|---|---|
| 1. It is due to the lesion of the lower motor neurons (LMNs), i.e, the spinal and cranial motor neurons that directly innervate the muscle | 1. It is due to the lesion of the upper motor neurons, i.e. the neurons that originate in the brain and spinal cord that can influence the activity of LMNs; lesion of the pyramidal tracts being the major cause |
| 2. Usually single or individual muscle is affected | 2. It involves a group of muscles |
| 3. Flaccid paralysis occurs, i.e. the muscles becomes completely paralyzed (hypotonia). This is due to complete loss of muscle tone as the integrity of reflex arc is it lost. | 3. Spastic paralysis occurs, i.e. affected muscles become hypertonic. It is due to:<br>i. Release phenomenon, i.e. loss of higher inhibitory control<br>ii. Denervation hypersensitivity of centers below the transaction |
| 4. All reflexes superficial and deep are lost as the motor pathway is damaged | 4. Superficial reflexes are lost but the deep reflexes are exaggerated. Deep reflexes are exaggerated because of increased $\gamma$ motor discharge |
| 5. Gross muscle wasting occurs as all muscles are paralyzed. Disuse atrophy of muscle occurs, i.e. shrinkage of muscle fiber occurs and is finally replaced by fibrous tissue | 5. Minimal wasting of occurs, i.e. minimal disuse atrophy occurs because muscles though not used in voluntary movements are continuously in action to maintain posture by reflexes. |
| 6. Fasciculation and fibrillation present | 6. No fasciculation and fibrillation |
| 7. Babinski sign/Plantar reflex not elicited | 7. Babinski sign positive (abnormal) |

suppressed, become manifested. In the newborn Babinski's sign is normally +ve: when PT develops fully, Babinski's sign is suppressed and flexor plantar response appears. The UMN lesions causes, the release and Babinski's sign appears again. Common examples of release phenomenon are Babinski's sign, decerebrate rigidity and cerebellar tremor.

***Note***

1. Babinski's sign is a release phenomenon.
2. Spasticity or spastic paralysis usually means a combination of following signs:
   a. Clasp-knife rigidity.
   b. Presence of babinski's sign.
   c. Loss of voluntary power.
   d. Exaggereated reflex.

## AUTONOMIC NERVOUS SYSTEM

The portion of nervous system that controls the body. Most striking feature of the system is rapidity and intensity of action.

### Classification

#### *Anatomical*

Craniosacral outflow: Cranial outflow supplies the visceral organs via 3, 7, 9, 10 cranial nerves and sacral outflow supplies pelvic viscera via pelvic branches of S2-S4. They are parasympathetic fibers.

Thoracolumbar outflow: T1-T12 and L1-L3 (mainly L1, L2). They are sympathetic fibers.

#### *Physiological (Table. 11.6)*

- Sympathetic (thoracolumbar)
- Parasympathetic (craniosacral).

#### *Chemical*

i. ***Cholinergic:*** Release acetylcholine. The neurons that are cholinergic are:
   a. All the preganglionic.
   b. The anatomically parasympathetic postganglionic neurons.
   c. The anatomically sympathetic postganglionic neurons that innervate sweat glands.
   d. Anatomically sympathetic neurons that end on blood vessels in skeletal muscles and produce vasodilation.

ii. ***Adrenergic:*** Producing epinephrine (adrenalin) or norepinephrine (noradrenaline) at neuroeffector junction. They are found in sympathetic postganglionic fibers except sweat glands, piloerector muscles, some blood vessels of skeletal muscle and adrenal medulla.

***ANS Includes the Following:***

1. Areas controlling visceral function located in cerebral hemispheres including part of cerebral cortex, limbic system and hypothalamus.
2. Autonomic centers in brainstem and in reticular formation contains cardiovascular, respiratory centers and cranial nerve nuclei (3, 7, 9,10).

**Table 11.6: Differences between somatic and autonomic nervous system**

| | *Somatic nervous system* | *Autonomic nervous system* |
|---|---|---|
| Efferent neuron | Single efferent neuron between CNS and effector organ | Two efferent neuron (pre and post ganglionic) |
| Ganglia | No ganglia in efferent pathway | Ganglia is the site of synapse between two efferent neurons |
| Neurotransmitter | Always acetylcholine | Acetylcholine or epinephrine/norepinephrine |
| Innervates | Skeletal muscle | Smooth, cardiac muscle and glands |
| Effect of stimulation | Always causes excitation (inhibition occurs centrally through inhibitory interneurons) | Either excitation or inhibition according to receptor (inhibition is peripheral) |
| Spinal column pathway | In anterior horn cells | In autonomic ganglia |
| Synapse | Well defined | Not well defined |
| Function | Controls voluntary movements | Controls involuntary movements |
| Miscellaneous | 1. Skeletal muscle activity is entirely dependent on its nerve supply<br>2. Activity is confined to certain muscle groups | 1. Activities controlled by ANS shows considerable autonomy<br>2. Activity is more generalized. |

3. Autonomic center in spinal cord-in lateral horn (sympathetic; thoracolumbar and parasympathetic; sacral).
4. Peripheral part of ANS—autonomic nerves and ganglia.

## Sympathetic Nervous System

Sympathetic fibers originate in spinal cord along the spinal nerve where its cell body is located. From there they first go to paravertebral sympathetic ganglion chain and then to tissues and organs that are stimulated by sympathetic nerve. Preganglionic fibers (myelinated 'B' fibers) originate from lateral horn and pass through anterior route immediately after the spinal nerve leaves the spinal canal. These fibers then leave the spinal nerve and pass through the white ramus into one of the ganglia (Fig. 11.39). From the ganglia the course of fibers can be one of the following:

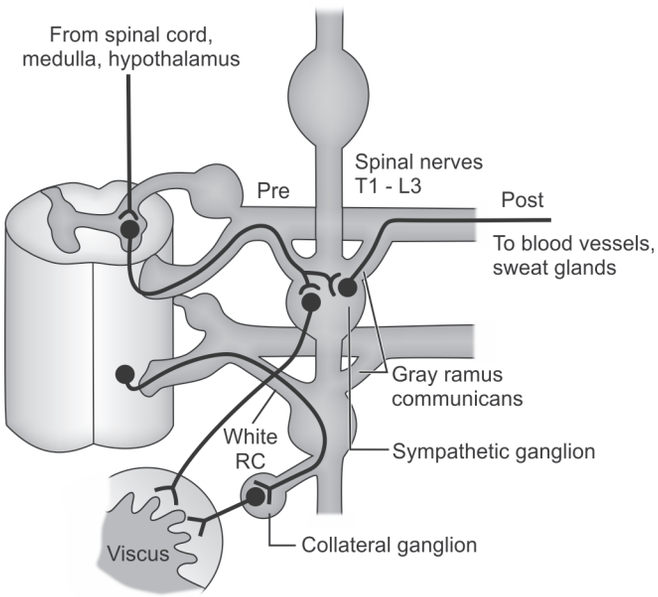



**Fig. 11.39:** Sympathetic division of nervous system

a. Most of them end on the cell bodies of the postganglionic neurons.
b. Some fibers pass upwards or downwards in sympathetic chain and synapse with ganglia at higher or lower level.
c. Some end in peripheral sympathetic ganglia other than preganglionic and postganglionic.

Postganglionic fibers originating from the ganglia innervate various organs. Some of the postganglionic fibers pass back from sympathetic chain and enter spinal nerve as gray ramus communicans (unmyelinated 'c' fibers). These fibers enter all parts of body through spinal nerves and supplies blood vessels, piloerector muscles, etc.

***Note:*** Sympathetic nerves also extends to adrenal medulla. Preganglionic fibers originating from lateral horn pass through sympathetic chain into splanchnic nerves (here there is no synapse). Splanchnic nerve enter adrenal medulla. In adrenal medulla, they end directly on modified neuronal cells. They secrete epinephrine or norepinephrine directly into blood stream. Postganglionic neurons are modified into secretory cells. Eighty percent secretion of adrenal medulla is epinephrine and 20% is norepinephrine.

## Parasympathetic Nervous System

Seventy-five percent of all parasympathetic fibers are from vagus nerve. Vagal fibers supply heart, lungs, esophagus, stomach, entire small intestine, poximal large intestine, liver, gallbladder, pancreas and upper portion of ureters. Occulomotor fibers supply pupillary sphincter and cilliary muscle. Facial nerve supply lacrimal glands and submandibular glands. Glossopharyngeal supply parotid gland. Sacral fibers are through pelvic nerve. From sacral plexus S2, S3, S4 supply portion of large intestine, external genitalia and lower portion of ureter (Fig. 11.40). In parasympathetic system, ganglia is

located in or near the organs. So preganglionic fibers are long and postganglionic fibers are short.

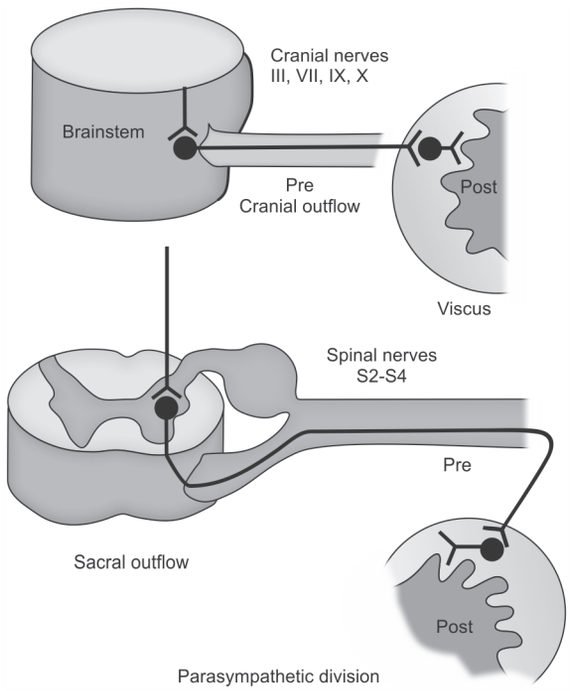



**Fig. 11.40:** Parasympathetic division of nervous system

## Neurotransmitters of ANS

1. Acetylcholine all ganglia, in adrenal medulla (preganglionic sympathetic), postganglionic parasympathetic endings, sympathetic cholinergic nerve endings.
2. Adrenaline and noradrenaline: Postganglionic sympathetic nerve endings (mainly noradrenaline), adrenal medulla (postganglionic sympathetic; mainly adrenaline).

### *Synthesis of Neurotransmitters*

1. Acetylcholine:
   *Site:*
   Terminal ends of nerve fibers and it is stored in vesicles.
   *Steps:*

$$\text{Acetyl CoA + Choline} \xrightarrow{\text{choline acetyl transferase}} \text{ACh}$$

   *Fate:*

$$\text{ACh} \xrightarrow{\text{cholinesterase}} \text{Acetate + Choline}$$

2. Epinephrine and norepinephrine:
   Site: Axoplasm of terminal nerve ending.
   *Steps:*
   *In vesicles:*

$$\text{Tyrosine} \xrightarrow{\text{hydroxylation}} \text{DOPA} \xrightarrow{\text{decarboxylation}}$$

$$\text{Dopamine} \xrightarrow{\text{hydroxylase}} \text{Norepinephrine}$$

   *In adrenal medulla:*

$$\text{Norepinephrine} \xrightarrow{\text{methylation}} \text{Epinephrine}$$

*Fate of noradrenaline:*
Reuptaken into terminal nerve endings and are diffused into surrounding tissue fluids. Some of them are destroyed by catechol -o- methyl transferase.

**Adrenergic and cholinergic receptors**
Seen on effector organs.

1. Adrenergic receptors: (see Table 11.8)
   - $\alpha_1$ and $\beta_1$ causes excitation
   - $\alpha_2$ and $\beta_2$ causes inhibition.
2. Cholinergic receptors:
   - *Nicotinic:* In all autonomic ganglia and NMJ of skeletal muscle
   - *Muscuranic:* In neuroeffector junction of smooth muscles and glands.

**Table 11.7: Differences between sympathetic and parasympathetic nervous system**

| | *Sympathetic* | *Parasympathetic* |
|---|---|---|
| Nerve fibers | Thoracolumbar (T1-L2/L3) | Craniosacral outflow (CNS 3, 7, 9, 10) |
| Preganglionic fibers | Short | Long |
| Postganglionic fibers | Long | Short |
| Sympathetic ganglia | Close to vertebral column | Lies in/close to organ supplied |
| Function | Prepare the individual to face emergency situation | Concerned in vegetative aspect of day-to-day living, i.e. digestion, absorption, sexual erectile function |
| Actions | Causes dilatation of pupil, increased heart rate, increased BP, provide better perfusion, constrict cutaneous vessels to limit bleeding, decreases threshold in reticular formation hence increases alertness, increase blood glucose, free fatty acid to provide more energy | Decreased heart rate, decrease SV, favors storage of absorbed nutrients |
| Known as | Catabolic nervous system | Anabolic nervous system |
| Neurotransmitter | At ganglia: Acetylecholine<br>At organ: Adrenaline/noradrenaline | At ganglia as well as postganglia: Acetylcholine |

**Table 11.8: Difference between α and β receptor**

| *α receptor* | *β receptor* |
|---|---|
| Vasoconstriction | Vasodilation ($\beta_2$) |
| Iris dilatation | Cardio acceleration ($\beta_1$) |
| Intestinal relaxation | Intestinal relaxation ($\beta_2$) |
| Intestinal sphincter contraction ($\alpha_1$) | Uterus relaxation ($\beta_2$) |
| Piloerector contraction | Bronchodilatation ($\beta_2$) |
| Bladder sphincter ($\alpha_1$) relaxation | Calorigenesis ($\beta_2$) |
| | Bladder sphincter relaxation ($\beta_2$) |

## SPINAL CORD LESIONS

Spinal cord transections can be divided into three types: complete, incomplete and hemisection of spinal cord.

### Complete Transection of Spinal Cord

The complete transection of spinal cord occurs due to:

a. Bullet injury which causes dislocation of spinal cord.
b. Accidents which cause dislocation of spinal cord/occlusion of blood vessels.

The complete transection causes immediate loss of sensation and voluntary movement below the level of lesion. Even though the higher centers remain unaffected, the spinal centers below the level of injury loose the function. The effects occur in three stages:

I. Stage of spinal shock.
II. Stage of reflex activity
III. Stage of reflex failure.

#### *Stage of Spinal Shock*

It is the first stage of effects that occurs immediately after injury. It is also called the stage of flaccidity. Patient feels as if he is cut into two portions. The various signs and symptoms that develop during this stage are:

1. *Paralysis of limbs:* Depending on the level of lesion the paralysis of limbs can be of the following types:
   - Hemiplegia (paralysis of one-half of the body)
   - Quadriplegia (paralysis of all the 4 limbs)
   - Paraplegia (paralysis of both the lower limbs).
2. *Flaccid paralysis:* Because of the transection, the isolated segments of the spinal cord have lost their power of mediating reflex functions, therefore the muscles are completely paralyzed (Flaccid paralysis)
3. *Loss of reflexes:* All the spinal reflexes are markedly decreased or lost because of the injury to anterior and posterior nerve roots.
4. *Loss of sensations:* All the sensations below the transection is lost because of the injury to posterior nerve roots and sensory neurons in the posterior gray horn.
5. *Effect on visceral organs:* The urinary bladder and rectum become paralyzed. Detrusor muscle becomes atonic. There will be retention of urine and constipation. The penis is flaccid and erection is not possible.
6. *Venous return:* Venous return is very much decreased. Venous return depends on the muscle tone during resting condition. During activity it depends upon contraction of skeletal muscle (muscle pump). But in complete transection of spinal cord, muscle tone is lost and flaccid paralysis occurs, leading to decreased venous return.

   In addition, the limbs are immobile and smooth muscles of blood vessels loose tone. So blood accumulates in the lower limb, becomes cold and blue (cyanotic) due to accumulation of blood in the lower limb.
7. *Effect on blood pressure:* The effect on BP depends upon the level of injury.

   *Lesion anywhere below L2 segment:* The blood pressure is not affected much because the sympathetic vasoconstrictor fibers leave the spinal cord between T1 and L2 segments.

   *Lesion at or above T1 segment:* All the sympathetic vasoconstrictor fibers leaving the spinal cord from T1 and L2 segments are transected, i.e. completely cut off from higher medullary cardiovascular center regulating BP. So the BP falls drastically. The mean arterial BP falls below 40 mm Hg.
8. Skin becomes dry and scaly and bed sores may develop.
9. No sweating in the region affected by vasomotor paralysis.

***Note:*** Severity of complete transection depends upon the level of lesion. The complete transection at the cervical region can be very fatal, because the diaphragm and other respiratory muscles are cut off from the respiratory centers. This leads to paralysis of these muscles leading to sudden arrest of breathing.

In humans stage of spinal shock usually last for a period of at least two weeks. There is functional depression of the nervous system, a phenomenon called **Diaschisis.**

#### *Stage of Reflex Activity*

This stage is also called stage of recovery. After 3 weeks period, depending largely upon the general health of the patient, the reflex activity begins to return to the isolated segments of the spinal cord.

i. First the functional activities return to the smooth muscle. Urinary bladder becomes automatic. Similarly reflex defecation also occurs.
ii. Next sympathetic tone of blood vessels is regained. As a result:
    a. Blood pressure is restored to normal at rest, but precise feedback regulation is absent and wide fluctuations in BP are common.
    b. The skin which has become dry and scaly now shows sweating again and it becomes more healthy.
    c. Bed sores heal up rapidly.
    d. Because of accompanying return of reflex activity to the skeletal muscle, circulation through the limbs is greatly improved and they become warm and of good color.
iii. *Muscle tone:* Tone in the skeletal muscle returns slowly after 2 or 3 weeks. The tone of flexor muscles return first, so that now even though both the flexors and extensors are hypotonic, the flexors are less hypotonic than extensors. The limbs in this condition adopt a position of slight flexion and the paralysis is therefore called ***paraplegia in flexion.***
iv. *Reflex activity:* Reflex activity begins to return after few weeks of return of muscle tone. The flexor reflexes appear first. The first reflex, which usually appears is the Babinski's reflex. Babinski's sign is +ve .

Mass reflex can be elicited in some cases by scratching the skin over the lower limbs or the anterior abdominal wall. This reaction constitutes the spasm in flexor muscles of both the lower limbs, evacuation of urinary bladder and profuse sweating.

Tendon jerks begin to appear. Initially the knee jerk returns then the ankle jerk.

***Note:*** The mass reflex can be utilized to provide paraplegic patients a degree of bladder and bowel control. Patients can be trained to initiate urination and defecation by intentionally producing mass reflex with the help of a stroke or a pinch on their thighs.

### *Stage of Failure of Reflex Activity*

As the stage of reflex activity continues, a time comes when the reflex activities of stage II fails because of the degeneration of neural tissue of spinal cord below the lesion and intercurrent infections. Once again there develops hypotonicity of muscles, mass reflex disappears, bed sores appears and the patient dies.

Though the reflex movements return, the muscles below the level of injury have less power and less resistance.

a. Usually the general condition of the patient starts detiorating.
b. In general, malnutrition, infection or toxemia causes failure of reflex function.
c. The reflexes becomes more difficult to elicit.
d. The threshold for stimulus increases.
e. Mass reflex is abolished.
f. The muscles become extremely flaccid and undergo wasting.

## Hemisection of Spinal Cord (Brown-Sequard Syndrome)

The lesion involving one lateral half of the spinal cord is called hemisection of the spinal cord (Figs 11.41 and 11.42). It can occur due to injury during accidents, gun shot injuries, tumor, etc.

### *Symptoms of Hemisection of Spinal Cord*

Here autonomic functions are usually normal. The other functional changes that take place can be divided into three categories:

- Changes below the level of lesion
- Chages at the level of lesion
- Changes above the level of lesion.

The effects in these places differ on the same side and on the opposite side. There are changes in sensory and motor function.

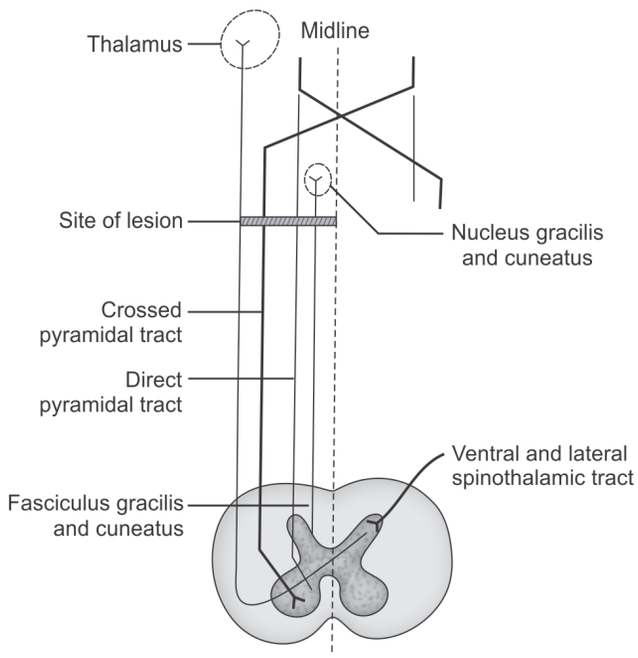



**Fig. 11.41:** Hemisection of spinal cord

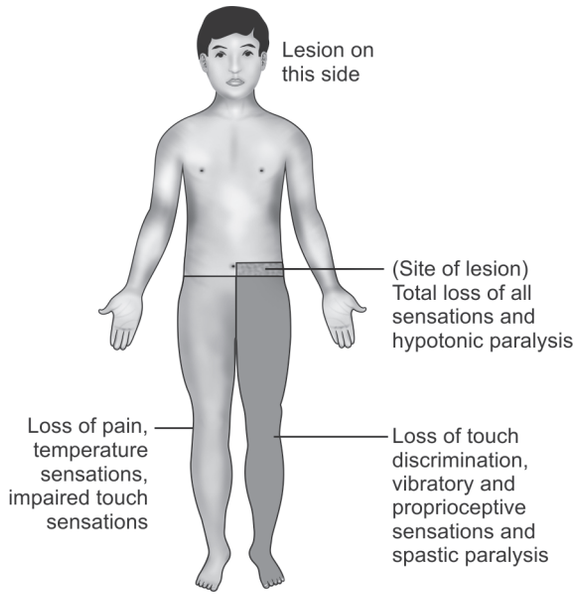



**Fig. 11.42:** Clinical features of Brown-Sequard syndrome

### *Changes Below the Level of Lesion*

#### *On the Same Side*

1. *Sensory changes:* Fine touch, tactile localization and tactile discrimination, stereognosis, vibration sense and kinesthetic sense (sense of movement and position) is lost due to damage to uncrossed fibers of dorsal column tract (Fig. 11.26).

   Pain, temperature and crude touch (Fig. 11.28) remain unaffected as the spinothamalic tracts (anterior and lateral) carrying these sensations cross to the opposite side and escape injury
2. *Motor changes:* The motor changes resembles the effects of UMN type of lesion, due to damage of the crossed pyramidal tracts. These include spastic paralysis, +ve Babinski's sign, loss of superficial reflexes, exaggerated deep reflexes.

Temporary loss of vasomotor tone due to damage of the descending fibers from the VMC in the medulla to the lateral horn cells. This leads to the dilation of blood vessels and fall in BP.

Since some fibers of direct pyramidal tract (15%) of opposite side (which end in same side) escape injury, therefore some muscles on the same side of the lesion may not be paralyzed.

#### *On the Opposite Side*

1. *Sensory changes:* Complete loss of pain, temperature and crude touch due to damage to the spinothalamic fibers which come from the opposite side.

   Kinesthetic sensations, fine touch, etc. will persist because the posterior columns of the opposite are not damaged.
2. *Motor changes:* Either no paralysis or paralysis of few muscles of UMN type. This is due to possible involvement of direct pyramidal tracts (15%) of the same side when these fibers cross.

   Therefore, below the level of the lesion, on the same side, there is extensive motor loss but little sensory loss; while on the opposite side there is extensive sensory loss but little motor loss. This phenomenon is called Brown-Sequard syndrome.

### *Changes at the Level of Lesion*

#### *On the Same Side*

1. *Sensory changes:* Complete anesthesia occurs due of damage to the posterior nerve root, posterior horn cells and spinothalamic fibers (which cross to the opposite side).
2. *Motor changes:* Complete lower motor neuron type of paralysis is seen due to damage to the anterior horn cells. Complete and permanent vasomotor paralysis occurs due to damage of the lateral horn cells.

#### *On the Opposite Side*

1. *Sensory changes:* There is loss of pain, temperature and crude touch sensations due to injury of pain fibers of spinothalamic tract which cross horizontally in the same segment.
2. *Motor changes:* Nil or very slight due to the damage of some pyramidal tract of the same side.

### Incomplete Transection of the Spinal Cord

In this type of lesion of the spinal cord, although the cord is severely injured, few tracts escape injury and are not cut.

### Stage of Spinal Shock

It is identical with that of complete transection of the spinal cord.

### Stage of Reflex Activity

Transection of the spinal cord is irregular. Therefore some of the descending tracts in the ventrolateral columns of spinal cord (especially vestibulospinal and reticulospinal) may escape injury and some connections persist between the brain and spinal cord. These tracts mainly reinforce the activity of the extensor motor neurons producing extensor hypertonia (Paraplegia in extension), i.e. the legs lie extended at hip and knee with toes pointing slightly downwards.

### *Characteristic Features*

1. All features of upper motor neuron lesion is seen.
2. Involuntary movements are relatively infrequent, but when they occur, involve an increase of extensor tone, producing downward movement of feet and toes.
3. *Reflex movements:* The stretch reflex reappears first, then the flexor reflexes appear.

### Sensory Disturbances

1. *Tabes Dorsalis:* In this condition degeneration of dorsal (sensory) nerve roots occurs. It affects the fibers specially in dorsal columns and fibers which convey pain. The disease is usually caused by syphilis.
   **Characteristic features:** In tabesdorsalis both sensory and motor functions are affected.
   - Numbness or paresthesia and lightning pains
   - Atonicity of bladder
   - Loss of position sense, vibration sense, passive movement.
   - Deep tendon reflexes like knee, ankle, biceps, triceps jerks are lost
   - Marked disturbance of voluntary movements
   - Loss of pain sensations particularly in the joints lead to deformities of the joints. There is no proper support and movements at the joint become uncontrolled is called **Charcot's joint**.
2. *Syringomyelia:* In this condition the gray matter around the central canal of spinal cord shows excessive growth of neuroglial tissue with cavity formation.

## VESTIBULAR APPARATUS

Vestibular apparatus is the sensory organ for detecting sensation of equilibrium. It is encased in a system of bony tubes and chambers located in the petrous portion of the temporal bone, called the bony labyrinth. Within this system are membranous tubes and chambers called membranous labyrinth. The membranous labyrinth is the functional part of the vestibular apparatus. It consists of: (1) Three semicircular canal, (2) The otolith organ-saccule and utricle (the two sac like organ) (Fig. 11.43).

### *Semicircular Canal*

Semicircular canals are the tubular structures placed at right angles to each other. Because of this type of arrangement, the semicircular canals represent the three axis of rotation: vertical, anteroposterior and transverse axis. The three membranous canals are: horizontal (lateral), superior (anterior) and inferior (posterior). They contain endolymph and are separated from bony canal by the perilymph. Each canal begins as a dilation

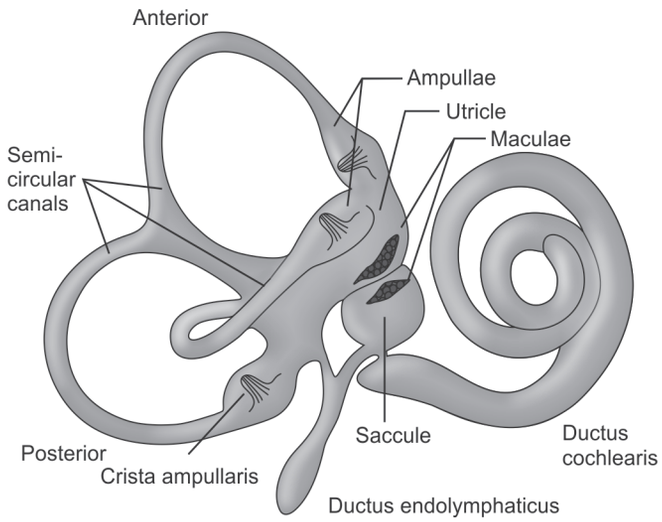



**Fig. 11.43:** Membranous labyrinth showing semicircular canals

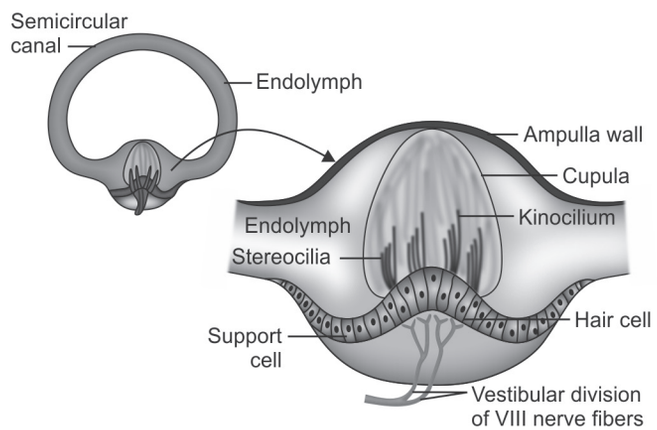



**Fig. 11.44:** Structure of crista (of semicircular canals) and macula (of Otolith organ)

(or ampulla), containing a projecting ridge (on its inner aspect), called crista ampullaris (Fig. 11.44). Cristae are the receptors in the semicircular canals.

Each crista (Fig. 11.44) consists of hair cells and sustentacular cells (supporting cell) surmounted by a gelatinous partition (cupula) that closes off the ampula. The processes of the hair cells are embedded in the cupula, and the bases of the hair cells are in close contact with the afferent fibers of the vestibular division of the vestibulocochlear nerve.

### *Otolith Organ: Utricle and Saccule*

The otolith organ (Fig. 11.45) is formed by utricle and saccule. The utricle communicates with the saccule by means of the ductus endolymphaticus. Both utricle and saccule contains a

projecting ridge called the macula (like cristae, they are the receptors in otolith organ). Like crista, macula is also formed by hair cells and supporting cells which project into a firm gelatinous material, the cupula.

A large nonmotile hair called kinocilium (Fig. 11.45) is located at one end of hair cells. In the remaining hair cells, small cilia with progressive increase in height are present, called stereocilia. Between the hair cells lie the fibers of origin of vestibular division of VIII nerve. In the saccule and utricle, the cupula contains many chalky ($CaCO_3$) particles called otoliths (or otoconia) hence the name otolith organ. The hairs plus gelatinous materials containing $CaCO_3$ is called otolith membrane (Fig. 11.45).

When head is in the normal erect position:

- The macula of each utricle is in horizontal plane
- The macula in each saccule is in vertical plane (Fig. 11.46).

### *Functions*

The vestibular apparatus plays an important role in postural activity. The otolith organ (saccule and utricle) is stimulated by gravity and the semicircular canals activated by rotational movements. It plays an important role in postural activity.

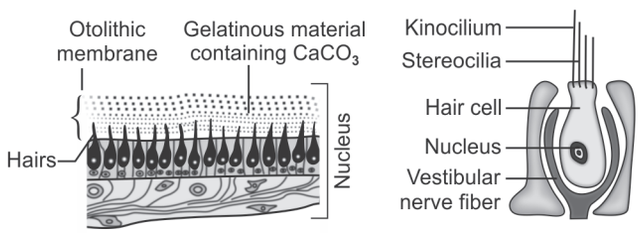



**Fig. 11.45:** Hair cell showing kinocilium and stereocilia

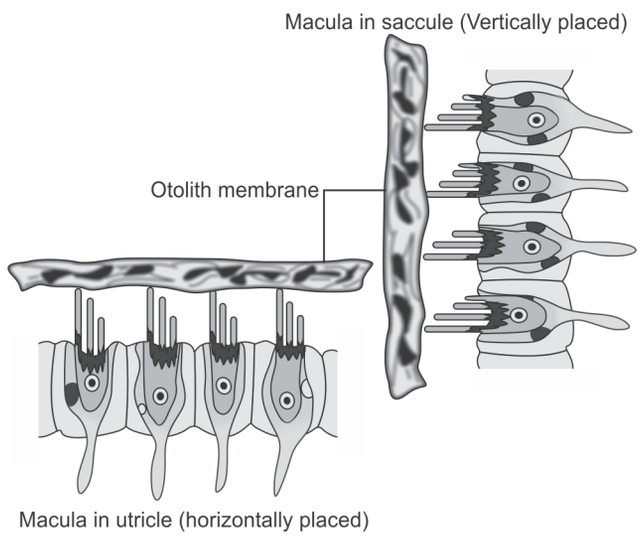



**Fig. 11.46:** Otolith organ (utricle and saccule with position of macula)

1. It gives rise to afferent impulses which reflexly adapt the position of the trunk and limbs to that of the head. Thus enable the erect position of the head and thus the normal posture of the head to be maintained.
2. Information from the vestibular apparatus also reaches cranial nerve nuclei (which supply eye muscles) and the cerebral cortex. This helps in the recognition of the position and the movements of the head. As a result the position of the eyes is held approximately constant allowing visual fixation on moving objects.

### *Vestibular Pathways*

Nerve fibers arise from the cristae and maculae to form vestibular division of VIII nerve.The nerve cell bodies are situated at the vestibular ganglion (Scarpa's ganglion). The central axons of the Scarpa's ganglion proceed towards the brainstem and end in ipsilateral vestibular nucleus and flocculonodular lobe of cerebellum (Fig. 11.47). Each vestibular nuclei has four subparts: lateral (Deiters), superior, medial and inferior (spinal) vestibular nuclei. Efferent fibers from vestibular nucleus terminate in the following regions:

1. 3rd, 4th and 6th cranial nuclei, via median longitudinal fasciculus. Therefore stimulation of vestibular nuclei leads to movement of the eyes.
2. In the anterior horn of spinal cord cells via anterior and lateral vestibulospinal tract.
3. In the cerebellum.
4. In the nuclei of reticular formation.
5. In the primary somatosensory cortex via the opposite thalamus.

## Functioning of Vestibular Apparatus

### *Mode of Action of Otolith Organ*

The saccule and utricle provide information about linear acceleration and change in head position relative to the force of gravity. Saccule respond to vertical acceleration and utricle to horizontal acceleration. The maculae of the saccule and utricle are stretch receptors. When in erect posture, the otolith membranes are so placed that the hair cells are least disturbed. Based on bending the head (e.g. sideways/ventro or dorsiflexion) gravity acts. The hair cells are thus deformed with resulting stimulation of the nerve fibers which lie between them (Fig. 11.48).

1. Saccule is stimulated when there is sideways flexion of neck.
   If head is tilted to right:
   - Cupula of right saccule hangs downwards and pulls on its macula; thus maximally stimulated.
   - In left saccule there is upward movement of cupula to produce minimal stimulation.

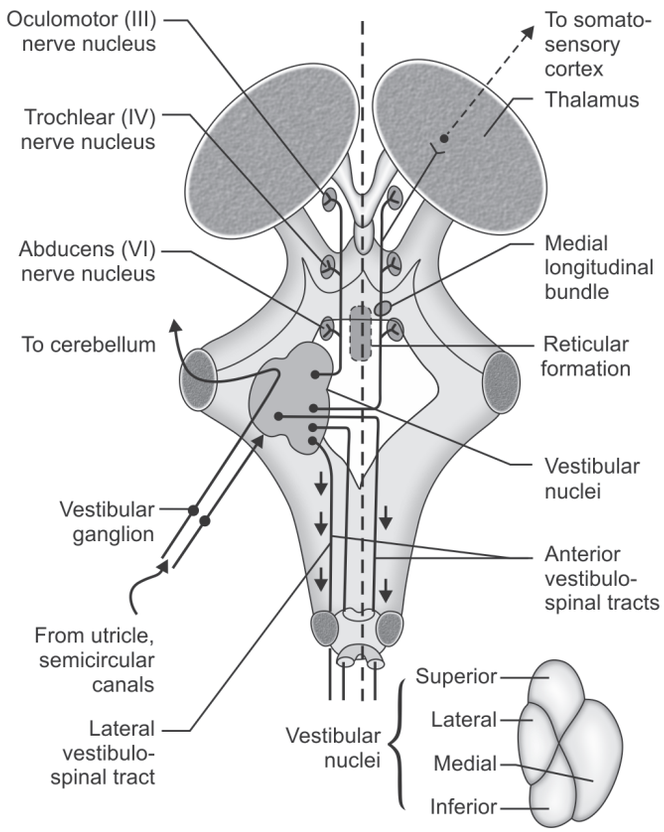



**Fig. 11.47:** Vestibular pathway

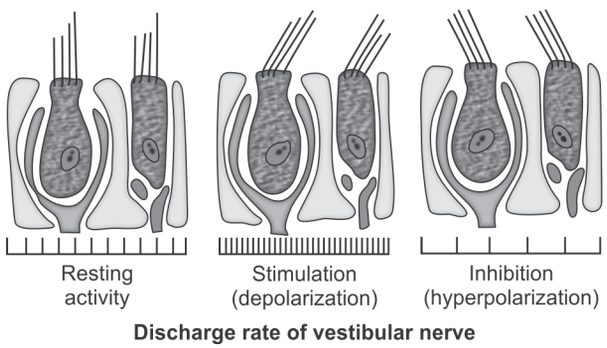



**Fig. 11.48:** Mode of action of Otolith organ

2. The utricular macula are stimulated when there is ventro- or dorsiflexion of neck.
   - Head erect (upright)-minimal stimulus.
   - Head is bend forward or backward-maximal stimulation.

For this reason, the maculae of saccule and utricle are called gravity receptors. The receptors of vestibular apparatus show little or no adaptation.

### *Mode of Action of Semicircular Canals*

The semicircular canal detects angular action during rotation of head along three perpendicular axis. When a person rotates in clockwise direction, i.e. in vertical axis, horizontal canal moves in clockwise direction. But there is no corresponding movement of endolymph inside the canal at the beginning of rotation due to inertia. This phenomenon causes relative displacement of endolymph in the direction opposite to that of the rotation of head. That is, fluid is pushed in anticlockwise direction.

Thus in the right semicircular canal, the endolymph flows towards the ampulla (stimulation) and in left canal fluid moves away from the ampulla (decreased impulse discharge). The combination of increased discharge from one ampulla and decreased discharge from other form the basis of detection of direction of movement (Fig. 11.49).

The movement of endolymph in semicircular canal, in turn causes corresponding movement of gelatinous cupula causing cilia of hair cell to bent leading to stimulation of hair cells. Thus at the beginning of rotation in clockwise direction around vertical axis, the hair cells at ampulla of horizontal canal in right ear are stimulated. But, the hair cells in horizontal canal of left ear are not stimulated. Because of stimulation, the hair cells in right horizontal canal send information (impulses) through sensory nerve fibers to vestibular, cerebellar and reticular centers. Now, these centers send proper instructions to various muscles of the body to maintain equilibrium of the body during angular acceleration (rotation). On the other hand, rotation in anticlockwise direction causes stimulation of hair cells in ampulla of horizontal canal in left ear only.

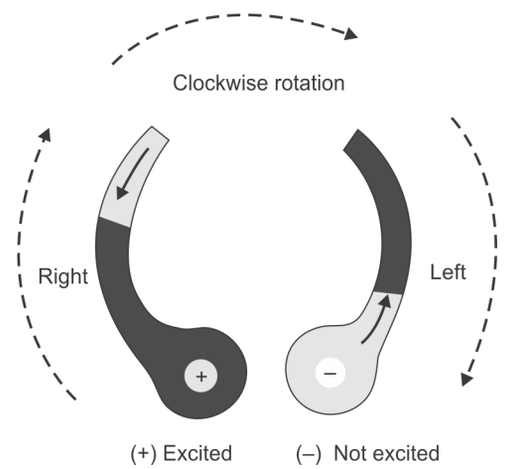



**Fig. 11.49:** Mode of stimulation of semicircular canals

### *Adaption of Receptors in Semicircular Canal During Rotation*

The hair cells of crista ampullaris generate impulse (50-100 impulse/min) at rest. At the beginning of rotation discharge increases to 600-800 impulse/min. However, rapid discharge of impulses lasts only for first 20–25 sec of rotation. Afterwards during continuous rotation, the frequency of impulses falls back to resting level as endolymph starts moving along with semicircular canal at the same speed. This causes adaption of the hair cells.

### *Role in Regulation of Posture*

1. The tract that descends from the vestibular nuclei into the spinal cord maintains tone in antigravity muscle and coordinates the adjustments made by the limbs and eyes in response to the change in body position. The vestibular apparatus thus plays a role in the support of the head during movement, orientation of the head in space and in reflexes (tonic labyrinthine and righting reflexes) accompanying locomotion. That is why the vestibular apparatus is sometimes called the sense organ of balance (equilibrium).
2. It controls eye movements via its ascending connections to the cranial nerve nuclei. Therefore, in spite of changes in head position the eye can remain fixed on the same point **(vestibulo-ocular reflex)**. For example, if the head is rotated to the left, the eyes move towards right in order to prevent an image from moving off the fovea.
3. Orientation in space: Orientation, i.e. relative position of various body parts in space depends on four inputs:
   a. From vestibular receptors.
   b. From visual information.
   c. By impulses from proprioceptors in joint capulse.
   d. By impulses from cutaneous exteroceptors.

## Vestibular Dysfunctions

1. **Motion sickness:** When a person, traveling by ship, rides a rough sea, he is expected to develop sea sickness; similar symptoms can develop when traveling by air or in a rough bus journey. All such sickness are called motion sickness. It is due to excessive and repeated stimulation of vestibular apparatus.

### *Symptoms*

Nausea, vomiting, sweating, diarrhea, pallor, salivation, discomfort, headache, disorientation and lack of emotion.

### *Prevention*

- Avoiding greasy and bulky food before travel
- Taking antiemetic drugs (drug preventing nausea and vomiting).

# REGULATION OF POSTURE

Physiologically maintenance of posture refers to subconscious adjustment of tone in different muscles so as to maintain balance during displacement of the body caused by gravity or acceleration. A particular posture is produced through one or more reflexes. In a particular posture, some muscles are in a state of contraction and others are relaxed. Regulation of posture can be studied under two headings:

1. Mechanisms involved in maintenance of posture.
2. Role of different regions of nervous system in maintenance of posture.

## Mechanisms Involved in Maintenance of Posture

The two main mechanisms involved in the maintenance of posture are:

**a. Muscle tone**

i. *In upright posture:* The muscle tone is maintained through reflex adjustments of tone in the antigravity muscles (flexors of arm and extensors of leg). The center of gravity of the head passes in front of the atlanto-occipital joint. Thus the head has always got a tendency to roll forwards. To hold the head in erect position, cervico-occipital muscles are to be maintained in a state of constant tension.

ii. *Lean forward:* Here there is increased tone in extensors of trunk and flexors of leg.

iii. *Lean backward:* Here there is increased tone in rectus abdominis and extensors of leg.

iv. *Lean sideways:* Contralateral extensor oblique muscle has increased tone.

***Maintenance of muscle tone:*** Stretch reflex plays the main role in maintenance of muscle tone. The center for muscle tone lies in the $\alpha$-motor neurons of spinal cord, which are stimulated through a constant $\gamma$-motor neuron discharge. The activity of $\alpha$ and $\gamma$ motor neurons is modified by both extrapyramidal and pyramidal fibers which terminate on them.

**b. Postural reflexes**

The postural reflexes help to maintain the body in balanced and upright position.

### *Reflex Pathway*

- *Afferent organ:* Eyes, vestibular apparatus and proprioceptors
- *Center:* Neuronal networks in brainstem and spinal cord.
- *Efferent organ:* Various skeletal muscles, supplied by $\alpha$ motor neurons.

Posture gives steady background for different movement mainly by two type of reflexes:

i. *Static reflexes:* These are elicited by gravitational pull and involve sustained contraction of muscles.
ii. *Statokinetic reflexes:* These reflexes, also called phasic reflexes and they are elicited by acceleratory displacement of the body. They maintain a stable postural background for voluntary activity.

Both these types of postural reflexes are integrated at various levels in the CNS from the spinal cord to the cerebral cortex and are affected largely by pyramidal pathways. The various postural reflexes are summarized in Table 11.9.

## Righting Reflexes

When the posture of the body has become suddenly abnormal, the animal (including man) corrects or rights the abnormality of the posture by righting (correcting) reflexes. There are various righting reflexes (Table 11.9). Righting reflexes operate to maintain the normal standing position and keep an animal's head upright. These reflexes are a series of responses integrated for the most part in the nuclei of the midbrain.

### Labyrinthine Righting Reflexes

When the midbrain animal is held by its body and tipped from side-to-side, the animal keeps its head in level (former position). This head reflex is known as labyrinthine righting reflexes. The stimulus is tilting of the head, which stimulates the otolithic organs; the response is compensatory contraction of the neck muscles to keep the head level.

### Body on Head Righting Reflex

If the animal is laid on its side, the pressure on that side of the body initiates reflex righting of the head even if the labyrinths have been destroyed. This is the body on head righting reflex. Pressure on the side of the body may cause body righting even if the head is prevented from righting.

### Neck Righting Reflexes

If the head is righted by either of these mechanisms and the body remains tilted, the neck muscles are stretched. Their contraction rights the thorax and initiates a wave of similar

**Table 11.9: Various righting reflexes**

| *Reflex* | *Stimulus* | *Response* | *Receptor* | *Integrated in* |
|---|---|---|---|---|
| Stretch reflexes | Stretch | Contraction of muscle | Muscle spindles | Spinal cord, medulla |
| Positive supporting (magnet) reaction | Contact with sole or palm | Foot extended to support body | Proprioceptors in distal flexors | Spinal cord |
| Negative supporting reaction | Stretch | Release of positive supporting reaction | Proprioceptors in extensors | Spinal cord |
| Tonic labyrinthine reflexes | Gravity | Contraction of limb extensor muscles | Otolithic organs | Medulla |
| Tonic neck reflexes | Head turned<br>1. To side<br>2. Up<br>3. Down | Change in pattern of extensor contraction<br>1. Extension of limbs on side to which head is turned<br>2. Hind legs flex<br>3. Forelegs flex | Neck proprioceptors | Medulla |
| Labyrinthine righting reflexes | Gravity | Head kept level | Otolithic organs | Midbrain |
| Neck righting reflexes | Stretch of neck muscles | Righting of thorax and shoulders, then pelvis | Muscle spindles | Midbrain |
| Body on head righting reflexes | Pressure on side of body | Righting of head | Exteroceptors | Midbrain |
| Body on body righting reflexes | Pressure on side of body | Righting of body even when head held sideways | Exteroceptors | Midbrain |
| Optical righting reflexes | Visual cues | Righting of head | Eyes | Cerebral cortex |
| Placing reactions | Various visuals, exteroceptive and proprioceptive cues | Footing placed on supporting surface in position to support body | Various | Cerebral cortex |
| Hopping reactions | Lateral displacement while standing | Hops, maintaining limbs in position to support body | Muscle spindles | Cerebral cortex |

stretch reflexes that pass down the body, righting the abdomen and the hindquarters.

### *Optical Righting Reflexes*

In cats, dogs and primates, visual signs can initiate optical righting reflexes that right the animal in the absence of labyrinthine or body stimulation. Unlike the other righting reflexes, these responses depend upon an intact cerebral cortex. In intact humans, the operation of these reflexes maintains the head in a stable position and the eyes fixed on visual targets despite movements of the body and the jerks and jolts of everyday life. The responses are initiated by vestibular stimulation, stretching of neck muscles and movement of visual images on the retina and the responses are the vestibulo-ocular reflex (VOR) and other remarkably precise reflex contractions of the neck and extraocular muscles.

## Role of Different Regions of Nervous System in Posture Maintenance

This can be experimentally investigated (usually in a cat) by producing transection in the neural axis at various levels.

### *Spinal Animal*

The role of spinal cord in the maintenance of posture can be studied in a spinal animal. The spinal animal can be produced by a transection in the spinal cord at cervical region and respiration is maintained artificially by respiratory pump.

***The posture in spinal animal during the stage of reflex activity***

Except the basic stretch reflex and supporting reflexes which are integrated in spinal cord, all the other postural reflexes are absent. This is because all the postural reflexes require the integrity of UMN coming from various levels of neural axis.

***Note***

i. Though stretch reflex and supporting reactions are present, they are very weak and cannot support the weight of the animal. Therefore the animal cannot stand on its legs.
ii. Muscle tone returns first in flexor muscles, therefore flexors become less hypertonic than extensors producing paraplegia in flexion (both lower limbs are in state of flexion).

### *Decerebrate Animal*

Decerebrate animal is one in whom the brainstem is transected at intercollicular level between superior and inferior colliculi. The intercollicular section causes total loss of the communications between the cerebral cortex and brainstem (that is why the name decerebration, i.e. removal of cerebrum is given to this operation, this is not to be confused with decortication). So this preparation can be used to study the role of brainstem in maintenance of posture.

### *Explanation*

i. The medullary inhibiting area having no intrinsic activity of its own, now becomes greatly (but not totally) non functioning. This center, however, continues to receive some impulses from the cerebellum.
ii. The brainstem facilitatory areas, having intrinsic activity of its own, continue to discharge the facilitatory impulses and now this impulses remain unopposed (as the inhibitory areas are now largely silent).
iii. The vestibular nucleus normally sends facilitatory impulses to the spinal center. In a decerebrate preparation, such facilitatory impulses are exaggerated.

### *Decerebrate Rigidity*

Decerebrate rigidity refers to the marked increase in the tone (hypertonia) of extensors, i.e. antigravity muscles occurring, immediately after decerebration of the animal.

Characteristic features of decerebrate rigidity (Fig. 11.50):

a. Hyperextension of all the four limbs.
b. Dorsiflexion (hyperextension of tail and head)

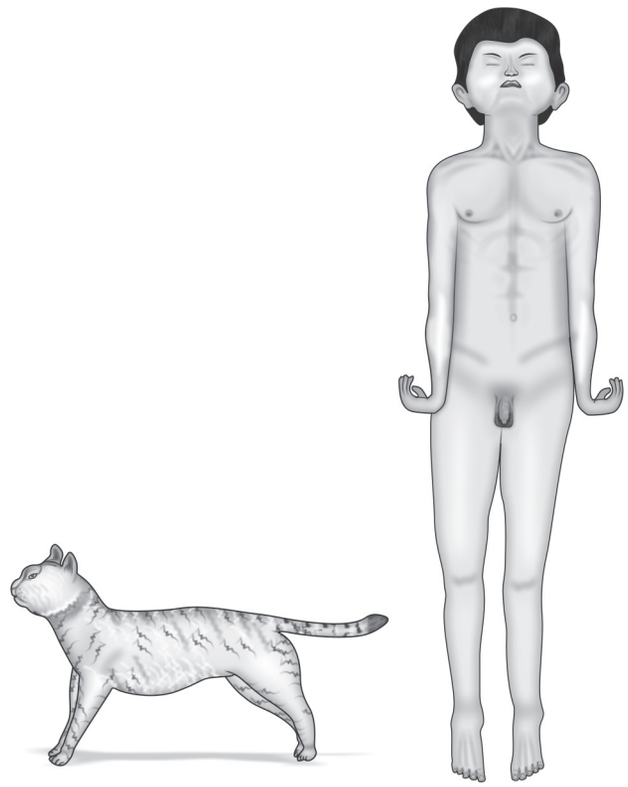


**Fig. 11.50:** Decerebrate rigidity

c. Extreme hyperextension of the spine (opisthotonos) which produces concave configuration of the back.
d. The animal can be made to stand on four limbs but is easily toppled by a slight push.
e. Postural reflexes which can be elicited in a decerebrate animal are stretch reflexes, positive supporting reaction, negative supporting reaction, crossed extensor reflex, tonic neck and labyrinthine reflexes.
f. Righting reflexes are absent, therefore decerebrate animal can stand on its four legs but slight displacement causes the decerebrate animal to topple over.

So the conclusion is, in decerebrate rigidity, there is a great preponderance of facilitatory influences reaching the spinal center from above. Experiments have established that these facilitatory influences cause stimulation of the γ efferent and thus increase the tone. Viewed in another way, the decerebrate rigidity is due to the release of the brainstem centers from the influences of the cerebral cortex, red nuclei and the basal ganglia. Lacking this input, the medullary reticular inhibitor system becomes nonfunctional; full overactivity of the pontine excitatory system occurs, and rigidity develops. The decerebrate rigidity therefore is another example of release phenomenon.

***Note***

**Tonic Labyrinthine Reflexes**

This reflex is best studied in decerebrate animal. In the decerebrate animal, the pattern of rigidity in the limbs varies with the position. No righting responses are present, and the animal stays in the position in which it is put. If the animal is placed on its back, then there is profound extension of all four limbs, but if the animal is turned to either side, the rigidity decreases. Rigidity is minimum when the animal lies at prone position. These changes in rigidity are due to the action of gravity on the otolithic organs and are effected via the vestibulospinal tracts. This reflex rigidity is known as the tonic labyrinthine reflexes. These reflexes are abolished by removal of the labyrinth (Fig. 11.51).

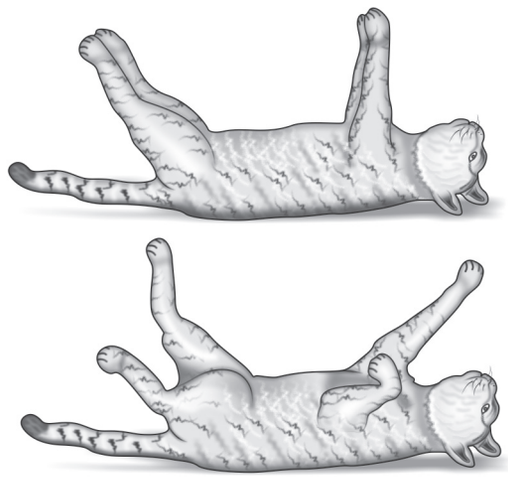



**Fig. 11.51:** Tonic labyrinthine reflex

**Fig. 11.52:** Tonic neck reflex

### *Tonic Neck Reflexes*

The reflexes are set up from neck muscles. If the head of a decerebrate animal is turned to side, up or down, changes in the pattern of rigidity occur. If the head is turned to right, the right limb is extended and the left limb is relaxed. This is the position often assumed by a normal animal looking to one side. Flexion of the head (head turned down) causes flexion of the forelimbs and continued extension of the hind limbs, the posture of an animal looking into a hole in the ground. Extension of the head (head turned up) causes flexion of the hind limbs and extension of the forelimbs, the posture of an animal looking over an obstacle. These responses are the tonic neck reflexes (Fig. 11.52). They are initiated by stretch of the proprioceptors in the upper part of the neck and they can be sustained for long periods.

## *Midbrain Animal*

Midbrain animal is prepared by the section of the neural axis at the superior border of the midbrain. So this preparation can be used to study the role of midbrain in maintenance of posture.

### *Characteristic Features*

a. Midbrain animal has extensor rigidity similar to that of a decerebrate animal only when the animal lies quietly on its back. The rigidity disappears when the limb is performing a reflex activity.
b. No spinal shock is present.
c. Righting reflexes, having integration center in the midbrain are present. These include labyrinthine righting

reflex, neck righting reflex, body on head righting reflex and body on body righting reflex.

### Decorticate Animal

Decorticate animal is one in which only the superficial few millimeters of cerebral cortex alone is removed with the basal ganglia and brainstem remaining intact. So this preparation can be used to study the role of basal ganglia in maintenance of posture.

Postural characteristics of a decorticate animal:

a. *Moderate rigidity:* Moderate rigidity is present due to loss of the cortical area that inhibits spinal γ-motor neurons discharges via reticular formation. It is seen only when the animal is at rest. This is because the basal ganglia which are intact in decorticate animal activate the descending inhibitory reticular formation and thereby prevent hypertonia.
b. *Typical posture:* The typical posture in a decorticate man consists of full extension of legs, arms lying across the chest, with some semiflexion at the elbow, slight pronation of forearm and flexion of wrist and fingers (Fig. 11.53).
c. *Postural reflexes:* In decorticate man or animal following reflexes like typical neck reflexes, righting reflexes can be elicited. Postural reflexes which are seriously disrupted by decortication are the hopping and placing reactions.

***Note***

Two types of postural reactions, the hopping and placing reactions, are seriously disrupted by decortication.

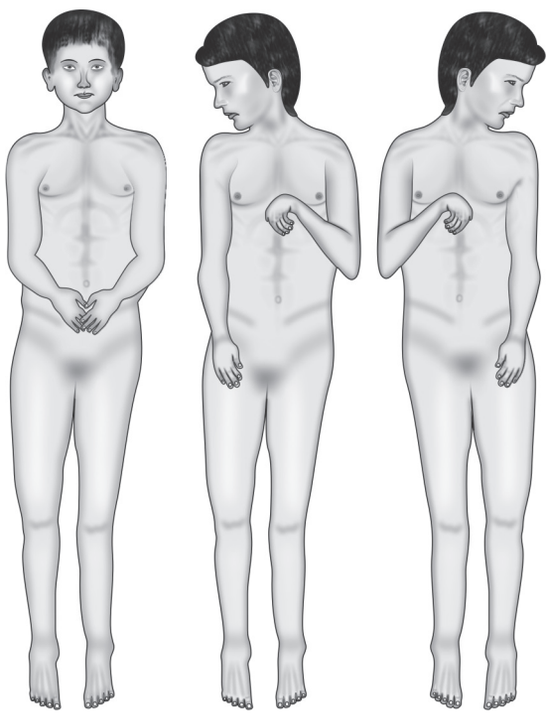


**Fig. 11.53:** Typical posture of a decorticate man

#### *Hopping Reaction*

When a standing animal is pushed laterally, hopping movements keep the limbs in position to support the body. This response is called hopping reaction.

#### *Placing Reaction*

If one limb of a standing animal is pushed out from under it, the limb is promptly replaced on the supporting surface in position to support the body. This response is known as placing reaction. Placing reactions are usually abolished on one side by unilateral decortications.

#### *Grasp Reflex*

If brain tissue in primates above the thalamus is removed and the animal is allowed to lie on one side, the limbs next to the supporting surface are extended. In such animals, the upper limbs are flexed and the hand on the upper side grasps firmly any object brought in contact with it (grasp reflex). This whole response is probably a supporting reaction that steadies the animal and aids in pulling it upright.

## RETICULAR FORMATION

Reticular formation (RF) includes those parts of brainstem which are characterized by fiber bundles and nuclear masses with discrete function. It is scattered throughout central part of brainstem. Its connections are complex and extensive. There is hardly any part of the CNS with which RF is not connected, and there is hardly any function of the body which it does not influence.

There are reticular excitatory and inhibitory areas. Excitatory areas are located in reticular substance of pons and midbrain. Excitatatory area is also called bulboreticular facilitatory area. Inhibitory area is located medially and ventrally in medulla. This inhibitory area can sent inhibitory impulses to spinal cord and to reticular facilitatory area. Reticular activating system is a complex polysynaptic pathway. The system is nonspecific. Reticular activating system has ascending and descending fibers. It is essential for life because:

- Vital centers such as CVS, respiratory, swallowing, vomiting, etc. are located in reticular formation.
- It receives and integrates information from all parts of CNS.
- Its neurons send axons to most regions of brain and spinal cord. Thus, it influence all parts of CNS.

Pathways that convey information from the reticular formation are divided into two systems—ascending and descending reticular system.

### Ascending Reticular System

The ascending reticular pathway (Fig. 11.54) is also called reticular activating system (RAS).

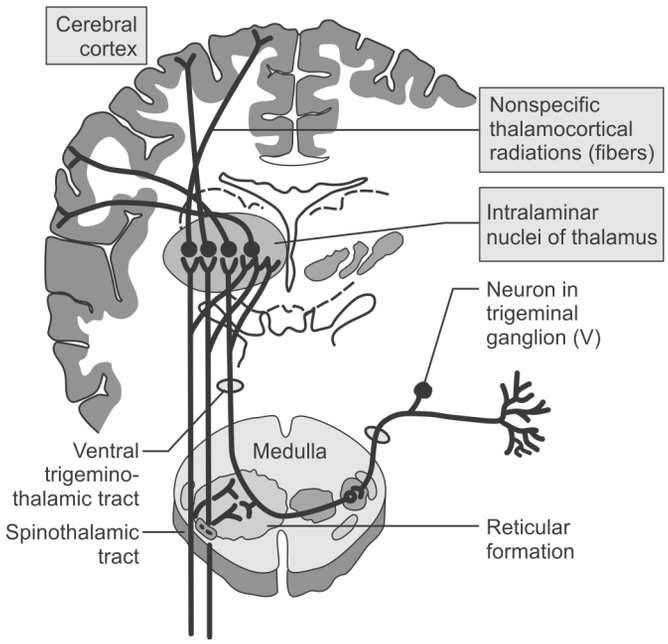



**Fig. 11.54:** Reticular activating system

1. It is a complex polysynaptic pathway whose fibers extend from brainstem to thalamus.
2. It receives afferent collateral from:
   - Specific sensory pathways
   - Trigeminal, auditory, olfactory, visual pathway.
3. A single peripheral stimulus gives rise to impulses which ascend to cerebral cortex via two pathways:
   - Specific sensory pathways which are responsible for sensory discrimination.
   - Collateral branch given to reticular formation.

From reticular formation, impulses reach nonspecific nuclei of thalamus and from there to cerebral cortex through nonspecific ascending pathway. Reticular system functions by arousing consciousness without which sensory discrimination is impossible.

### *Pathway for Arousal and Alertness*

Some fibers from cerebral cortex, especially from the superior temporal gyrus and frontal lobe descend and join to form corticofugal fibers. Together with RAS, the system provide pathway by which intracortical events can initiate arousal and is responsible for alerting emotions.

## Descending Reticular System

The reticular fibers that descend to the spinal cord form the reticulospinal tracts. It modifies the activities of spinal motor neurons. This system comprises the descending inhibitory reticular system and descending facilitatory reticular system.

## Functions of Reticular Formation

1. The RAS and related components are concerned with alertness, maintenance of attention and wakefulness that make perception possible.
2. Control of muscle tone and regulation of postural reflexes.
3. Role in the integration of autonomic activity through connections to ANS.
4. Conditioning and learning.
5. Reticular formation is connected to hypothalamus and limbic system. Hence, it plays an important role in emotional reactions.

# CEREBELLUM

## Anatomical Divisions

The cerebellum is divided into three parts by two transverse fissures. The posterolateral fissure separates the medial nodulus and the lateral flocculus on either side from rest of the cerebellum. The primary fissure divides the remainder into an anterior and posterior lobe.

## Functional Divisions

Functionally the divisions/lobes are named according to the connections they make with other components of the motor control system (Fig. 11.55).

a. *Flocculonodular lobe:* It is functionally related to the vestibular apparatus and therefore also called the vestibulocerebellum. It is concerned with control of body posture.
b. *Spinocerebellum:* The entire anterior lobe and parts of the posterior lobe that receive information from the spinal cord, are called spinocerebellum. It occupies the median portion of the cerebellar cortex and receives proprioceptive input from the body. It is concerned with control of axial (trunk) and limb muscles and postural reflexes.
c. *Neocerebellum:* The remaining part of the posterior lobe (lateral portions of cerebellar hemispheres) forms the

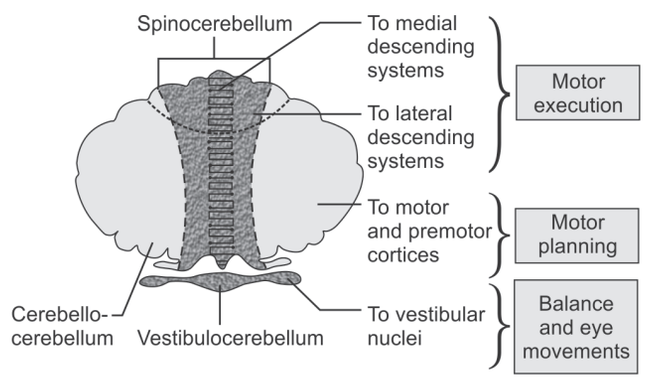



**Fig. 11.55:** Functional division of cerebellum

neocerebellum. It receives information from the cerebral cortex and pons. It is concerned with skilled voluntary movements. It is also called cerebrocerebellum.

***Note***

On each side cerebellum is connected to the brainstem by three peduncles:

a. Superior cerebellar peduncle-connects midbrain to cerebellum.
b. Middle cerebellar peduncle-connects pons to cerebellum.
c. Inferior cerebellar peduncle-connects medulla to cerebellum.

## Organization

The cerebellum has an external cerebellar cortex separated by white matter from the deep cerebellar nuclei. The primary afferent inputs; the mossy and climbing fibers send collaterals to the deep nuclei and pass to the cortex. There are four deep nuclei: Dentate, globose, emboliform and the fastigial nuclei.

### *Cerebellar Cortex*

Microscopically the gray matter of cerebellar cortex consists of five main types of neurons:

1. Stellate cells
2. Basket cells
3. Purkinje cells
4. Granule cells
5. Golgi cells

Purkinje cells are one of the largest neurons in the body. These five types of neurons are arranged in three layers:

a. **Molecular layer:** This layer is most superficial and is composed of two types of neurons (Stellate and basket cells) and unmyelinated nerve fibers.
b. **Purkinje cell layer:** It is composed of a single layer of large flask-shaped Purkinje cells and dendrites of Purkinje cells.
c. **Granule cell layer:** It consists of granule and Golgi cells with their processes and sensory mossy fibers with their synaptic glomeruli.

## Neuronal Circuits and Neuronal Activity in Cerebellum

Cerebellum executes its functions through excitatory output of the deep cerebellar nuclei to the brainstem and thalamus. Neural connections (Fig. 11.56) within the cerebellar cortex is basically concerned with modulating or timing the excitatory output of the deep cerebellar nuclei via the fibers of Purkinje cells. This is done in accordance with the signals received by the cerebellar cortex from different parts of the brain and body. Neuronal activity in cerebellum involves three processes:

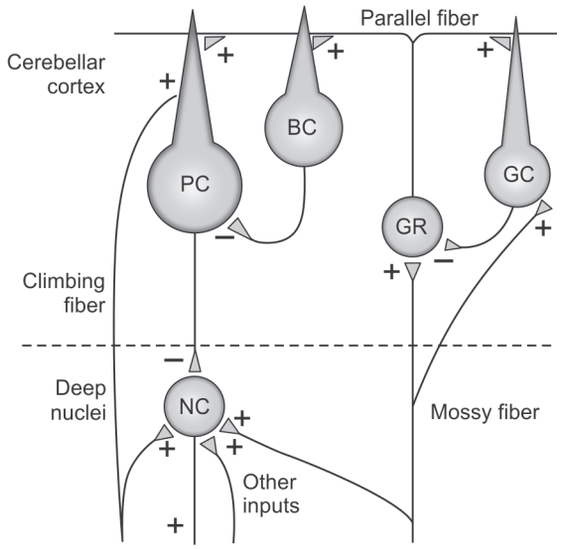



**Fig. 11.56:** Diagram of neural connections in the cerebellum. + and – signs indicate whether endings are excitatory or inhibitory. BC: Basket cell; GC: Golgi cell: GR: Granule cell; NC: Cell in deep nucleus; PC: Purkinje cell

a. Afferents to cerebellar cortex.
b. Neuronal activity of intrinsic cerebellar circuitry.
c. Neuronal activity of deep cerebellar nuclei.

a. **Afferents to cerebellar cortex:** Afferents to cerebellar cortex reach via two types of fibers:
   i. *Climbing fibers:* These fibers represent terminations of axons reaching the cerebellum from the inferior olivary nucleus. The climbing fibers excite Purkinje cells and the deep cerebellar nuclei.
   ii. *Mossy fibers:* All the afferent fibers of cerebellum other than the olivocerebellar are called mossy fibers. The mossy fibers excite Purkinje cells, granule cells and the deep cerebellar nuclei.
b. **Neuronal activity of intrinsic cerebellar circuitry:** As a result of excitatory input from the climbing fibers or mossy fibers following activity is set up in the intrinsic cerebellar circuitry:
   i. Feed forward inhibition of Purkinje cells.
   ii. Feed forward inhibition of granule cells.
   iii. Feedback inhibition of granule cells.
c. **Neuronal activity of deep cerebellar nuclei:** The deep cerebellar nuclei receive excitatory inputs via collaterals from the mossy fibers, climbing fibers and also other excitatory inputs. The neuronal activity in the cerebellar cortex plays an important role in modulating the excitatory signals of the pathways from the deep cerebellar nuclei to thalamus, cerebral cortex and to brainstem nuclei. Because of this modulating or timing effect the cerebellar cortex is able to well organize and coordinate the different movements of the body.

## Connections of the Cerebellum (Fig. 11.57)

### *Afferent Connections*

#### *Tracts through Superior Cerebellar Peduncle*

1. *Ventral spinocerebellar tract (VST):* It carries a large portion of extroceptive (cutaneous) and proprioceptive fibers from all parts of the body. The fibers enter the cerebellum via the ipsilateral superior cerebellar peduncle and is distributed mainly to the vermis and anterior lobe.
2. *Tectocerebellar tract (TCT):* It arises from the superior and inferior colliculi which relays fibers respectively from the eye and ear. This tract carries visual impulses from superior colliculus and auditory impulses from the inferior colliculus to spinocerebellum through the superior cerebellar peduncle (SCP).
3. *Rubrocerebellar tract (RCP):* It arises from the red nucleus, may be both crossed and uncrossed. It enters via the superior cerebellar peduncle (SCP) and is distributed mainly to the dentate nucleus. It transmits impulses which have originated from the motor cortex and relays in the red nucleus.
4. *Olivocerebellar tract (OCT):* This tract is formed by the climbing fibers arising from the inferior olivary nucleus in medulla. After taking origin, these fibers cross the midline and reach the spinocerebellum through the superior cerebellar peduncle of the opposite side. It carries proprioceptive inputs from whole body via relay in inferior olive. The inferior olivary nucleus receives afferent fibers from three sources:
   a. Brainstem nuclei of the same side.
   b. Spinal cord through spino-olivary tract of same side.
   c. Cerebral cortex of opposite side.

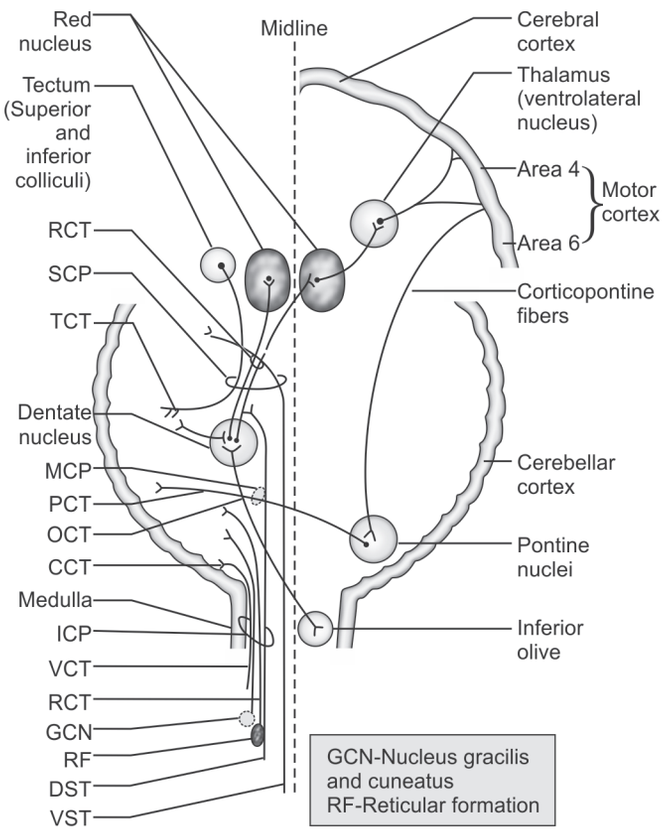



**Fig. 11.57:** Afferent cerebellar connections

#### *Tracts through Middle Cerebellar Peduncle*

1. *Cortico-ponto-cerebellar tract:* It arises in the motor cortex (areas 4 and 6) and other parts of cerebral cortex. It ends in the nuclei pontis. From the nuclei pontis the pontocerebellar fibers cross to enter the opposite side in the middle cerebellar peduncle (MCP) and are distributed to all parts of the cerebellar cortex (except flocculonodular lobe).

#### *Tracts through Inferior Cerebellar Peduncle*

1. *Dorsal spinocerebellar tract (DST):* It carries mainly extroceptive (cutaneous) and proprioceptive impulses from the trunk and leg. It is an uncrossed tract, and reaches the spinocerebellum through the inferior peduncle of the same side. It is distributed to the anterior lobe, pyramis, uvula and the median part of the paramedian lobe.
2. *Vestibulocerebellar tract (VCT):* It arises in the vestibular nuclei. It passes through the inferior cerebellar peduncle (ICP) of the same side and reach the deep cerebellar nuclei. It supplies mainly the flocculonodular lobe and uvula.
3. *Cuneocerebellar tract (CCT):* This tract arises from the external arcuate nucleus. It reaches the spinocerebellum through the inferior cerebellar peduncle of the same side to anterior lobe, pyramis and uvula. It carries proprioceptive impulses from the arm and neck muscles to spinocerebellum.
4. *Reticulocerebellar tract (RCT):* It arises in the lateral reticular nucleus and is uncrossed. It is distributed via the inferior cerebellar peduncle of the same side to the whole of cerebellar cortex.

### *Efferent Connections*

Purkinje cell axons pass to the deep cerebellar nuclei in an orderly manner. Their influence on these nuclei is purely inhibitory via release of GABA.

## Functions of Cerebellum

The cerebellum controls the motor activities both voluntary (via pyramidal system) as well as nonvoluntary, like tone, posture and equilibrium (via the extrapyramidal system).

1. *Control of body posture and equilibrium:* The flocculonodular lobe (vestibulocerebellum) is concerned with the control of body posture and equilibrium. Afferents from the vestibular apparatus pass directly or after relay in the vestibular nuclei to the flocculonodular lobe. The efferents from them return back to the vestibular nuclei. From these nuclei the vestibulospinal tract connects with spinal motor neurons.
2. *Control of muscle tone and stretch reflexes:* Spinocerebellum regulates the postural reflexes by modifying the muscle tone. It facilitates the γ motor neurons in the spinal cord. The γ motor neurons reflexly modify the activity of the motor neurons and thus regulate the muscle tone. Thus, cerebellum forms an important site of linkage of α-γ systems responsible for muscle tone.
3. *Control of voluntary movements:* Cerebellum is not able to initiate any motor activity, but coordinates the movements initiated by motor cortex. Coordination of movements is the result of appropriate regulation of time, rate, range (extent), force and direction of muscular activity. This is made possible because the cerebellum establishes reciprocal connections with most regions of CNS to which it is connected.
4. *Control of eyeball movements:* The oculomotor, trochlear and abducent nuclei which supply the extraocular muscles of eye movements are brought under cerebellar control by vestibular nuclei. Pyramis is concerned with the movement of eyeball because its stimulation causes upward eye movement to ipsilateral side. It also has a role in the judgment of distance.

## Cerebellar Lesions

The cerebellar lesion of one hemisphere produces dysfunction on the same side of the body whereas the lesions of the vermis affect both the sides (due to double crossing, each cerebellar hemisphere influences the opposite cortex; which in turn influences the motor cortex via the corticospinal tracts which controls the movement of the opposite side of the body. Because of the double decussation each cerebellar hemisphere controls the voluntary movements on its own side of the body).

### *Characteristic Features*

#### *Disturbance of Posture*

a. **Atonia or hypotonia:** The muscle tone is either completely lost (atonia) or markedly decreased (hypotonia) on the affected side due to loss of facilitatory effect of the neocerebellum. Therefore, the muscles feel soft and the limb moves to and fro slowly.
b. **Attitude:**
   i. Trunk is bent with concavity towards the affected side. This is because the weight of the body is thrown on the unaffected leg.
   ii. Face is rotated towards the opposite side (pulled by the healthy muscles).
   iii. The homolateral shoulder is lower than the opposite normal shoulder.
   iv. The leg is abducted and rotated outwards.
c. **Spontaneous deviation:** If the eyes are closed and the arms are held straight out in front of the body, homolateral arms bend laterally.
d. **Nystagmus:** It is a tremor of the eyeballs which occurs when the patient attempts to fix his eyes on an object. It consists of a slow to and fro movement on looking to the affected side due to hypotonia and a rapid to and fro movement on looking to the opposite side.
e. **Deep/Tendon reflexes:** The deep reflexes become weak and pendular. For example, pendular knee jerk, i.e. after the initial reflex response, the leg on falling continues to swing freely to and fro. This is due to hypotonia of quadriceps muscle.

#### *Disturbance of Voluntary Movements*

a. **Ataxia:** It is the lack of coordination of movements due to errors in the rate, range, force and direction of movement. It is the hallmark of cerebellar disorder and characterized by:
   i. **Decomposition of the movement:** The movement seems to occur in stages. The patient cannot easily combine the movements of several joints into a single smooth, coordinated motion. For example, to move the arm, they might first move the shoulder, then the elbow and finally the wrist.
   ii. **Asynergia:** There is lack of coordination between protagonists, antagonists and synergists.
   iii. **Dysmetria:** The movement is poorly carried out in direction, range and force, therefore, the movements overshoot their intended mark, i.e. post pointing (hypermetria) or fall short of it (hypometria). It results from the loss of the neural circuit required to control the duration and strength of a movement.
b. **Intention tremor:** It is a common remarkable feature of cerebellar lesions. Such patients cannot perform movements smoothly. If they reach for an object, their movements are jerky and accompanied by oscillating, to and fro tremors that become more marked as the hand approaches the object. The tremors are coarse and they occur at a frequency of 4–6/sec. Clinically these disturbances can be demonstrated by finger nose test, rebound phenomenon, adiadochokinesis and heel-knee test.

c. **Gait:** Patients walk in a clumsy manner, with their feet wide apart (wide-based gait). They have such difficulty in maintaining balance that their gait appears drunken, called ***drunken gait.*** The patient walks in a zig-zag line and deviates to the affecters side due to hypotonia.
d. **Speech:** Slurred, scanning type of speech results. It is also slow and lalling (like a baby) due to imperfect use of the movements of the laryngeal muscles and tongue.

## THALAMUS

The thalamus is a major sensory relay station. All general and special sensations (except the smell) and afferent impulses from the RAS synapse here. It is an important integrating center for most inputs before relaying them to the cerebral cortex.

### Anatomical Classification of Thalamic Nuclei

The thalamus is divided into three nuclear groups (Fig. 11.58) by the internal medullary lamina (consists of white matter).

1. *Anterior group of nuclei:* The mass of gray matter enclosed within the bifurcation of the internal medullary lamina is called anterior nucleus.
2. *Lateral group of nuclei:* The mass of gray matter present in the lateral part of the thalamus is subdivided into ventral and dorsal group of nuclei.
   a. The ventral group of nuclei contains:
      i. Ventral anterior nucleus
      ii. Ventral lateral nucleus
      iii. Ventral posterior nucleus
      iv. Medial geniculate body
      v. Lateral geniculate body.
   b. The dorsal group of nucleus contains:
      i. Pulvinar (cluster of neurons lying most posteriorly)
      ii. Lateral posterior
      iii. Lateral dorsal.

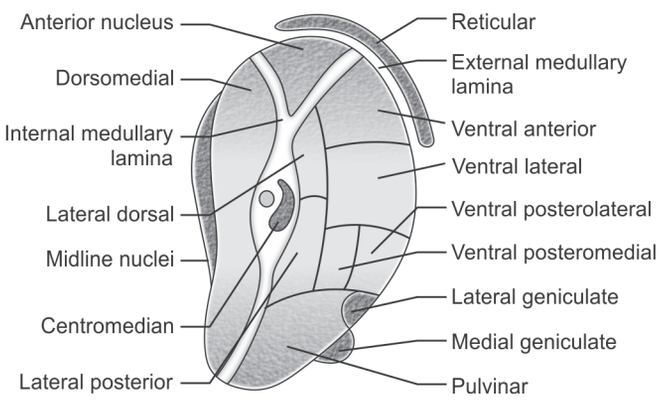



**Fig. 11.58:** Nuclei of thalamus

3. *Medial group of nuclei:* It includes the following nuclei:
   i. Centromedian and other intralaminar nuclei
   ii. Dorsomedial nucleus.
   iii. Midline nucleus.

### Functional Classification of Thalamic Nuclei

Functionally the thalamic nuclei can be grouped under 2 divisions:

- Non-specific projection nuclei
- Specific projection nuclei

#### *Nonspecific Projection Nuclei*

They receive afferents from RAS and project diffusely to neocortex. Impulse in them is responsible for diffuse secondary response and the alerting effect of RAS. Nuclei involved are:

a. Anterior group
b. Midline nucleus
c. Intralaminar
d. Dorsomedial nucleus.

**a. Anterior group of nuclei**
Afferent - From mammillary body of hypothalamus via mammillothalamic tract
Efferent - To cingulate gyrus
Function - Part of Papez circuit
- Associated with limbic system
- Concerned with recent memory and emotion.

**b. Midline nucleus**
Afferents - Spinothalamic
- Trigeminothalamic
- Medial lemniscus
- Reticular formation
- Hypothalamus
- Other thalamic nuclei
Function - Center for integrating 'crude' visceral and somatic sensations.

**c. Intralaminar nuclei**
Afferents - RAS
- Basal ganglion
- Other thalamic nuclei.
Function - Integrates somatic and visceral sensory impulses before projecting this information to cortex. It is also responsible for alerting affects of RAS.

**d. Dorsomedial nucleus**
Afferents - Hypothalamic nuclei
Efferents - Prefrontal cortex (8, 9, 10, 11)
Function - Association center for synthesis of crude and somatic sensation.

### *Specific Projection Nuclei*

Specific projection nuclei are classified as part controlling motor, sensory and integrative functions.

#### *Motor Function*

**a. Ventral lateral**
Afferents - Cerebellum (dentate nucleus), globus pallidus
Efferents - Premotor area
Functions - Relay proprioceptive information and voluntary motor function, i.e. motor control and planning programming.

**b. Ventral anterior**
Afferents - Basal ganglia (substantia nigra and globus pallidus)
Efferents - Area 6
Functions - Motor controlling, planning and programming.

#### *Sensory Function*

**a. Ventroposterolateral nucleus**
Afferents - Spinothalamic tract, medial leminscus (ML)
Efferents - Postcentral gyrus (3, 1, 2).

**b. Ventroposteromedial**
Afferents - Trigeminal and ML (face and taste fibers)
Efferents - Postcentral gyrus (3, 1, 2).

#### *Integrative Functions*

**a. Lateral dorsal nucleus**
Afferent - Superior colliculus
Efferent - Cingulate gyrus and hippocampal area.

**b. Lateral posterior:** Has reciprocal connection with areas 5 and 7 of parietal association area.

**c. Pulvinar**
Afferent - Thalamic nuclei and cortex
Efferent - Cortex (parietal, temporal and occipital areas)
Function - Integrates auditory, somatic and visual information.

**d. Medial geniculate body:** Concerned with audition.

**e. Lateral geniculate body:** Concerned with vision.

### Functions of Thalamus

1. The thalamus is a great sensory relay station and integrating center for most inputs before relaying them to the cerebral cortex.
   i. Relay station in the pathway of somesthetic sensation coming from opposite side of the body.
   ii. Relay station for impulses coming from opposite side of cerebellum on their way to motor cortex.
   iii. Relay station for impulse from RF.
   iv. Relay station in the auditory and visual pathways.
   v. Relay station for autonomic and emotional reactions due to its connections with the hypothalamus and limbic lobe.
2. It is responsible for maintenance of conscious and alerting responses of RAS.
3. It is responsible for subcortical perception of sensations particularly that of pain.
4. It is concerned with control of muscular movements via its connections with basal ganglia, cerebellum and motor cortex.

## ELECTROENCEPHALOGRAM

The record of electrical activity of the brain (cerebrum) is called electroencephalogram (EEG). It can be recorded by placing two electrodes on the scalp and connecting them via a suitable amplifier to a cathode ray oscilloscope (CRO). It was first introduced by Hans Berger. EEG obtained by placing the electrodes directly on the exposed surface of cerebral hemisphere (pial surface of the cortex) called electrocorticogram (ECoG).

### Normal EEG

The EEG can be recorded by using two methods: Bipolar and unipolar.

1. *Bipolar method:* It is a record of potential difference between two cortical electrodes. For example, frontal area, occipital area, etc.
2. *Unipolar method:* It is a record of potential difference between an active electrode and an indifferent electrode applied on some part of the body distant from the cortex such as ear lobe. The waves of EEG are classified according to the frequency and voltage (Table 11.10).

### α- Rhythm

They are present at rest (physical as well as mental) when the eyes are closed and form the most prominent component of the EEG (Fig. 11.59). Its frequency is decreased by low blood glucose, low body temperature high arterial $pCO_2$ and sleep; also its frequency is increased by high blood glucose, rise in body temp, low arterial $pCO_2$ alerting states. The α-waves are associated with decreased levels of attention and when α-rhythms are being generated subjects report that they feel relaxed and happy.

The replacement of regular α-rhythm with fast, high frequency, irregular low amplitude (voltage) activity is called α block/desynchronization of EEG. It represents a breaking up of the synchronized activity of the cortical neurons responsible for the α-wave pattern. A break up of

**Table 11.10: Main features of normal EEG rhythm**

| *EEG Rhythm* | *Frequency (Hz)* | *Amplitude (μV)* | *Associated features* |
|---|---|---|---|
| 1. Alpha (α) | 8–12 | 50–100 | Present maximally in the occipital and parieto-occipital areas when the eyes are closed |
| 2. Beta (β) | 14–30 | 5–10 | Generally seen in frontal region (normal awake pattern); commonly seen in infants |
| 3. Theta (θ) | 4–7 | 10 | Often found over the parietal and temporal areas (normal in children and in early sleep) |
| 4. Delta (δ) | 1–4 | 20–200 | Usually appear during sleep; can be produced by over breathing or evidence of organic brain diseases when seen in awake state |

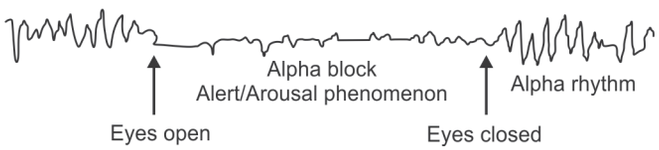



**Fig. 11.59:** Replacement of alpha rhythm by an asynchronous, low voltage beta rhythm when the eyes are opened

the α-pattern is produced by any form of sensory stimulation such as opening of the eyes or mental concentration.

### *Uses of EEG*

1. Localization of pathological condition
   - Subdural hematoma/fluid collection is associated with decreased EEG activity over that area.
   - Lesion in the cortex causes local formation of irregular or slow waves in EEG
2. **Diagnosis of epilepsy:** Epilepsy is due to excessive discharge of cerebral neurons. Epileptic foci generate high voltage (amplitude) waves in the EEG, which can be localized.

### *Forms of Epilepsy*

#### *Grandmal Epilepsy*

It is characterized by loss of consciousness without aura (warning sign). This is followed by generalized convulsions with tonic muscle contractions and clonic jerks. Here, EEG shows high voltage (up to 1000 μV) activity during the tonic phase, slow waves each preceded by a spike at the time of each clonic jerk and slow wave over sometime even after the attack is over.

#### *Petit Mal Epilepsy*

It is a form of epilepsy in children characterized by abrupt loss of consciousness without falling or incontinence, and lasting for a few seconds. Here, EEG shows 3 doublets per second each consisting of typical spike and rounded waves.

## SLEEP

Sleep is defined as unconsciousness from which the person can be aroused by sensory or other stimuli. It is a physiological process by which bodily functions are periodically rested. It is to be distinguished from coma, which is unconsciousness from which the person cannot be aroused.

### Physiological Changes During Sleep

1. *CVS:* Heart rate, cardiac output, vasomotor tone and BP decrease.
2. *Respiratory system:* Tidal volume, respiratory rate, pulmonary ventilation decreases:
3. BMR decreases.
4. Urine volume decreases while phosphate content and specific gravity increases. Therefore, more concentrated urine is formed.
5. *Secretions:*
   a. Salivary and lacrimal secretion decreases
   b. Sweat secretion increases
   c. Gastric secretion either remains unaltered or increases.
6. Muscles are completely relaxed and the tone is minimum.
7. *Eye:*
   a. Eyeballs roll up and out due to flaccidity of external ocular muscles
   b. Eyelids come closer due to drooping of the upper eyelid
   c. Pupils constrict.
8. Blood volume increases resulting in the dilution of the plasma.
9. *Nervous system:*
   a. EEG shows appearance of δ waves.
   b. Deep reflexes are reduced.
   c. Superficial reflexes remain unchanged.
   d. Light reflex is retained.

### Types of Sleep

1. **NREM (Nonrapid eyeball movement sleep/Slow wave sleep):** In NREM sleep (Table 11.11) is divided into 4 stages each successive stage will have an EEG pattern with

**Table 11.11: Behavioral and EEG changes in two types of sleep**

| *Stage* | *Behavioral observation* | *EEG changes* |
|---|---|---|
| NREM (slow wave sleep) | | |
| Stage 1 | This is the stage of drowsiness and falling asleep (light sleep). It is characterized by:<br>i. Easily aroused by moderate stimuli or even by neck muscle jerks<br>ii. Continuous lack of awareness | $\alpha$-waves reduced in frequency and amplitude |
| Stage 2 | True sleep and there is further lack of sensitivity to activation and arousal | Characterized by the appearance of sleep spindles (due to reverberating activity between the thalamus and the cerbral cortex). These are bursts of regular alpha like waves (10–14 Hz, 50 $\mu$V). Appearance of $\alpha$ rhythm is between $\beta$ rhythm is known as sleep spindles |
| Stage 3 | Sleep deepens | Sleep spindles are occasional and are now superimposed on a background of waves of $\delta$ type |
| Stage 4 | Stage of deep sleep in which, it is difficult to arouse the person. Arousal occurs only with vigorous stimulation and when awakened, person does not report dreaming | Slow high voltage $\delta$ waves |
| REM (Paradoxical) sleep | Deepest sleep<br>1. REM sleep is also called paradoxical sleep because the sleeping person is difficult to arouse despite having a desynchronized EEG that is characteristic of alert, awake state<br>2. Skeletal muscle tone is markedly reduced except in the eye where REM occurs<br>3. REM sleep and dreaming are closely associated. REM sleep is more towards morning and hence dreams are more frequent towards waking hours | EEG becomes desynchronized, i.e. low voltage fast activity seen (resembling awake state with eyes open) Large spikes are seen in the EEG called PGO spikes (ponto-geniculo-occipital) which are characteristic of REM sleep |

slower frequency and high voltage than the preceding one. Initially there is a considerably tone in postural muscle and it progressively decreases. The eyes begin slow, rolling movements until they finally stop in stage 4 (deep sleep) with the eyes turned upwards. During NREM sleep there is release of both growth hormone and gonadotropins from the pituitary. Body metabolism is lowered. Also there is decrease in BP, heart rate and respiratory rate. When awakened, person does not report dreaming. After a person has been in NREM (slow wave) sleep for about an hour, the sequence of sleep stages is repeated in reverse order, i.e. the person passes from stage 4 to 3, 2 and 1; then he finally enters into the REM sleep.

2. REM (Rapid eyeball movement sleep)/Paradoxical sleep: During REM sleep, the eyeballs move frequently (saccadic eye movements). Saccadic eye movements are small jerky, fast movements that rapidly bring the eye from one fixation point to another and may be associated with watching visual images of dreams. Here, EEG shows desynchronized pattern. Dreaming is closely associated with this sleep. When awakened the persons report that 80–90% of the time they had been dreaming. REM sleep is associated with increase and irregularity in BP, heart rate and respiratory rate. The skeletal muscle tone is markedly reduced. This is responsible for snoring during sleep as relaxed tongue in supine posture partially obstructs the air passage.

REM sleep is associated with large phasic potentials in groups of 3–5. They originate in the pons and pass rapidly to the lateral geniculate body and thence to the occipital cortex, therefore called ponto-geniculo-occipital (PGO) spikes. This activates the reticular inhibiting area in the medulla, producing the hypotonia.

Teeth grinding (bruxism) in children, erection of penis, engorgement of clitoris, and twitches of the facial or limb muscles may occur in REM sleep.

### *Sleep Cycle*

A sleep cycle consists of two phases: NREM sleep followed by REM sleep. Continuous recordings of adults show that the average total sleep period comprises of 4 or 5 such cycles, each lasting 90–100 minutes. In a typical 90 minute sleep cycle NREM sleep occupies the 1st 70 minutes and REM the last 20 minutes.

**Table 11.12: Differences between NREM and REM sleep**

| *NREM* | *REM (Paradoxical sleep)* |
|---|---|
| 1. Hypotonia | 1. More hypotonia |
| 2. Slow-high voltage 'δ' waves | 2. Fast low voltage 'β' rhythm waves |
| 3. No rapid movement of the eyeballs | 3. Rapid movement of the eyeballs |
| 4. Dreams cannot be recalled or vague recalling | 4. Dreams can be recalled easily |
| 5. No ponto-geniculo-occipital spikes (PGO) | 5. PGO spikes are present. These can be recorded from the occipital cortex. PGO spikes take origin from the pontine RF |
| 6. Pulse, BP, respiration are lowest and regular | 6. Pulse, BP, respiration increased and are irregular |
| 7. Serotonin content of the Raphe nucleus is associated with SWS (slow wave sleep) | 7. Noradrenaline content of the locus-coeruleus is associated with paradoxical sleep |
| 8. Threshold for arousal by the sensory stimulus is elevated | 8. Threshold for arousal by the sensory stimulation is further elevated |
| 9. 75% of total sleep | 9. 25% of total sleep |
| 10. Brain activity is less | 10. Brain activity is more |
| 11. $O_2$ consumption is less | 11. $O_2$ consumption is more |

## Genesis of Sleep

### *Genesis of NREM Sleep*

1. Inhibition of RAS inputs by the descending pathways which arise from preoptic and diagonal band of Broca.
2. Stimulation of sleep promoting mechanism (i.e. the rhythmic discharge from the thalamus). These mechanisms get influenced by:
   a. **Diencephalic sleep zone:** Present in posterior hypothalamus, intralaminar and anterior thalamic nuclei.
   b. **Medullary synchronizing zone:** It is present in the reticular formation of the medulla oblongata.

### *Mechanism that can Cause Sleep*

The most important stimulation area for sleep is the raphe nuclei in the lower half of pons and in the medulla. Nerve fibers from this nuclei spread locally in the brainstem reticular formation and also upward into the thalamus, hypothalamus, most areas of the limbic system, and even the neocortex of the cerebrum. In addition, fibers extend downward into the spinal cord, terminating in the posterior horns where they can inhibit incoming sensory signals, including pain. Nerve ending of fibers from the raphe neurons secretes serotonin. When a drug that block the formation of serotonin is given, then the sleep is deprived for several days. Therefore it is assumed that serotonin is a transmitter substance associated with production of sleep.

Stimulation of some areas in the nucleus of the tractus solitarius also cause sleep. Stimulation of several regions in the diencephalon can also promote sleep, including rostral part of hypothalamus and an occasional area in the diffuse nuclei of the thalamus.

### *Genesis of REM Sleep*

Genesis of REM sleep is due to two factors:
1. Discharge of NE (Norepinephrine) from the neurons located in the pontine reticular formation and locus coeruleus.
2. The cholinergic system is necessary for shifting NREM to REM sleep.

***Note***

a. Resperine, which depletes the serotonin and catecholamines, block the slow wave sleep.
b. Barbiturates decrease the amount of REM sleep.

### *Sleep Disorders*

1. **Insomnia:** It is a condition of being unable to sleep.
2. **Somnambulism or sleep walking:** It is more common in children and may last several minutes. Such individuals walk with their eyes open and avoid obstacles, but when awakened they cannot recall the episode.
3. **Nocturnal enuresis:** Involuntary voiding of urine during sleep at night.
4. **Narcolepsy:** It is a disease of unknown cause in which there is an uncontrollable urge to sleep during day time activities.

## BASAL GANGLIA

The term basal ganglia (BG) is applied to group of nuclei (mass of gray matter) in the forebrain and upper part of the brainstem that have motor activity of great importance (Table 11.13). It influences the pyramidal system activity. The basal ganglion differ from the cerebellum in the way they regulate motor activity. Unlike the cerebellum, the basal ganglia does not receive input from the spinal cord, but they do receive direct input from the cerebral cortex. The main action of basal ganglia is on the motor area of the cortex by the way of the thalamus. In addition to the role in motor control, basal ganglia also contributes to affective and cognitive function. The lesions of basal ganglia produce abnormal movement and posture.

**Table 11.13: Basal ganglia**

| | | |
|---|---|---|
| Lenticular nucleus | 1. Caudate nucleus | Striatum |
| | 2. Putamen | Striatum |
| | 3. Globus pallidus (pallidum) | |
| | 4. Subthalamic nucleus (body of Luys) | |
| | 5. Substantia nigra | |

### *Caudate Nucleus*

It possesses a head and tail (terminating at the amygdaloid nucleus). The caudate nucleus and putamen are together called the corpus striatum or neostriatum.

### *Putamen and Globus Pallidus*

Putamen and globus pallidus are together called lenticular nucleus. Globus pallidus (GP) is also called paleostriatum. Globus pallidus is subdivided into external (ES) and internal segment (IS) by medial medullary lamina. Substantia nigra is subdivided into two parts: Pars compacta (SNPC) and pars reticularis (SNPR). It is particularly rich in copper content.

***Note***

In basal ganglia three biochemically distinct pathways normally operate in a balanced fashion

1. Nigrostriatal dopaminergic system
2. Intrastriatal cholinergic system.
3. GABA ergic system that project from striatum to GP and SN.

### *Unique Feature of Basal Ganglia*

High $O_2$ consumption and high copper content.

## Connections (Flow chart 11.1)

i. **Afferent connections:** The main afferent connections to the basal ganglia terminate in the neostriatum and are excitatory (cholinergic neurons). They include:
   a. *Corticostriate projection:* They form afferents from all four lobes of the cerebral cortex but mainly from the frontal (motor areas) and parietal lobes to the neostriatum.
   b. *Thalamostriate fibers:* They are a projection of fibers from intralaminar, medial, ventral anterior and centromedian nuclei of thalamus to neostriatum.

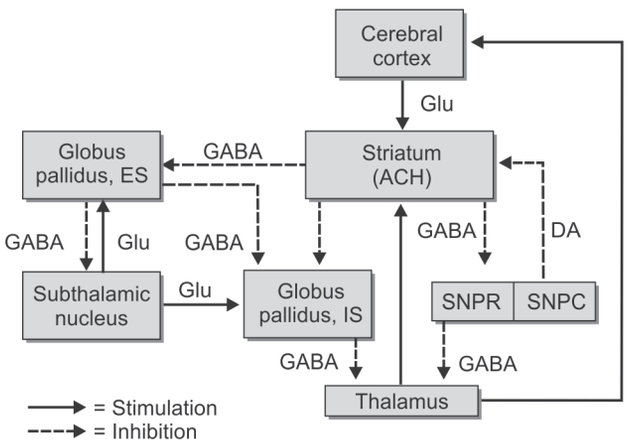
ii. **Internuclear connections:**
   a. *Dopaminergic nigrostriatal tract:* Pars compacta of SN contains cell body having dopamine (inhibitory transmitter) and its axons terminate in neostriatum. Degeneration of this neurons cause Parkin-sonism/paralysis agitans/shaking palsy.
   b. GABA-ergic inhibitory projections
      i. Neostriatum projects to:
         - Pars reticularis of the substantia nigra.
         - To both internal and external segment of globus pallidus.
      ii. The external segment of the globus pallidus projects to the subthalamic nucleus.
   c. Subthalamic nucleus projects via glutamic acid secreting excitatory neurons to:
   - Both internal and external segments of globus pallidus.
   - Substantia nigra.

iii. **Efferent connections:** The main output from the basal ganglia is from the globus pallidus and substantia nigra.
   a. From internal segment of globus pallidus: Via the thalamic fasciculus to the ventral lateral, ventral anterior and centromedian nuclei of the thalamus. From the thalamic nuclei, fibers project to prefrontal and premotor cortex.
   b. Ventrolateral pars reticulata of the substantia nigra projects to ventrolateral and ventroanterior nuclei of the thalamus. There a few additional projections from this part to the habenula and superior colliculus.

***Note***

1. The main feature of connections of BG is that cerebral cortex projects to the striatum, the striatum to internal segment of globus pallidus, internal segment of GP to thalamus and the thalamus back to the cortex thus forming a loop (Flow chart 11.1 and Fig. 11.60).
2. The output from internal segment of GP → thalamus is inhibitory whereas the output from the thalamus → cerebral cortex is excitatory.

**Flow chart 11.1:** Prinicipal connections of basal ganglia



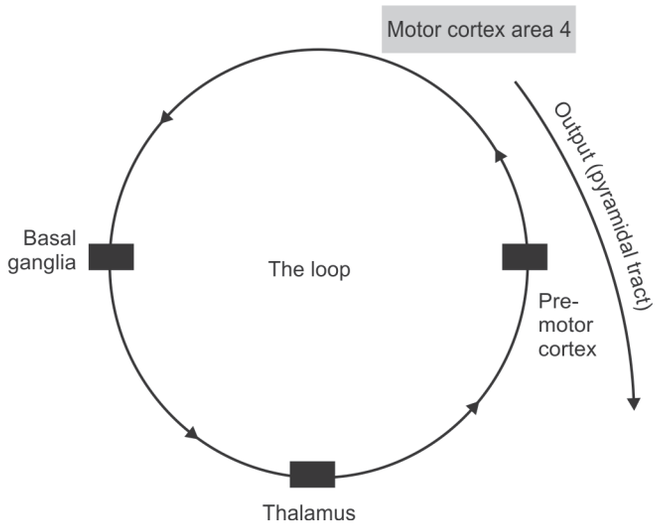



**Fig. 11.60:** Loop showing connection between basal ganglia and cortex

## Functions of Basal Ganglia (BG)

1. **Role in planning and programming of motor activity:** It is process by which an idea of involuntary movement is converted into precise action.
   *Mechanism:* Activity in the circuit between subthalamic nuclei and globus pallidus is an important regulator of basal ganglia output that in turn maintains movements in a smooth and appropriate state.
2. **Control of muscle tone:** Basal ganglia inhibits the stretch reflex (muscle tone) by stimulation of caudate nucleus and by the stimulation of inhibitory motor cortex as well as inhibitory reticular formation. This is why damage to BG cause rigidity.
3. **Cognitive function:** Caudate nucleus plays a role in cognitive processes (thinking process of brain, using both sensory inputs to the brain plus information already stored in memory). Lesion of head of the left caudate nucleus associated with dysarthric aphasia (difficulty in articulating words).
4. **Subconscious execution of some movements:** Basal ganglia is responsible for control of normal automatic and associated movements such as swinging of arms during walking. These movements are initiated by motor cortex.
5. Neostriatum regulates subconscious gross movements occurring in group of muscle.
6. The activity of basal ganglion increases during slow, steady damp movement and is silent during rapid, saccadic movement.
7. Globus pallidus provide muscle tone for performance of skilled movements.
8. Substantia nigra is center for coordination of impulses essential for skilled movements.

## Diseases of the Basal Ganglia

### *Parkinson's Disease (Paralysis Agitans/Shaking Palsy)*

It is caused due to degeneration of substantia nigra or globus pallidus or both and usually occurs in late middle age. Therefore, concentration of dopamine in this region, i.e. nigrostriatal system is reduced. Hence the balance between the excitatory discharge of cholinergic interneurons and inhibitory dopaminergic input in the neostriatum is disrupted. Parkinsonism occurs in:

- Primary or idiopathic, i.e. condition occuring without apparent cause.
- Cerebral arteriosclerosis.
- Complication of encephalitis.
- Complication of drugs such as phenothiazine which blocks the dopamine ($D_2$) receptors.

Symptoms appear when 60–70% of nigrostriatal dopaminergic neurons are lost.

#### *Characteristic Features*

It has both hyperkinetic and hypokinetic features (Fig. 11.61).

1. **Rigidity (Hyperkinetic):** Due to increased discharge of γ efferents supplying the muscle spindle.
   - It affects mainly large proximal group of muscle of limbs involving both antagonists and protagonists (biceps, knee flexors, sternomastoids).
   - Here posture is that of ***flexion attitude***. The back is flexed, the arms adducted and flexed and the knees are bent (stooped posture).

   Rigidity may be:
   - *Cogwheel type:* Here resistance is intermittently released.
   - *Lead pipe type:* Here resistance is through out movement.

   *Mechanism:* Activity of neostriatum is influenced by excitatory effect on cholinergic fibers and inhibitory influence of the dopaminergic fibers. Normally there exists a balanced effect of these two opposite innervations on the neostriatum activity. Lack of dopaminergic activity due to degeneration of substantia nigra shifts the balance towards the excitatory cholinergic fibers.
2. **Tremor (Hyperkinetic):** It consists of regular, rhythmic, alternate contraction of antagonist and agonist muscle at 6–8 times/sec. It is commonly seen as pill-rolling movements, i.e. rhythmic contraction of thumb over 1st two fingers. As it is present during rest and disappears during activity it is called resting (static) tremor. It increases in emotional states, excitement or anxiety due to secretion of epinephrine, which in turn excites RAS .The

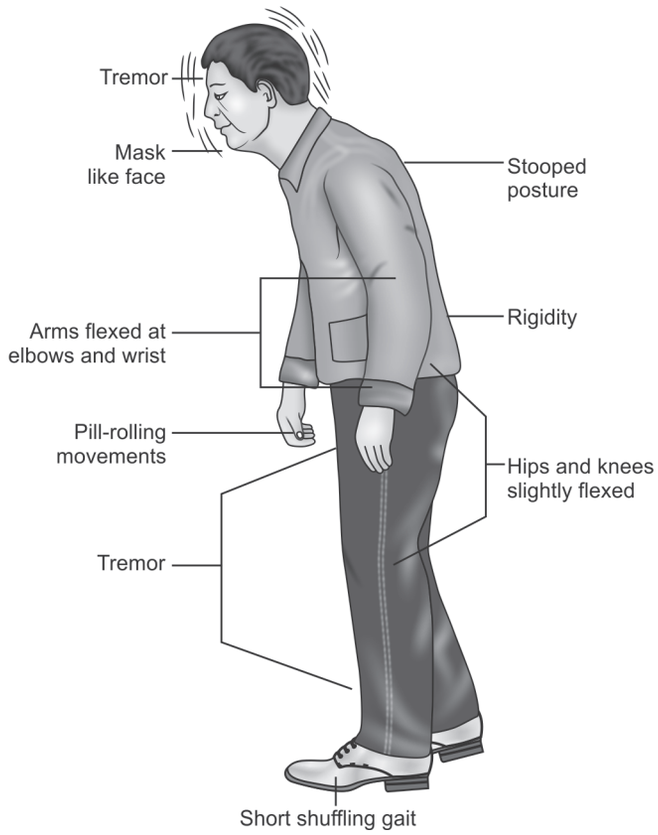



**Fig. 11.61:** Clinical features of Parkinson's diseases

tremor disappears during sleep (due to decreased activity of RAS).

*Cause:* Due to degenerative lesions in reticular formation and its ascending connections.

3. **Weakness and poverty of movements (Hypokinesia):**
   - Difficulty in initiating voluntary movements (akinesia). This produces defects in fine movements of fingers.
   - Defects in fine variations of speech.
   - Mask like facial expression due to decrease in movements of facial muscles.
   - Loss of normal subconscious associated movements. For example, swinging of arms during walking.
   - Tendon reflex is more difficult to elicit as rigidity increases.
4. **Gait:** Festinant type (shuffling gait)—Patient is bent forward and walks quickly with short steps as if trying to catch up the center of gravity or preventing himself from falling down.
5. **Retropulsion:** If the patient is suddenly pulled backwards, he begins to to walks backwards and is unable to stop himself.
6. **Tendon jerks:** Tendon jerks become progressively difficult to elicit as the rigidity increases.

### *Treatment*

1. Administration of the drug L-dopa. It can cross blood-brain barrier and reach the brain tissue where it is converted to dopamine.
2. Transplantation of dopamine secreting cells (cells obtained from brains of aborted fetuses) into caudate nucleus and putamen has been used with some short term success to treat Parkinson's disease.
3. Surgical treatment by making lesions in the internal segment of the globus pallidus (pallidotomy) or in the subthalamic nucleus helps to restore the output balance towards the normal.

## *Chorea, Athetosis and Ballism*

These three disorders are characterized by spontaneous involuntary movements due to the interruption of the inhibitory pathway from area 4S via the caudate nucleus to the thalamus.:

1. **Chorea:** It is mainly due to involvement of caudate nucleus and is characterized by rapid irregular involuntary "dancing" movements of short duration. It is also associated with decreased muscle tone and muscular weakness.
2. **Athetosis:** It is due to lesion of lenticular nucleus and is characterized by continuous slow twisting/writhing movements.
3. **Ballism:** Involuntary flailing, intense and violent movements occur.

## *Hemiballism*

It is due to damage of the subthalamic nucleus and is characterized by spontaneous attacks of incoordinated movements affecting whole of the opposite side of the body.

## *Wilson's Disease/Hepatolenticular Degeneration*

It is an autosomal recessive disease. Here copper content of substania nigra is high. In this condition the ceruloplasmin (plasma copper binding protein) is low. Thus copper accumulation causing degeneration of lenticular nucleus with cirrhosis of liver. The condition is characterized by muscular rigidity, tremor, cirrhosis of liver and emotional disturbances.

## *Huntington's Disease*

It is a autosomal dominant inherited disorder. The abnormal gene responsible for the disease is located in the short arm of chromosome 4. It usually occurs between 30 and 50 years of

age. It is due to the damage to GABA-ergic and cholinergic neurons that projects to the putamen. Damage to this inhibitory pathway results in hyperkinetic features, which include:

- Hyperkinetic choreiform movements.
- Slurred speech.
- Progressive loss of memory (dementia).

It is a gradually progressive disease with no effective treatment which eventually leads to death.

## HYPOTHALAMUS

Hypothalamus is the integrating center where several neural and endocrine influences originating throughout the brain converge. It is then processed and the processed outputs are diverged to all parts of the body. Thus, it acts like a funnel (Fig. 11.62) which transmits the influences of the brain on several homeostatic mechanisms to the body.

### Nuclei of Hypothalamus (Fig. 11.64)

It is divided into three groups:

#### *Anterior or Preoptic Group*

1. Preoptic nucleus
2. Paraventricular nucleus
3. Anterior nucleus
4. Supraoptic nucleus

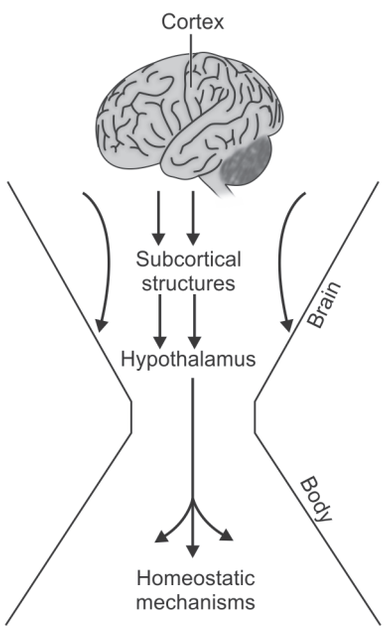



**Fig. 11.62:** Hypothalamus as an integrating center

#### *Middle or Tuberal Group*

1. Dorsomedial group
2. Ventromedial group
3. Lateral nucleus
4. Arcuate (tuberal) nucleus

#### *Posterior or Mammillary Group*

1. Posterior nucleus
2. Mammillary body

### Connections of Hypothalamus (Fig. 11.63)

#### *Afferents*

1. *From limbic system:* Hippocampus and amygdala. They are concerned with emotion and behavior.
2. *From cortex:* From frontal lobe (area-6 and prefrontal area). They enter directly.
3. From olfactory lobe and paraolfactory area.
4. Collaterals from lemniscal system and fibers from RAS (Reticular activating system). Fibers from RAS is associated with alertness.
5. *From corpus striatum:* It has strong control over tone and some involuntary movements.
6. From thalamus.
7. *From brainstem:* Raphe nucleus, locus coeruleus, medulla.

#### *Efferents*

1. **To brainstem and the spinal cord:** Efferents pass via pontine nuclei and then through reticulospinal fibers. Descending impulses from hypothalamus terminate on the lateral horn cells, controlling the spinal sympathetic

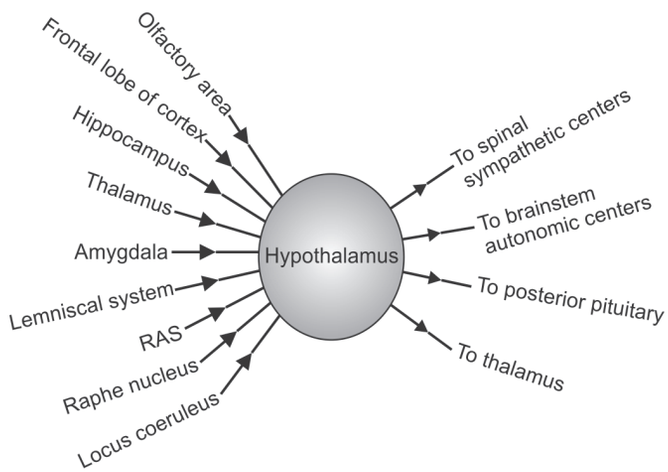



**Fig. 11.63:** Connections of hypothalamus

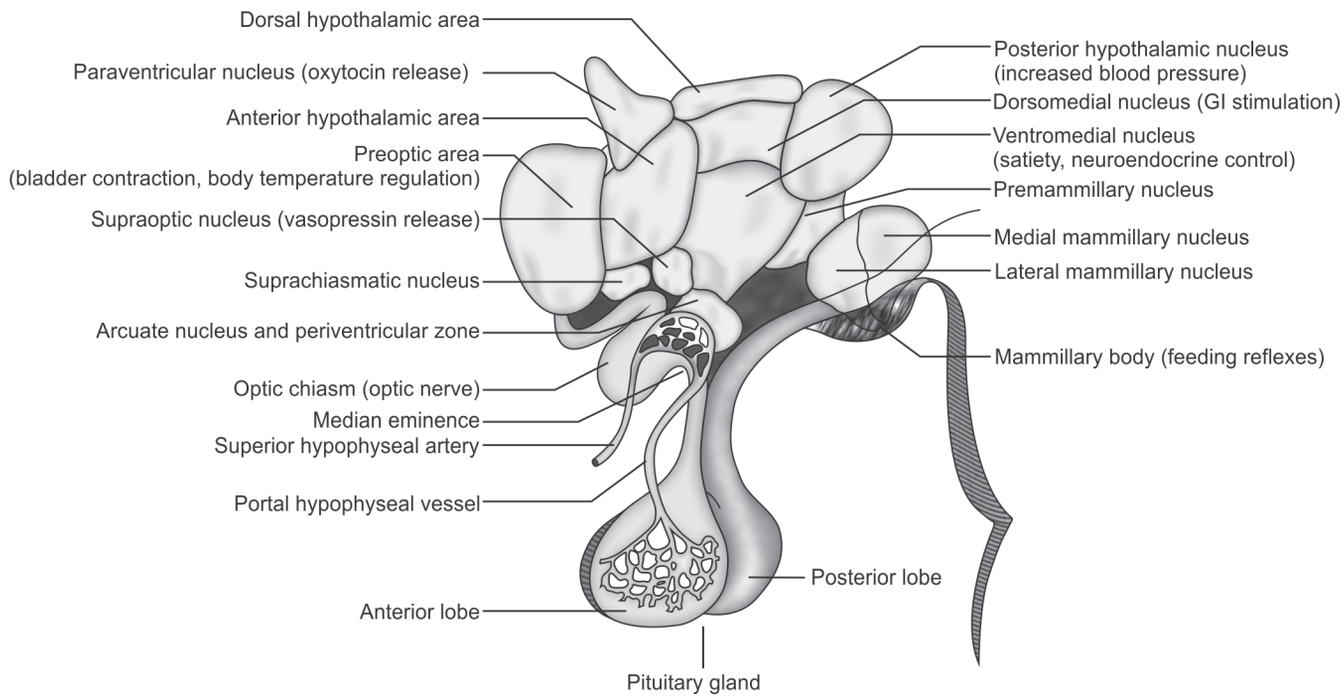



**Fig. 11.64:** Nuclei of hypothalamus

centers. Hypothalamus thus controls BP, heart rate, diameter of the blood vessels.

2. Fibers from supraoptic and paraventricular nuclei form the hypothalamic hypophyseal path to end in posterior pituitary.
3. To thalamus.
4. To midbrain.

## Functions of Hypothalamus

1. **Regulation of body temperature:** The anterior portion of the hypothalamus, especially the preoptic area is concerned with regulation of body temperature. An increase in temperature of the blood through this area increases the activity of the temperature sensitive neuron, while a decrease in temperature decreases the activity.
   *Anterior hypothalamus:* Response to heat
   *Posterior hypothalamus:* Response to cold.
2. **Regulation of anterior pituitary activity:** Through the release of releasing and inhibiting factors into hypothalamo-hypophysial portal system.
3. **Regulation of postpituitary hormones:**
   - *ADH:* Synthesis from supraoptic nucleus
   - *Oxytoxin:* From paraventricular nucleus.
4. **Control of circadian rhythm**

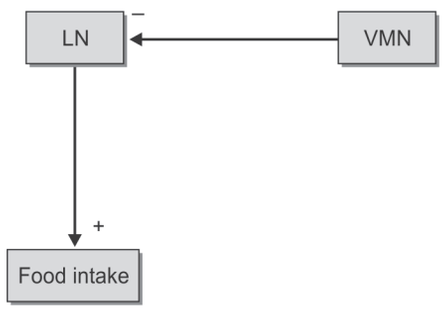
   There is a diurnal variation for many body functions, which is about 24 hours. For example, rhythm in the secretion of GH, ACTH, melatonin, gonadotropin, etc.

   *Neural basis of circadian rhythm:* The suprachiasmatic nuclei are the main site for circadian rhythm. These nuclei receive inputs from:
   - Eye via reticulohypothalamic fibers
   - Lateral geniculate nuclei.
5. **Control of sleep-waking cycle:** The basic rhythm is controlled by the biological clock function of the suprachiasmatic nucleus. Two sleep centers in the hypothalamus are:
   a. **Diencephalic sleep zone:** It is present in posterior hypothalamus, intralaminar and anterior thalamic nuclei.
   b. **Basal forebrain sleep zone:** It includes preoptic area and diagonal band of Broca. Stimulation of these centers at 8 Hz induces a slow wave sleep. In the lesions of hypothalamus narcolepsy is developed.
6. **Control of ANS:** Hypothalamus is the head ganglion of the ANS. Its stimulation produces autonomic responses.
   a. Stimulation of anterior hypothalamus produces parasympathetic response like contraction of urinary bladder.
   b. Stimulation of lateral areas of the hypothalamus produces sympathetic responses such as rise in BP, papillary dilatation, piloerection, etc.
   c. Stimulation of dorsomedial nuclei and posterior hypothalamic areas produces increased adrenal medullary secretion which is one of the physical changes associated with rage and fear.

7. **Control of hunger and feeding (Fig. 11.65):** Two centers are connected with it:
   a. Ventromedial nuclei (VMN) act as a satiety center and its bilateral lesions causes hyperphagia (hypothalamic obesity).
   b. Lateral nucleus (LN) acts as a feeding center. Its lesion cause anorexia (loss of appetite especially when prolonged) and animal dies of starvation.

### *Mechanism*

Satiety center is the primary center that controls the food intake. It functions by inhibiting the feeding center. Thus VMN inhibit food intake and LN stimulate food intake.




### *Glucostastic Theory*

The cells of VMN acts as glucoreceptors. Thus activity of satiety center is governed by the level of glucose utilization within the cell. An increase in blood glucose level increases the activity of VMN. A decrease in blood glucose level decreases the activity of VMN.

***Note:*** Deficient glucose utilization in the cells of the satiety area (VMN) of hypothalamus is the probable cause for hyperphagia in diabetes mellitus. This decreases its inhibitory effect on feeding center (LN) and thus food intake is increased.

## Role of Hypothalamic Peptides

Important hypothalamic peptides that seem to plays an important role in regulation of food intake are:

i. Food intake is increased by:
   a. Neuropeptide Y (synthesized by neurons in arcuate nucleus of hypothalamus)
   b. Orexin-A and Orexin-B (synthesized by lateral hypothalamic neurons)
   c. Ghrelin (secreted by stomach and hypothalamus)

ii. Food intake is decreased by:
   a. CART (cocaine and amphetamine regulated transcript)
   b. CRH (corticotropin releasing hormone)

### *Lipostatic Hypothesis*

According to this hypothesis the adipose tissue produces a hormone leptin, the production of which is proportional to the amount of fat. This acts on hypothalamus to decrease the food intake.

### *Gut Peptide Hypothesis*

According to this hypothesis, presence of food in the GIT causes the release of gut peptides. These are glucagon, somatostatin, CCK which acts on the brain to cause satiety.

### *Thermostatic Hypothesis*

According to this, the body temperature influences the food intake. Appetite is stimulated and the food intake increases when the body temperature goes below a given set point and is inhibited when the body temperature rises above a set point.

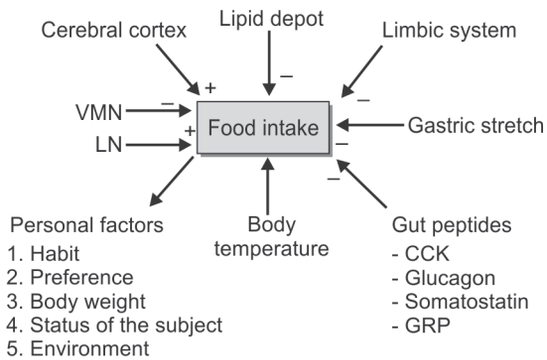



**Fig. 11.65:** Factors influencing food intake

## Role in Regulation of Water Balance

Hypothalamus regulates body water in two ways:
a. Creating the sensation of thirst
b. By controlling excretion of water into the urine.

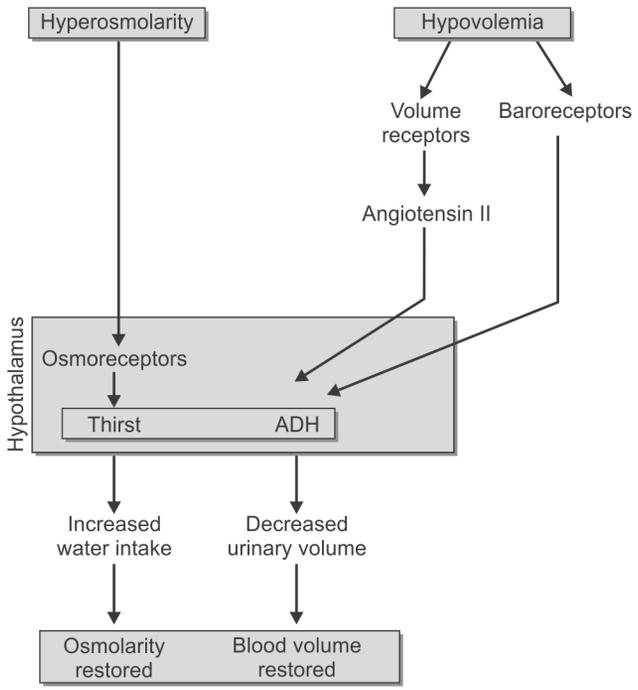
### *Hypothalamic Mechanism*

***Creating the sensation of thirst:*** Hypothalamus contains osmoreceptors which can detect changes in osmolality of the ECF. Thus, if there is lack of water, the osmolality of ECF rises → osmoreceptors of hypothalamus are stimulated → thirst develops → drive for water intake develops.

*A second hypothalamic mechanism is as follows:* In conditions, where the kidneys produce renin (hemorrhage/hypovolemia), renin converts the plasma angiotensinogen to angiotensin II. Apart from its normal actions, angiotensin II also acts on the hypothalamus → development of thirst → development of thirst behavior. Cardiovascular shock therefore is associated with thirst, as this condition generates angiotensin in high quantity.

***By controlling excretion of water into the urine:*** The increased plasma osmolarity stimulates osmoreceptors in supraoptic nucleus (SON). The stimulated neurons of SON in turn send impulses to postpituitary to secrete hormone ADH. ADH is also secereted in response to angiotensin II (when fluid volume is low). Secretion of ADH increases water absorption from the collecting ducts of the kidney (Flow chart 11.2).

**Flow chart 11.2:** Role of hypothalamus in regulation of water balance




***Note:*** Apart from the hypothalamus the regulation of water balance is also controlled by the following mechanisms:

i. *Buccal mucosal mechanism:* If the mucous membrane of buccal cavity becomes dry, there develops thirst. Drying of mouth and throat occurs during speaking, smoking, breathing through mouth or by eating dry food.
ii. Diarrhea, vomiting and hemorrhage decreases ECF volume which in turn reduces the blood volume and thereby the baroreceptors are stimulated, inducing thirst.

### Control of Emotional Behavior

It is regulated by limbic cortex. The two centers in hypothalamus involved in behavior and emotional changes are reward (center located along the course of medial forebrain bundle, especially in lateral and ventromedial nucleus of hypothalamus) and punishment center (located in medial hypothalamus and paraventricular zone).

### Sexual Behavior

Controlled by anterior ventral hypothalamus and male piriform cortex.

## CORTICAL AREAS

Electrostimulation of different areas of cortex (Figs 11.66 and 11.67) was performed to study their functions. This test was performed in conscious human beings, in whom brain has been exposed for some purpose and effects studied.

### Frontal Lobe

The major areas in this lobe are:

i. **Area 4 (Primary motor area):** This area is situated in the precentral gyrus (in front of central sulcus) of frontal lobe of this area. The body is represented upside down from medial to lateral surface. The lower parts of the body are represented in medial surface and upper parts of the body. The order of representation from medial

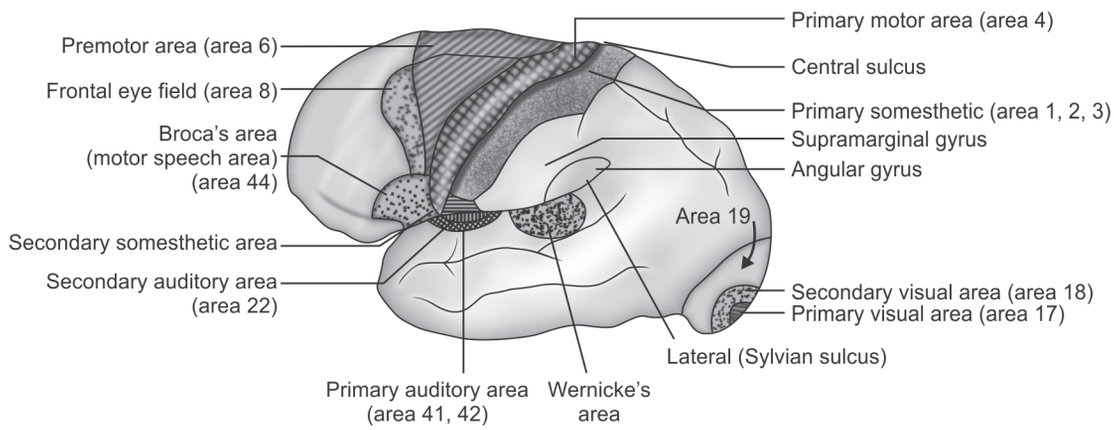



**Fig. 11.66:** Lateral view of cerebral cortex (left lobe)

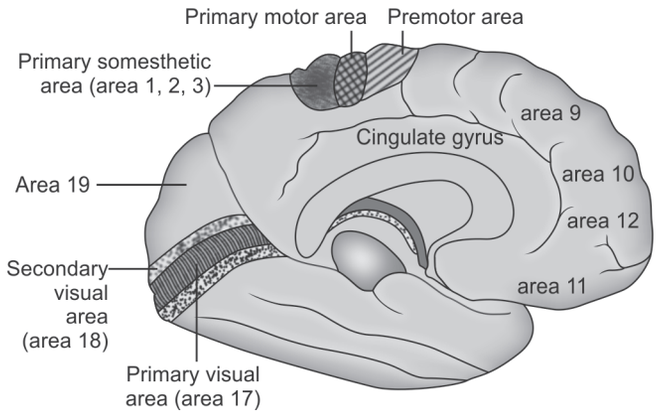



**Fig. 11.67:** Medial view of cerebral cortex (left lobe)

to lateral surface-toes, ankle, knee, hip, trunk, shoulder, arm, elbow, wrist, hand fingers and face. The size of representation is directly proportional to skill of the part. However, the parts of the face are not represented in an inverted manner.

*Functions:* This area is concerned with contraction of discrete muscles. It sends motor signals to the facial muscles of both sides (bilateral) and to the other muscles of the opposite side. Many of the fibers of pyramidal tract arise from the motor cortex (area 4).

***Note:*** There is another area called suppressor area (Area 4S). This area lies anterior to area 4 and inhibits the movements initiated by area 4 thus preventing the exaggeration of actions.

ii. **Area 6 (premotor area):** Premotor area lies in front of area 4. It contributes to both pyramidal and extrapyramidal fibers.

*Functions:* It is concerned with coordination of movements initiated by area 4. It is believed to be the cortical center for extrapyramidal system.

iii. **Area 8 (frontal eye field):** This lies anterior to area 6 in the precentral cortex. Its stimulation causes conjugate deviation of eyes to the opposite side.

*Functions:* Area 8 appears to be mainly responsible for voluntary eye movements. This area is also concerned with accommodation reflex mechanism.

iv. **Supplementary motor area:** It is situated in medial surface of frontal lobe rostral to primary motor area.

*Functions:* The exact function is not clearly known but it is suggested that it is concerned with coordinated skilled movements.

v. **Prefrontal cortex (areas 9, 10, 11 and 12):** This is the anterior part of frontal lobe of cerebral cortex, in front of areas 8 and 44.

*Functions:* It forms the center for higher functions like emotional, learning, memory and social behavior. Short-term memories are registered here. It is the center for planned actions. This area is also concerned with intelligence.

vi. **Broca's area (area 44):** It is the motor speech area. It lies anterior to the primary motor cortex and above the Sylvian fissure.

## PARIETAL LOBE

The major areas in this lobe are:

i. **Primary sensory area (somesthetic area I):** It is also called Brodmann's area 3, 1, 2. Fibers conveying impulses by spinothalamic tract, lemniscal system (touch, pain, temperature senses, etc.), after relaying in the thalamus end here and thus we become aware of the specific senses.

*Functions:* It is the highest area of general, conscious, sense perception.

ii. **Somesthetic area II:** It lies below the area of somesthetic area I, so that it is buried in the lateral (Sylvian) sulcus. This area receives sensory impulses from somesthetic area I and from the thalamus directly.

*Function:* It is concerned with perception of sensation.

iii. **Somsthetic association area:** It includes area 5 and 7 of Brodmann. It lies posterior to somesthetic area I in the parietal lobe.

*Functions:* This area is concerned with the synthesis of various sensations perceived by somesthetic area I. Thus, this area forms the center for combined sensations like stereognosis.

***Note***

*Sensory motor area*

The sensory area of cortex is not limited to postcentral gyrus in parietal lobe. It extends anteriorly into motor area in precentral gyrus of frontal lobe. Similarly the motor area is extended from the precentral gyrus posteriorly into post central gyrus. Thus, the precentral and postcentral gyri are combined together by association neurons and they are functionally interrelated. So, this area is called sensory motor area.

## TEMPORAL LOBE

Major areas in this lobe are:

i. **Primary auditory area:** This includes areas 41, 42 and Wernicke's area (area 22). Areas 41, 42 are situated in the anterior transverse gyrus and lateral surface of superior

temporal gyrus. Wernicke's area is located in the upper part of superior temporal gyrus posterior to areas 41 and 42.

*Functions:* This area is concerned with perception of auditory impulses, analysis of pitch and determination of intensity, source of sound.

ii. **Auditopsychic area (area 22):** This occupies the superior temporal gyrus.

*Functions:* This area is concerned with interpretation of auditory sensation along with Wernicke's area.

## OCCIPITAL LOBE

Major areas in this lobe are:

i. **Primary visual area (area 17):** It is concerned with perception of visual impulses.
ii. **Visual association area (area 18):** It is concerned with interpretation of visual impulses.
iii. **Occipital eye field (area 19):** It is concerned with the movement of the eyes.

## LIMBIC SYSTEM

The term limbic has been derived from the word 'limbus' which means a ring. Thus the limbic system is applied for that parts of the cortex (limbic cortex or limbic lobe) and subcortical structures that form a ring around the brain stem.

Limbic cortex/limbic lobe surrounds the subcortical structures of the limbic system (Fig. 11.68). Phylogenetically, limbic cortex is an older part of the cerebral cortex (allocortex) having primitive histological structures.

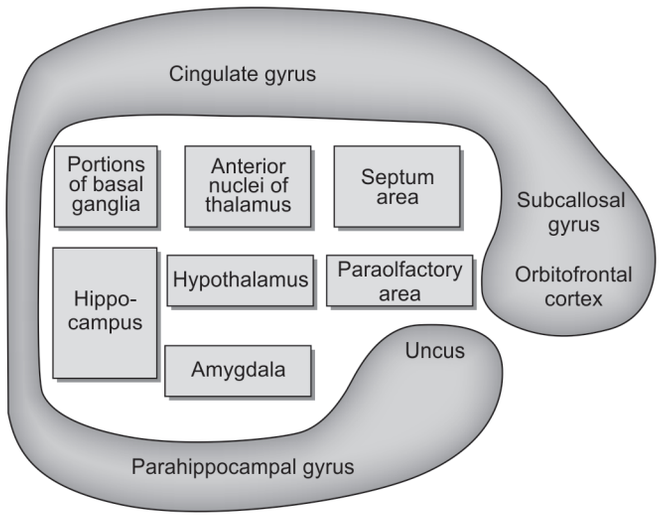



**Fig. 11.68:** Limbic system, showing the key position of hypothalamus

*Limbic cortex is composed of:*

a. Orbitofrontal cortex
b. Subcallosal gyrus
c. Cingulate gyrus
d. Parahippocampal gyrus
e. Uncus

*Subcortical structures included under the limbic system are:*

a. Hypothalamus
b. Septum
c. Paraolfactory area
d. Anterior nucleus to thalamus
e. Amygdala
f. Portions of basal ganglia
g. Hippocampus.

### Connections

#### *Papez Circuit*

Papez circuit refers to a closed circuit formed by connections between the cingulate gyrus (located in the prefrontal lobe), hippocampus, mammillary bodies and anterior nucleus of thalamus (Fig. 11.69). It links limbic lobe with hypothalamus and thalamus. This circuit is responsible for resting EEG and plays an important role in control and genesis of emotions.

Information passes from the cingulate gyrus to hippocampus and from there via the fornix to the mammillary bodies in the hypothalamus. The mammillothalamic tract then connects the hypothalamus with the anterior thalamic nuclei, which project back to cingulated gyrus.

### Functions of Limbic System

1. **Autonomic functions:** Stimulation of many parts of the limbic system specially that of amygdala produces autonomic responses such as changes in cardiovascular, respiratory and gastrointestinal system through hypothalamus.

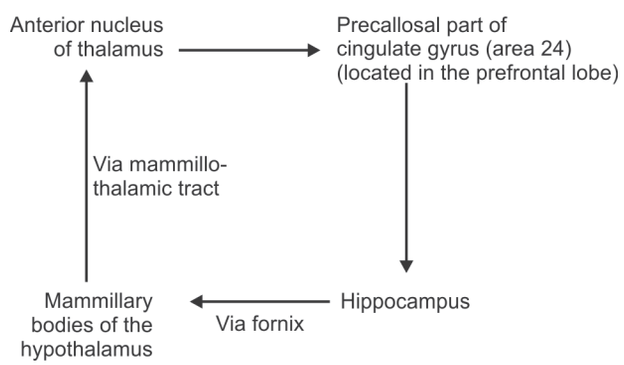



**Fig. 11.69:** Papez circuit

2. **Regulation of feeding behavior:** Limbic system regulates feeding behavior mainly through hypothalamus and amygdala.
3. **Emotional behavior:** Limbic system is concerned with various emotions including various emotions of fear, rage, reward-punishment, etc.
4. **Regulation of sexual behavior:** Sexual behavior, the basic sex drive is a function of limbic system and hypothalamus which in turn are influenced by gonadal hormones and cerebral cortex.
5. **Motivational behavior:** Motivational behavior is also an important function of limbic system.

## HIGHER FUNCTIONS OF NERVOUS SYSTEM

The higher functions of the nervous system include: Language (speech) and other intellectual functions like learning, memory and judgment. In general, higher functions of the nervous system in humans depend more on one cerebral hemisphere (dominant/categorical hemisphere) than on the other.

## LANGUAGE (SPEECH)

Language refers to the faculty of nervous system which enables the human to understand the spoken and printed words and to express ideas in speech and writing. It is brought about by coordinated activity of different parts of the brain, particularly the motor, sensory and psychic areas.

### Development of Speech

Development of speech in children occurs in two stages:

*First stage:* In this stage there occurs association of certain words with visual, tactile, auditory and other sensations, aroused by objects in the external world which is stored in the memory.

*Second stage:* This stage of development of speech involves establishment of new neuronal circuits. When a definite meaning has been attached to certain words, pathway between the auditory area (area 41) and motor area for the muscles of articulation which helps in speech (area 44) is established. At this point of time the child attempts to formulate and pronounce the words, which are learnt.

### Mechanism of Speech and Speech Centers

*Two major types of speech are:*

a. *Spoken speech:* This means understanding the spoken words and expressing ideas in speech.
b. *Written speech:* This means understanding written words and expressing the ideas in writing.

### Understanding of Speech (Sensory Aspects of Communication)

#### *Understanding of Spoken Speech*

1. **Hearing of the spoken words:** To hear a sound we require an intact auditory pathway from the ears to the primary auditory center (area 41).
2. **Understanding of the spoken words:** For understanding a sound, there must be activity of the adjacent auditory-psychic areas (area 20, 21).
3. **Interpretation and comprehension of speech ideas:** In order to express the ideas in speech, the activity of sensory speech center, called Wernicke's area (area 22) is essential. Wernicke's area is located in the region at the posterior end of the superior temporal gyrus in the dominant (categorical) hemisphere. It is concerned with comprehension, i.e. interpretation and understanding of auditory and visual informations.

#### *Understanding of Written Speech*

1. **Perception of written words:** In order to see the words it requires an intact visual pathway from the eyes to the primary visual cortex (area 17).
2. **Interpretation of written speech:** Inorder to interpret the written symbols (of past experience), it requires the activity of visuo-psychic areas (area 18, 19).
3. **Generation of ideas in response to written speech:** To express the ideas in writing, it involves the activity of visual speech center, called the **Dejerine area (area 39).** Dejerine area is located in the angular gyrus behind the Wernicke's area in the dominant hemisphere. It processes informations from printed words in such a way that they can be converted into the auditory forms of the words in the Wernicke's area (internal speech). Sensory speech centers include Wernicke's and Dejerine areas.

### Expression of Speech (Motor Aspect of Speech)

Expression of speech requires the skilled use of many muscles, such as muscles of the lip, tongue, larynx, hand or fingers. There is a motor speech center for both spoken and written speech in the prefrontal lobe in the dominant (categorical) hemisphere. Motor speech centers include Broca's and Exner's areas:

1. **Expression in the form of spoken speech:** Expression in the form of spoken speech involves the activity of motor speech (Broca's area) area.

   *Broca's area (area 44):* It is located in the inferior frontal gyrus, in the region of the anterior and ascending rami

of the lateral sulcus in the dominant (categorical) hemisphere. It processes the information received from sensory speech centers into a detailed and coordinated pattern for vocalization. (Wernicke's area projects via the arcuate fasciculus to Broca's area). This pattern is then projected to the motor cortex which initiates the appropriate movements of the lips, tongue and larynx to produce speech.

2. **Expression in the form of written speech:** Expression in the form of written speech is the function of Exner's area.

   *Exner's area (motor writing center):* It is located in the middle frontal gyrus in the dominant (categorical) hemisphere anterior to motor cortex (i.e. in the premotor cortex). It processes the informations from Broca's area into detailed and coordinated pattern, which then along with motor cortex initiates the appropriate movements of the hands and fingers to produce written speech.

3. **Expression of both spoken and written speech:** Suppose somebody is reading a book aloud and then wishes to write what he has read, the sequence will be as follows (Fig. 11.70):
   1. The printed words will be seen first by the primary visual area (area 17), highest area for perception of visual sense.
   2. The printed words seen are properly interpreted and understood by the visual association area (area 18).
   3. The printed words which are understood are converted into internal speech by the Dejerine area (in angular gyrus).

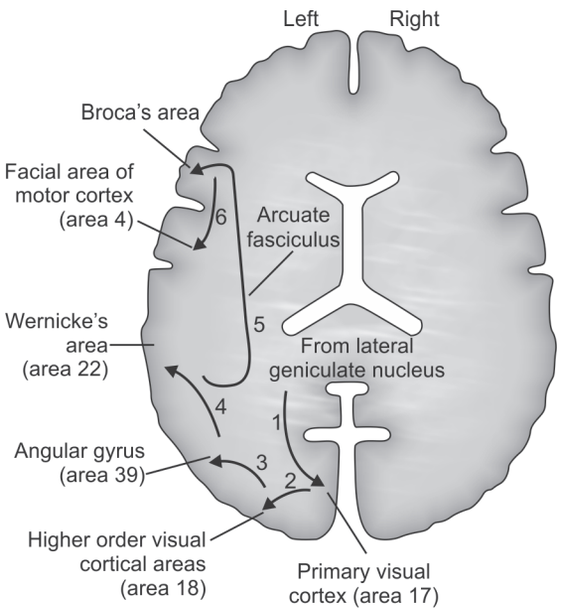



**Fig. 11.70:** Path taken by impulses when a subject names a visual object

   4. The Wernicke's area (area 22) then interprets and understands the internal speech.
   5. This in turn sends the information to the Broca's area for pattern coordination.
   6. The Broca's area (area 44) sends detailed pattern coordination information to:

   a. Motor area (area 4) for the spoken speech.
   b. Exner's area for the written speech (motor writing center), the Exner's area along with motor area (area 4) initiates appropriate muscle movements of hand and fingers to produce written speech.

## Speech Disorders

### *Aphasia*

Aphasias are abnormalities of language functions (inability to understand spoken or written speech or inability in expressing the spoken or written speech) that are not due to defects of vision or hearing or due to motor paralysis. They are caused by lesions in the categorical hemisphere. The most common cause is embolism or thrombosis of a cerebral blood vessel. The aphasia may be:

i. Sensory aphasia
ii. Motor aphasia
iii. Global aphasia

i. **Sensory aphasia:** Sensory aphasia also known as Wernicke's aphasia is the result of lesion in the Wernicke's area.

   *Characteristic features:*

   a. Difficulty in understanding the meaning of the speech.
   b. Motor speech area is intact, and the patients talk very fluently that is why it is also called fluent aphasia. However, the speech does not make any sense.

ii. **Motor aphasia:** Motor aphasia, also known as Broca's aphasia results from lesions involving the Broca's motor speech area (area 44) in the frontal lobe.

   *Characteristic features:*

   a. Speech is slow, and words are hard to come and are limited to two or three words with which the whole range of meaning and emotion is to be expressed.
   b. Speech is nonfluent (nonfluent aphasia).
   c. Inability to write (agraphia).

iii. **Global aphasia**: Global aphasia refers to the total inability to use language communication. This condition is produced as a result of loss of both Wernicke's and Broca's areas. In this situation, speech is scant as well as nonfluent.

***Note***

1. Another form of fluent aphasia is a condition in which patients can speak relatively well and have good auditory

comprehension but cannot put parts of words together or conjure up words. This is called conduction aphasia. It is due to lesions in and around the auditory cortex (areas 40, 41, and 42).

2. When there is a lesion damaging the angular gyrus (Dejerine area) in the categorical hemisphere without affecting Wernicke's or Broca's areas, there is no difficulty with speech or the understanding of auditory information, but there is trouble in understanding written language or pictures, because visual information is not processed and transmitted to Wernicke's area. The result is a condition called anomic aphasia.

**Table 11.14: Aphasia**

| *Type of aphasia and site of lesion* | *Characteristic naming errors* |
|---|---|
| Nonfluent (Broca's area) | "Tssair" |
| Fluent (Wernicke's area) | "Stool" or choss" (neologism) |
| Fluent (areas 40, 41 and 42; conduction aphasia) | "Flair.....no swair.....tair |
| Anomic (angular gyrus) | "I know what it is... I have a lot of them |

Characteristic responses of patients with lesions in various areas when shown a picture of a chair

### *Dysarthria*

It is a disorder of speech in which articulation of words is impaired, but the comprehension of spoken and written speech is not affected.

## LEARNING AND MEMORY

Learning and memory are closely related. Learning is impossible without memory and memory has no meaning without learning.

### Learning

Learning refers to a natural mechanism by which the individual changes his or her behavior on the basis of past experience. Learning is of two types:

a. Nonassociative learning
b. Associative learning

a. **Nonassociative learning:** In nonassociative learning the subject learns about the properties of a single stimulus. It results when an animal or a person is repeatedly exposed to a single type of stimulus. Two forms of nonassociative learning are common in everyday life-habituation and sensitization.

b. **Associative learning:** In associative learning the subject learns about the relationship between two stimuli or between a stimulus and a behavior. Two forms of associative learning have been distinguished based on the experimental procedures used to establish the learning-classical conditioning and operant conditioning.

i. ***Classical conditioning:*** Classical conditioning involves learning a relationship between two stimuli. It is also termed as Pavlovian conditioning or conditioned reflex type I.

*Characteristic features*

1. A conditioned reflex is a reflex response to a stimulus that is acquired by repeatedly pairing the stimulus with another stimulus that normally does produce the response. It depends for its appearance on the formation of new functional connections in CNS.
2. *Reinforcement:* It is a process of following a conditioned stimulus with a basic unconditioned stimulus which is a must for retaining a conditioned reflex otherwise it will extinct.

### *Pavlov's Experiment*

This experiment demonstrates classical conditioned reflex.

a. When food, i.e. an unconditioned stimulus is presented to a hungry dog, it produces salivation (an unconditioned response).
b. If a bell is rung (a conditioned stimulus), just before the food is presented, the dog learns to associate the bell with the food.
c. Eventually, ringing the bell (a conditioned stimulus), alone causes salivation.

***Note:*** If the food fails to appear consistently when the bell is rung, the conditioned response fades away, a process called extinction or internal inhibition. Therefore a conditioned reflex needs to be reinforced frequently, otherwise it dies out.

Physiologically the occurrence of conditioned reflex is explained by the formation of a new functional connection in the nervous system.

ii. ***Operant conditioning:*** Operant conditioning is a form of conditioning in which the animal is taught to perform some task ("operate on the environment") in order to obtain a reward or avoid punishment. Operant conditioning is of two types:

a. *Reward conditioning:* In it a naturally occurring response is strengthened by positive reinforcement (reward).
b. *Adverse conditioning:* In it a naturally occurring response is weakened by a negative reinforcement (punishment).

## Memory

Memory is the ability to recall the past events at the conscious or unconscious level. It is the relatively permanent storage form of learned information. They can be either declarative or non-declarative.

## Declarative/Explicit/Recognition Memory

It is associated with consciousness or at least awareness. It is dependent on the hippocampus and other parts of the medial temporal lobes of the brain for its retention. Explicit memory is divided into the memory for events (episodic memory) and the memory for words, rules and language, etc. (semantic memory).

## Non-declarative/Implicit/Reflexive Memory

It does not involve awareness. Its retention does not involve processing in the hippocampus (in most instances) and includes skills, habits, conditioned reflexes, etc.

Explicit memory and many forms of implicit memory involve:

1. **Short-term memory,** which lasts seconds to hours, during which processing in the hippocampus and elsewhere lays down long-term changes in synaptic strength.
2. **Long-term memory,** which stores memories for years and sometimes for life. During short-term memory, memory traces are subject to disruption by trauma and various drugs, whereas long-term memory traces are remarkably resistant to disruption.

### *Mechanism of Memory (Physiological and Cellular Basis)*

Studies of memory retention and disruption of memory have revealed that both explicit and implicit memory are stored in stages by different mechanisms. Input to the brain is processed into short term memory before it is transmitted through one or more stages (intermediate long-term memory) into more permanent long-term storage.

### *Mechanism of Implicit Memory*

i. **Mechanism of short-term storage of implicit memory:** The various mechanisms for simple forms of learning result from the changes in the effectiveness of synaptic transmission. It includes: (a) Habituation, (b) Sensitization.

ii. **Mechanism of long-term storage of implicit memory:** The process by which transient short-term memory is converted into a stable long-term memory is called consolidation. Consolidation of long-term implicit memory for simple forms of learning involves three processes:
   a. Gene expression
   b. New protein synthesis
   c. Growth (pruning) of synaptic connections

Much information is transferred between the two hemispheres through the corpus callosum, although some is transmitted through other commissures (e.g the anterior commissure or hippocampal commissure).

## Alzheimer's Disease

It is characterized by progressive loss of memory and cognitive function in middle aged individuals. Thus, the condition is frequently associated with:

a. Memory failure for recent events
b. Lack of spontaneous activity and initiative with loss of intellectual functions
c. Extrapyramidal and akinetic hypertonic symptoms.
d. Loss of spatial orientation.

After 2 or 3 years, dementia (memory loss) becomes well established and focal symptoms occur, such as aphasia (speech disorder), apraxia (inability to perform voluntary movements and agnosia (inability to recognize objects in spite of intact sensory modality). Similar features in the old age (over 65 years) are called senile dementia. Both the conditions are caused by degeneration of cholinergic nerve terminals in the cerebral cortex and hippocampus.

Chapter

# 12 Special Senses

## VISION

### Structure of Eye

The eye (Fig. 12.1) is a special organ of the sense of sight. In the adult human eyeball the A-P diameter is about 24 mm. The human eyeball has three principle layers:

a. Outer protective layer, sclera
b. Middle vascular layer, choroid (uveal tract)
c. Inner neural retina (lines the posterior 2/3rd of the choroid).

The light rays enters through the transparent cornea (Sclera is modified anteriorly to form transparent cornea). The crystalline lens is a transparent structure held in place by suspensory ligament (zonule). The zonule is attached to thickened rim of smooth muscle, the ciliary body. The functions of the ciliary body are:

a. Formation of aqueous humor
b. Keeps lens in position.

The ciliary body contains circular and longitudinal muscle fibers that attach near the corneoscleral junction. In front of the lens, lies the pigmented and opaque iris (colored portion of the eye). Iris has two sets of smooth muscles:

a. Sphincter pupillae (circular) constricts the pupil and is supplied by parasympathetic fibers through oculomotor nerve (nucleus is Edinger-Westphal).
b. Dilator pupillae (radial) is supplied by sympathetic fibers.

#### *Retina*

The retina extends from the margin of the optic disk to just behind the ciliary body where it ends abruptly as a dentated border known as ora serrata. It is organized in 10 layers and contains the rods and cones, which are the visual receptors (Fig. 12.2).

Retina has four types of neurons; bipolar cells, ganglion cells, horizontal cells and amacrine cells. The rods and cones which are next to the choroids, synapse with bipolar cells, and the bipolar cells synapse ganglion cells. The axons of ganglion cells converge and leave the eye as the optic nerve. Horizontal

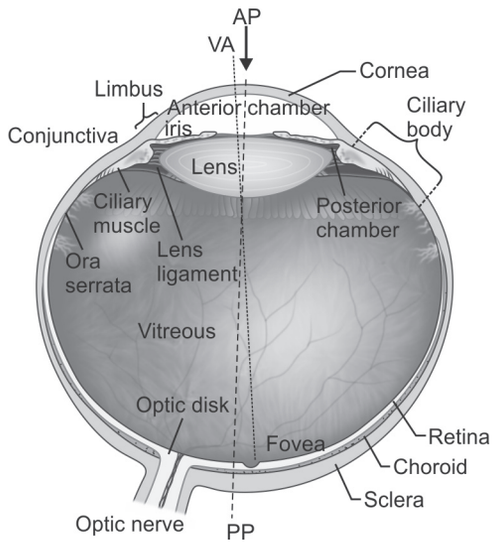



**Fig. 12.1:** Structure of eye

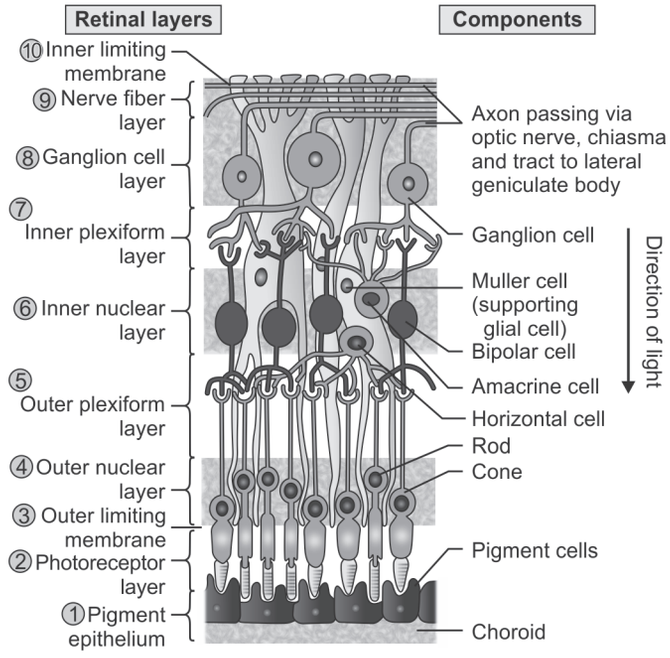



**Fig. 12.2:** Layers of retina

cells connect receptor cells to other receptor cells in the outer plexiform layer. Amacrine cells connect ganglion cells to one another in the inner plexiform layer via processes of varying length and patterns. The neural elements of retina are bound together by glial cells called Muller cells. The processes of these cells form an internal limiting membrane on the inner surface of the retina and an external limiting membrane in the receptor layer. Optic nerve leaves retina from optic disk which lies 3 mm medial to and slightly above posterior pole.

### Fundus Oculi/Fundus

The posterior part of interior of the eyeball is called fundus oculi or fundus. The fundus can be examined by ophthalmoscope. The fundus has two important structures:

#### Optic Disk/Blind Spot

It is situated near the center of the posterior wall of eyeball. Optic disk (1.5 mm in diameter) is formed by the convergence of axons from ganglion cells. It contains all the layers of retina except rods and cones. Therefore, it is insensitive to light (object is not seen if image falls on this area). Because of this, the optic disc is known as blind spot.

#### Macula Lutea/Yellow Spot

Near the posterior pole of the eye is a yellowish pigmented spot called macula lutea (5.5 mm in diameter). The central 1.5 mm of the macula is termed as fovea, which has a small, central depression called *foveola*. The fovea is region of greatest acuity of vision as it contains:

a. Only cones
b. Each cones directly relay to a single cone
c. Wide presentation in occipital primary visual area
d. All layers of retina are shifted aside leaving cones to be hit directly by the cones.

### Vitreous Humor

Space between lens and the retina is filled primarily with a clear gelatinous material called vitreous humor containing water, collagen fibrils, mucopolysaccharides and hyaluronic acid.

#### Functions

a. Prevents collapse of the eyeball.
b. Helps in maintaining normal intraocular pressure.
c. Keeps intraocular structures in position and thus helps in normal positioning of image on retina.

### Aqueous Humor

Aqueous humor is a thin clear liquid that fills the space between the lens and cornea. It is produced in the ciliary body by ultrafiltration and active transport from the plasma at the rate of 2 cu.mm/min. It flows through the pupil and fills the anterior chamber of the eye. It is normally reabsorbed through a network of trabaculae into the canal of Schlemm and uveoscleral outflow (venous channel at the junction between iris and cornea). Refractive index of aqueous humor is 1.336 and pH is 7.1– 7.3. The space between the lens and cornea is divided into anterior and posterior chamber by iris. Space between iris and cornea is anterior chamber, space between iris and lens is posterior chamber. Both the chambers are filled with aqueous humor and they communicate with each other through the pupil.

#### Functions

a. Helps to maintain normal intraocular pressure.
b. It is the 2nd medium of refraction.
c. Provides nutrition to cornea and lens.
d. Takes the place of lymph that is absent in eye.

#### Contents

Protein, electrolytes ($Na^+$, $K^+$, $HCO_3^-$, $Cl^-$), non-electrolytes (glucose, urea and uric acid), organic acid (ascorbic acid, lactic acid and hyaluronic acid), dissolved $O_2$.

#### Mechanism of Formation

Mainly ultrafiltration and some amount by active secretion.
*Circulation of aqueous humor:* Formed in posterior chamber by ciliary processes.

Posterior chamber → pupil → anterior chamber → canal of Schlemm (at the limbus) → episcleral venous plexus. Circulation is necessary for both metabolic process and to regulate the intraocular pressure.

***Note:*** Any disturbance in this normal flow may increase the intraocular tension leading to glaucoma.

### Glaucoma

It is a degenerative disease in which there is loss of retinal ganglia cells. Obstruction of canal of Schlemm leads to increased intraocular pressure. Increased intraocular pressure does not cause glaucoma but it worsens glaucoma. There are two types of glaucoma:

### *Open Angle Glaucoma*

Here the cause of increased pressure is decreased permeability through the trabecular meshwork, through which aqueous humor is drained.

### *Angle-closure Glaucoma*

Here there is forward movement of iris, which obliterates the anterior chamber angle (angle between the iris and the cornea) thereby block the opening of trabecular meshwork at the angle.

***Note:*** Normal intraocular pressure is 10–21 mm Hg. Pressure in venous plexus is 10–15 mm Hg. This difference helps in continuous drainage of aqueous humor to venous plexus. The two important factors maintaining normal intraocular pressure are rate of formation and rate of reabsorption.

## Visual Process

### *Receptors*

Visual pathway starts from receptors that respond to electromagnetic stimulation. Each rod and cone (Fig. 12.3) is divided into an outer segment, an inner segment that includes a nuclear region and a synaptic zone. The outer segments are modified cilia and are made up of regular stacks of flattened saccules or disks composed of membrane. These saccules and disks contain the photosensitive compounds that react to light, initiating action potentials in the visual pathways. The inner segments are rich in mitochondria. The rods are named for the thin, rod like appearance of their outer segments. Cones generally have thick inner segments and conical outer segments (Table 12.1).

### ***Photoreceptor Mechanism***

Visual or phototransduction is the process by which light energy is converted into receptor potential in visual receptors. The potential changes that initiate action potentials in the retina are generated by the action of light on photosensitive

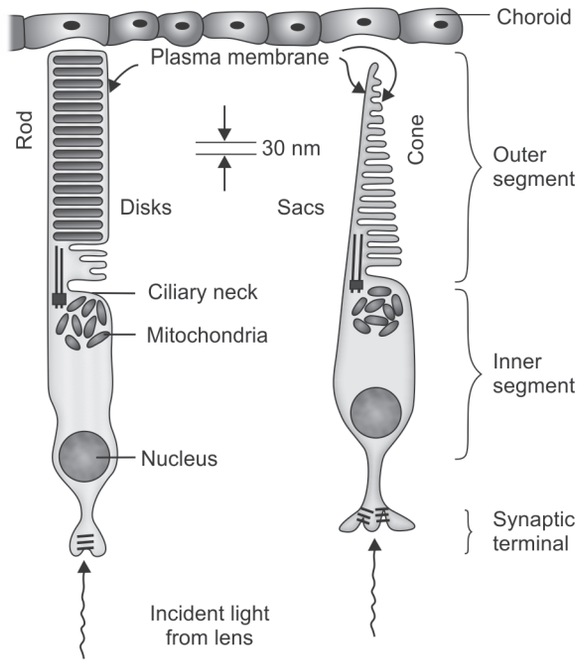



**Fig. 12.3:** Electron microscopic appearance of rods and cones

compounds in rods and cones. The conformational change which happens when light falls on these substances triggers a sequence of events that initiate generation of action potential.

***Ionic basis***

In the dark $Na^+$ channels in the outer segments of the photoreceptors are kept open by cGMP, so there is a steady current flow from the inner to the outer segments of the rods. The steady current also flows in the synaptic ending of the photoreceptors. Light leads to increased conversion of cGMP to 5′–GMP, resulting in the closing of $Na^+$ channels (due to decrease in concentration of cGMP). This decreases current flow and resulting hyperpolarization generates local graded potentials (generator potential) in the synaptic terminal of the photoreceptor. In the dark, retinine1 in rhodopsin is present in 11 *cis* configuration (Figs 12.4 and 12.5).

**Table 12.1: Difference between rods and cones**

| *Rods* | *Cones* |
|---|---|
| Outer segment is rod shaped with regular stocks of membranes disks. | Outer segment is cone shaped. |
| Disks or saccules are separated from the cell membrane. | Disks are infoldings of cell membrane. |
| Has photo pigment called rhodopsin. It contains opsin (scotopsin) and vitamin C. | Three types of cone pigments; erythrolabe (red), cyanolabe (blue), chlorolabe (green). |
| Except in fovea, rods predominates. | Abundant in fovea. |
| Helps in dim light vision. | Helps in bright light vision, color vision, visual acuity. |
| There are 120 million rods. | There are 6 million cones. |

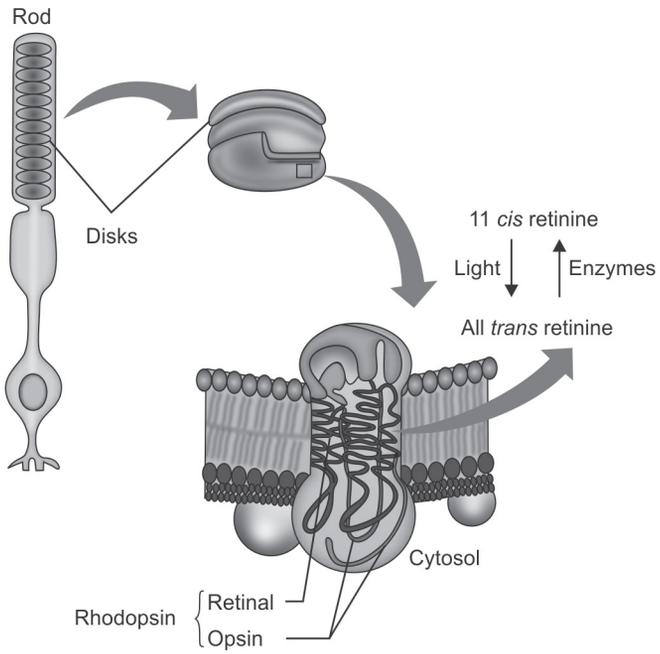



**Fig. 12.4:** Ionic basis of photoreceptor mechanism

**"Development of receptor potential or phototransduction (Fig. 12.6").**

It is a local graded potential generated in the ganglion cells only. The sequence of events involved in phototransduction of rods and cones are:

Light stimulus → structural changes in the retinine1 of rhodopsin (11 *cis* retinine → all transretinine) → conformational change of opsin → activation of tiransducin (G protein; Gt1 in rods and Gt 2 in cones) → α subunit separates from G protein → activation of phosphodiesterase converts cGMP → 5'GMP → decreased intracellular concentration of cGMP → closure of $Na^+$ channels → hyperpolarization of receptor → decreased release of synaptic transmitter (glutamate) cause disinhibition of bipolar cells and thus an action potential develops in ganglion cells.

## Dark Adaptation

When a person enters a dark room from a brightly lit outdoor, at first he sees nothing but gradually gets adapted to the dark.

*Reason:* In bright light, vision was only due to cones. Cones have high threshold for stimulation. So when the person enter

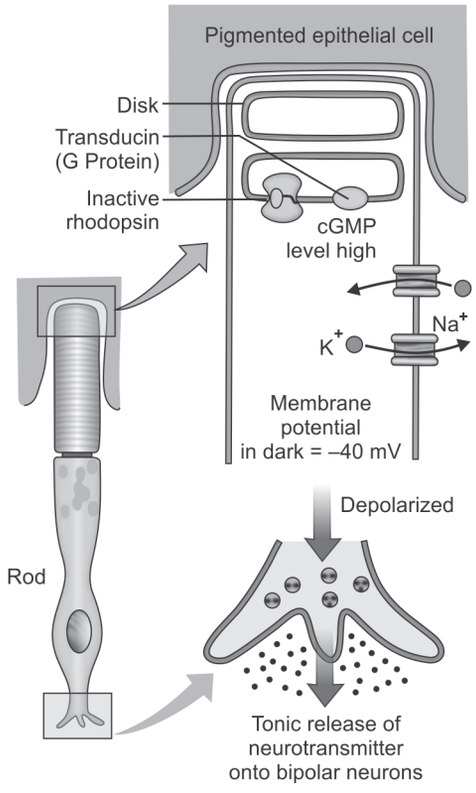



**Fig. 12.5:** Events involved in the depolarization step (in dark) of phototransduction in rods and cones

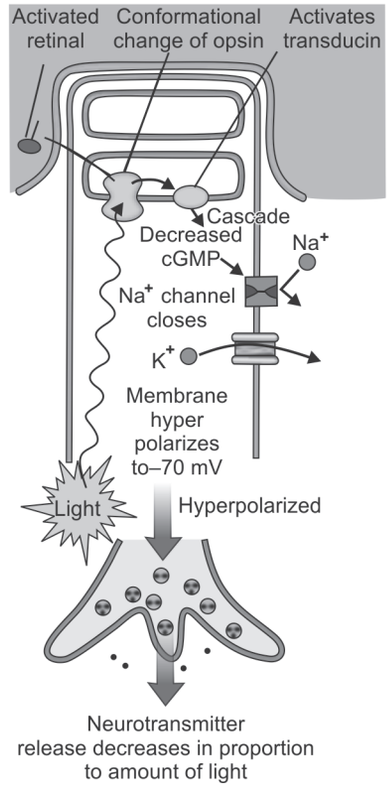



**Fig. 12.6:** Events involved in the hyperpolarization (activation) step of phototransduction in rods and cones

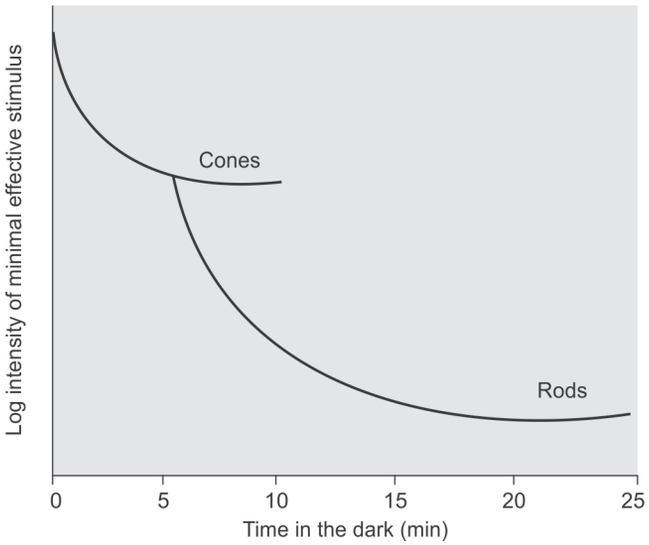



**Fig. 12.7:** The curve shows the change in the intensity of a stimulus necessary to just excite the retina in dim light as a function of the time the observer has been in the dark

darkroom, the low intensity light that is available in the dark is unable to stimulate cones, but visual perception improves quickly at first and more slowly thereafter. This decrease in visual threshold and increase in sensitivity of eye to light is dark adaptation.

*There are two components for this:*

1. *Fast response:* This is first drop in visual threshold and is rapid due to dark adaptation of cones. This is called paradoxical adaptation of cones. Its duration is 4–5 min.
2. *Slow response:* Further drop in visual threshold occurs over a period of 20–25 min due to dark adaptation of rods. Time for dark adaptation depends on time taken for resynthesis of rhodopsin.

### *Important Changes*

a. Dilatation of pupil (mydriasis).
b. Change of photoreceptors from cones to rods.
c. Resynthesis of rhodopsin (occurs when the activated rhodopsin is inactivated by the enzyme rhodopsin kinase thereby a reversal of all reactions occurs).

## Visual Acuity

It is the degree to which the details and contours of objects are perceived. It is usually defined in terms of the minimum separable, i.e. the shortest distance by which 2 lines can be separated and still be perceived as 2 lines. It is tested using snellen letter charts. Normally, snellens letter charts are viewed at a distance of 20 ft (6 m). It is 20/20 normally.

### *Visual Fields*

Visual field of each eye is the portion of the external world visible out of that eye. It can be mapped using perimeter. The extent of normal visual field with a 5 mm white color object is superiorly 50°, nasally 60°, inferiorly 70°, temporally 90°.

### *Duplicity Theory*

The rods are extremely sensitive to light and they are receptors for night vision (scotopic vision). Cones have high threshold for stimulation (photopic vision), i.e. there are two types of inputs from rods and cones to central nervous system. The existence of these two types of inputs working maximally under different degrees of stimulation is known as duplicity theory.

## Optics of Eye

When a ray of light passing from one media to another having different refractive index, it refracts or bends; greater the difference in refractive index greater will be the refraction. Light passes through the following refractive medias: Cornea → Aqueous humor → Lens → Vitreous humor.

Power of lens (in diopter) = 1/f (in meter)

All parallel rays that stike on biconvex lens get refracted and converge to a point; this point is called focus. Difference between optical center of lens and focus is called focal length.

### *Reduced Eye*

Due to the differences in the refractive indices of the eye structures, the refraction of light is 'complex'. Therefore, 'compound' eye refraction can be simplified as reduced or schematic eye as proposed by listing. The reduced eye of listing is 24 mm long in AP diameter (Fig. 12.8). It consists of a single refracting plane (resultant of all refractive media in the eye)

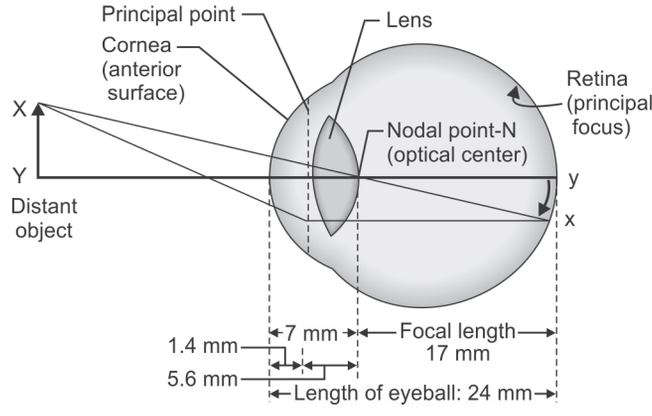



**Fig. 12.8:** Reduced/schematic eye

situated 1.5 mm behind the anterior surface of cornea and a single nodal point N (Nodal point-center of optical system). A ray passing through nodal point suffers no refraction. In Listing's reduced eye, the nodal point is 17 mm anterior to retina (focal length of the optical system). Hence, power of the single lens of Listing's eye (equivalent to combined powers of all lenses of natural eye) is about 59 D (1000/17).

## Visual Pathway

It is a three order neuronal pathway. The visual fibers arise in the layer of nerve cells (bipolar and ganglion cells) in the retina.

***1st order neuron***

These are bipolar cells with which receptors synapse. It is of 3 types: rod bipolar cell with rods, flat bipolar cell with cones, midget bipolar cell. Bipolar cell synapse with ganglion cell.

***2nd order neuron***

These are ganglion cells. Ganglion cells are of two types: large magno and small parvo. Axons of ganglion cells emerge out of the eyeball as optic nerve. Optic nerve consists of two groups of fibers:

a. Fibers from the nasal half of retina which carry light sensation from temporal half of field of vision.
b. Fibers from temporal half of retina which carry light sensation from nasal half of field of vision.

Partial crossing of optic nerve fibers occurs at optic chiasma and two optic tracts are thus formed. The optic tract ends in lateral geniculate body (LGB).

***3rd order neurons***

These arise from LGB and ends in visual cortex. LGB has 6 layers, from the layer 1 and 2 of LGB magnocellular pathway and from layers 3–6 parvocellular pathway projects to visual cortex (Fig. 12.9).

Magnocellular pathway is concerned with detection of movement, depth, flicker. Parvocellular pathway is concerned with color of object, texture, shape and other fine details of object. Some fibers in intralaminar region of LGB ends in blobs in visual cortex and is concerned with color vision only.

Pathways ends in 1° visual area 17, visual association area 18 (concerned with depth perception, visual orientation, relay of information), area 19 (occipital eye field for conjugate movement of eye to opposite side) and area 8 (frontal eye field for visual reflexes).

***Note:*** Some fibers from optic tract deviate from main tract and end in:

a. Midbrain (which mediate visual reflexes).
b. Suprachiasmatic nucleus (which mediate light and dark cycles).

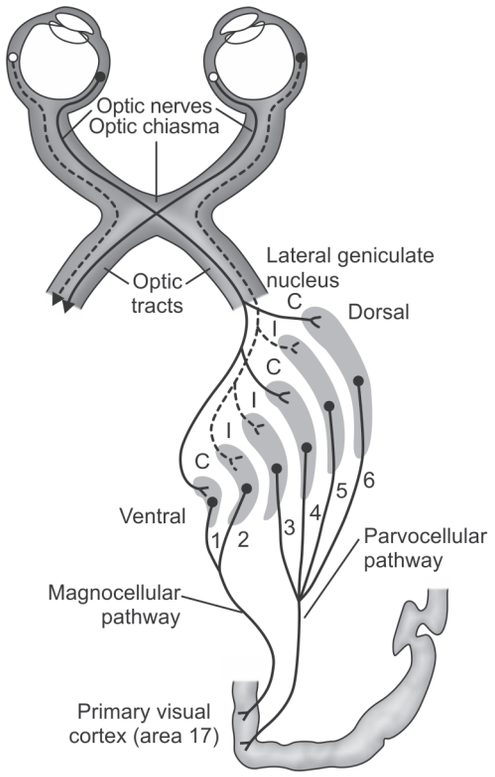



**Fig. 12.9:** Visual pathway

### *Effects of Lesion of Optic Pathway*

The effect of lesion of the visual pathways are described in term of field of vision. The following definitions will help to understand these defects.

***Anopia:*** Complete loss of visual field in an eye.

***Hemianopia:*** Blindness of ½ of visual field.

***Quadrant anopia:*** Loss of ¼ of visual field.

***Homonymous hemianopia:*** When same side (right/left) of visual field of both eyes are lost.

***Heteronymous hemianopia:*** When different sides of field of vision of both eyes are lost.

***Scotoma:*** Loss of vision in eye which is confined to center of visual field.

1. *Lesion of optic nerve (at A in Fig. 12.10):* Anopia of affected side.
2. *Lesion of optic chiasma (at B in Fig. 12.10):* Heteronymous hemianopia.
3. *Lesion of optic tract (at C in Fig. 12.10):* Homonymous hemianopia.
4. *Lesion of LGB:* Homonymous hemianopia.
5. *Lesion of optic radiation/Geniculocalcarine tract:* Homonymous hemianopia with macular sparing.
6. *Lesion of occipital cortex:* Scotoma/quadrant anopia

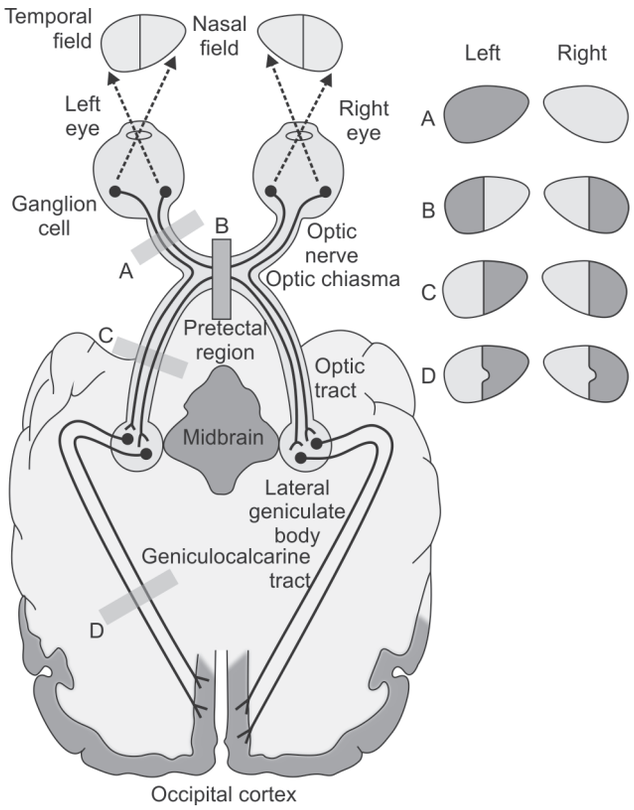



**Fig. 12.10:** Efffect of lesion on optic pathway

### *Macula Sparing (at D in Fig. 12.10)*

Loss of peripheral vision with intact macular vision. This is because the macula has large area of representation in the occipital lobe and it is greater than that of peripheral part of the retina.

### *Binocular Vision*

The central parts of the visual fields of the two eyes co-incide, therefore, anything in this portion of the field is viewed with both eyes and is fused at the cortical level into a single image and is important in depth perception.

## Visual Reflexes

### *Light Reflex (Direct, Indirect)*

When light is directed to one of the eye, pupil of that eye constricts, it is called direct/pupillary light reflex. In addition it also results in the constriction of pupil of the opposite eye, called as indirect/consensual light reflex both sides it forms the basis of indirect light reflex.

***Pathway of Light Reflex***

Light sensation → optic nerve → optic chiasma → optic tract → enter midbrain via superior colliculus → pretectal nucleus of both sides → Edinger-westphal nucleus of 3rd cranial nerve (parasympathetic) → ciliary ganglion → short ciliary nerve → sphincter pupillae of iris.

Effect is constriction of pupil of both sides.

### *Accommodation Reflex*

Accommodation is defined as the ability of the eye to focus an object at varying distances. It is a reflex action. When a person changes his gaze from distant object to a near object, three adjustments are made in the eyeballs (Flow chart 12.1).

a. Convergence of eyeball due to the contraction of medial recti.
b. Constriction of the pupil due to contraction of constrictor pupillae of iris.
c. Increase in anterior curvature of lens due to contraction of ciliary muscle.

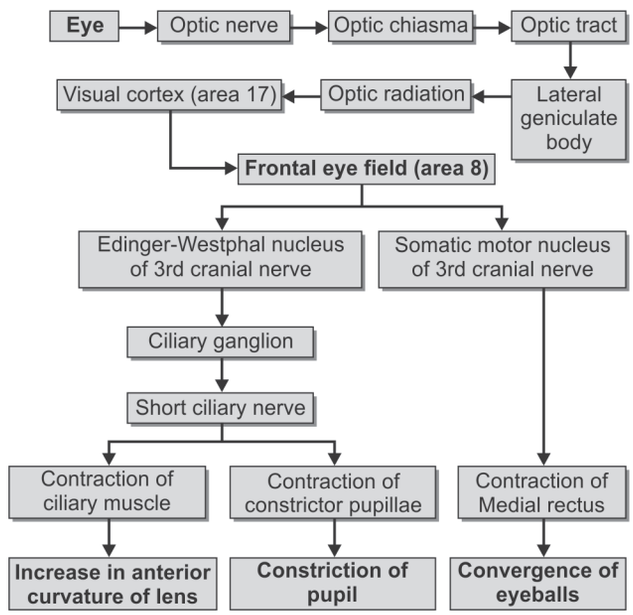
This is also called near response.

***Pathway***

*Afferent:* Visual impulse from retina pass through the optic nerve, optic chiasma, optic tract, LGB and optic radiation to visual cortex. From here, the association fibers carry the impulses to the frontal lobe.

*Center:* Center for accommodation lies in the frontal eyefield, situated in the frontal lobe area 8.

**Flow chart 12.1:** Schematic diagram of accommodation reflex



*Efferent pathway*

a. *Efferent fibers to ciliary muscle and sphincter pupillae:* From area 8, the corticonuclear fibers pass via internal capsule to the Edinger-Westphal nucleus of 3rd cranial nerve. From here, the preganglionic fibers pass through the 3rd cranial nerve to ciliary ganglion. The postganglionic fibers from ciliary ganglion pass via the short ciliary nerves and supply the ciliary muscle and sphincter pupillae.
b. *Efferent fibers to medial rectus:* Some of the fibers from frontal eyefield terminate in the somatic motor nucleus of 3rd nerve. The fibers fro motor nucleus supply the medial rectus.

## Applied Aspects

### *Argyll Robertson Pupil*

In this condition pupillary constriction in response to a light stimulus is absent or decreased while the response to accommodation is present. Pupillary reflex pathway is dorsal to the pathway for near response. Cosequently, even if the light response is lost the response to accommodation still remains intact. Usually seen in midbrain lesion. The effects can be remembered like this (ARP—Accommodation reflex present, PRA—Pupillary reflex absent).

### *Strabismus or Squint*

Normally visual axis of the two eyes are parellel to each other and this alignment is maintained in all positions of gaze. A misalignment of the visual axis of the two eyes is called squint or strabismus.

### *Near Point of Vision*

Nearest point to the eye at which an object can be clearly seen with maximal accommodation.

### *Far Point*

Under resting condition, eye is adapted for distant vision, there is complete relaxations of lens. So parallel rays are focused in retina. At this point power is 59 D. This is taken as zero position of object.

## Common Errors of Refraction

The errors of refraction (Fig. 12.11) can be studied under two groups. Normal eye is emmetropic (emmetropia is defined as the normal refractive condition of the eye in which the accommodation is relaxed and all the parallel rays of light are brought accurately to a focus upon the retina).

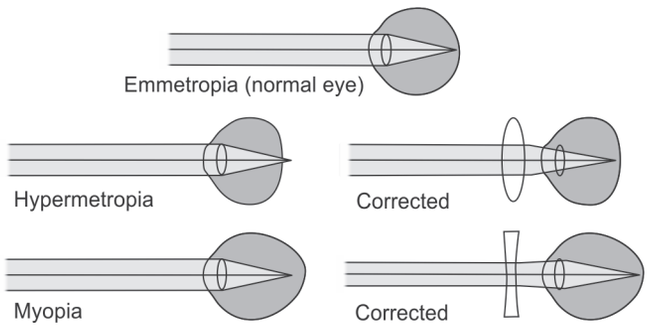



**Fig. 12.11:** Common errors of refraction

### *Pathological Errors*

***Myopia /shortsightedness***

Parallel rays are focused in front of retina. Person fails to see distant objects but near vision is normal.

*Causes*

i. Increased A-P diameter of eyeball.
ii. Changes in curvature of lens and cornea.

*Correction:* Using biconcave lens.

***Hypermetropia/longsightedness***

Parallel rays are focused behind the retina.

*Causes*

i. Smaller A-P diameter of eye.
ii. Abnormalities in curvature of lens and cornea.

*Correction:* Using biconvex lens.

***Astigmatism***

In some cornea, curvature varies from meridian to meridian. Refractive index of astigmatic cornea is different in different meridians, all the rays are not focused in retina and the image is blurred.

*Correction:* Using cylindrical lens.

***Presbyopia***

Clinical condition seen after 40 years due to the loss of accommodation.

*Causes:* Loss of elasticity of crystalline lens due to changes in lens protein. So lens become rigid and during accommodation, though the ciliary muscles are contracting, curvature of lens is not changed and person cannot see near objects when held at normal distance.

*Correction:* Use convex lens.

### Physiological Errors of Refraction

***Spherical aberration***

When pupil is fully dilated, rays passing through peripheral portion of lens are not focused on the retina as the power of lens at extreme periphery is not identical to that at the center due to difference in curvature at the center and periphery. Thus, vision is blurred.

***Chromatic aberration***

At the periphery of lens, rays of different wavelengths are refracted differently.

***Cataract***

As age advances lens or its capsule become opaque and fails to transmit light due to the denaturation of lens fiber protein; elevated by exposure to strong sunlight and UV rays.

*Correction:* Surgical removal and artificial insertion of lens.

***Aphakia***

Condition where lens is absent. It may congenital or surgical.

***Note:*** *Amplitude of accommodation:* This is the difference in refractive power of the eye between the two states, complete relaxation and maximal accommodation.

## Color Vision

### The Young-Helmholtz Theory

According to this theory, there are 3 kinds of cones that are maximally sensitive to one of the 3 primary colors and when all the 3 primary colors are mixed in correct proportion, sensation of white is produced. Normal person is said to be trichromatic.

### Color Blindness

It is a clinical condition when people are unable to distinguish certain colors or have color weakness. It is an X-linked recessive disorder.

### Types

***Monochromatism***

Only one type of cone is present and other two are absent.

***Dichromatism***

Two types of cones are present but one is absent. It is of three types:

a. *Protanopia:* Red sensitive cone is absent.
b. *Deutranopia:* Green sensitive cone is absent.
c. *Tritanopia:* Blue sensitive cone is absent.

If cones are present and functioning is defective, it is called *anomaly* and it is of 3 types: protanomaly, deutranomaly and tritanomaly. Color blindness is tested using ishihara charts.

***Achromatopsia***

Color blindness due to lesion of V8 (Projection area for color vision).

***Nyctalopia/night blindness***

Prolonged deficiency of vitamin A leads to anatomic changes in the rods and cones followed by degeneration of neural layers of the retina causing visual abnormalities leading to nyctalopia.

***Note:*** Individual taking sildenafil (viagra), used for treating erectile dysfunction cause trasient color blindness as it inhibit the enzyme phosphodiesterase.

# AUDITION

## Structure of Ear

The ear consists of 3 parts namely external ear, middle ear and internal ear. The external ear is formed of 2 parts: auricle/pinna and the external auditory meatus (Fig. 12.12).

### External Ear (24 mm Length)

External ear funnels sound waves to the external auditory meatus. From the meatus, the external auditory canal passes inward to the tympanic membrane.

### Middle Ear

The middle ear is an air-filled cavity in the temporal bone that opens via the auditory (Eustachian) tube into the nasopharynx and through it to the exterior. The 3 auditory ossicles, the

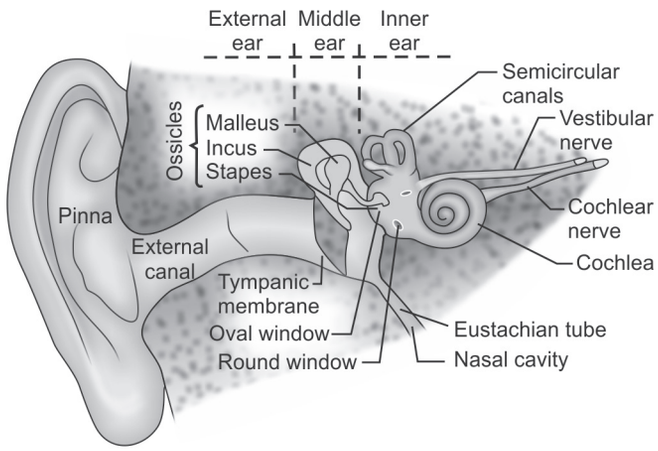



**Fig. 12.12:** Structure of ear

malleus, incus, and stapes are located in the middle ear. The ear ossicles are arranged in the form of a chain extending across the middle ear from the tympanic membrane to oval window. Function of ear ossicles is to magnify the intensity of sound waves to about 1.2-1.3 times.

### Functions of Middle Ear

***Tympanic membrane as resonator***

It acts as a resonator, i.e. it starts vibrating (in and out movements) freely when the sound waves strike.

***Impedance matching***

The sound waves have to pass from the air to the liquid medium in the internal ear. So there will be resistance to the transmission of sound waves. This is overcome by increasing the pressure of sound waves at the level of oval window. The mechanisms are:

a. Ear ossicles move as a single unit. The size of handle of malleus is less than the size of incus, while size of stapes is less than the incus; moreover handle of malleus is longer than the long processes of the incus. The auditory ossicles thus function as a lever system that converts the resonant vibrations of the tympanic membrane into movements of the stapes against the perilymph-filled scala vestibuli of the cochlea. The lever action of the malleus and incus multiplies the intensity of sound waves to about 1.3 times.
b. Effective surface area of tympanic membrane is 50–54 mm sq and that of oval window is 3–4 mm sq, i.e. there is a reduction in surface area by 17 times at the level of oval window.

Both these mechanisms lead to corresponding increase in sound pressure at the oval window. So total increase in sound pressure is about 22 times (17 × 1.3).

***Tympanic/acoustic/attenuation reflex***

It is a protective reflex against the loud sound. Loud sound initiates a reflex contraction of the middle ear muscles.

a. Contraction of tensor tympani pulls the handle of malleus medially which makes tympanic membrane more taut and decreases the vibration of tympanic membrane. Tensor tympani is the muscle attached to neck of malleus. It is supplied by 5th CN.
b. Stapedius is attached to neck of stapes which is supplied by the 7th CN. Its contraction pulls footplate of stapes away from the oval window, thus, preventing transmission of sound waves to internal ear.

Both of these muscles contract reflexly in response to loud sound and thus excessive sound is prevented from going to oval window. This is known as tympanic/acoustic/attenuation reflex.

***Equalization of pressure on either side of tympanic membrane***

It equalizes the pressure on both sides of tympanic membrane with the help of eustachian tube. The eustachian tube is usually closed, but during swallowing, chewing and yawning it opens and equalizes the pressure on both sides of tympanic membrane.

## Inner Ear

The inner ear (labyrinth) is made up of two parts; the bony labyrinth and the membranous labyrinth. The bony labyrinth is a series of channels in the petrous portion of temporal bone. The membranous labyrinth is present inside these channels and it is surrounded by a fluid called perilymph. This membranous labyrinth more or less duplicates the shape of bony channels and is filled with a fluid called endolymph. There is no communication between the spaces filled with endolymph and those filled with perilymph.

Internal ear is divided into 3 chambers; scala vestibuli, scala media and scala tympani by 2 membranes: Reissner's and Basilar membrane (Figs 12.13 and 12.14). Scala vestibuli and tympani are filled with perilymph and are continuous at the

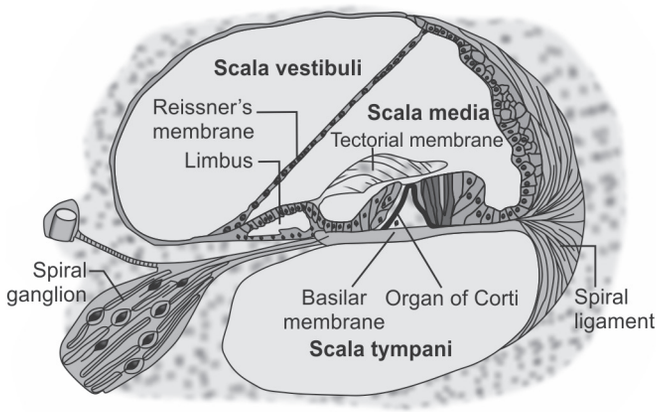



**Fig. 12.13:** Vertical section through cochlea

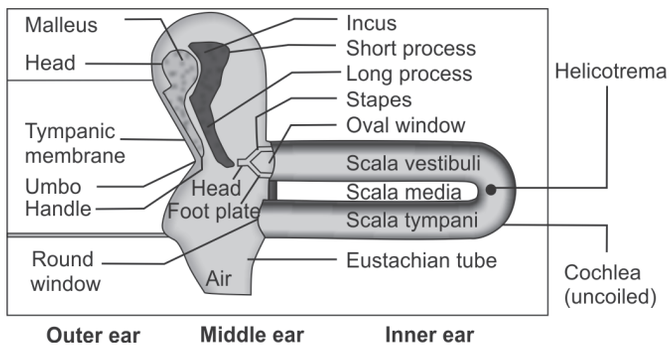



**Fig. 12.14:** Schematic diagram showing outer, middle and inner ear

apex (helicotrema). Scala media is continuous with membranous labyrinth and is filled with endolymph.

### *Organ of Corti*

It is located on the basilar membrane and it contains the hair cells. Hair cells are receptor cells that transduce sound energy into electrical energy. It extends from the apex to the base of the cochlea and has a spiral shape. There is one organ of Corti in each ear. The processes of hair cells pierce the tough, membrane-like reticular lamina that is supported by rods of Corti. The hair cells are arranged in 4 rows; 3 rows of outer hair cells lateral to the tunnel formed by rods of Corti and 1 row of inner hair cell medial to the tunnel (Fig. 12.15). There are 3500 inner hair cells which are important for fine sensory transduction. There are about 20,000 outer hair cells which is responsible for detecting the presence of sound.

Outer hair cells are capped with gelatinous material called tectorial membrane. Cell bodies of afferent neuron that surround the bases of hair cells are located in the spiral ganglion. About 90–95% fibers innervate inner hair cells and only 5–10% innervates outer hair cells. In each hair cell, there are about 30–50 hairs called stercocilia. It has actin and myosin. Very fine processes called tip links tie the tip of each stercocilia to the side of its higher neighbor. At the junction, there are cation channels which are mechanically sensitive. When hair cells move in one direction towards longer stercocilia, channels open and there is $Ca^{2+}$ and $K^{+}$ influx. If hair cells move in opposite direction the ion channel closes.

*Supporting cells are:*

a. Inner phalangeal cells (for supporting inner hair cells).
b. Outer phalangeal cells/dieter's cell (support outer hair cells).

The outer phalangeal cells are supported by Hansen's cells which is again supported by Claudius cells. The junctions between hair cells and other supporting cells are tight junctions to prevent mixing of endolymph and perilymph.

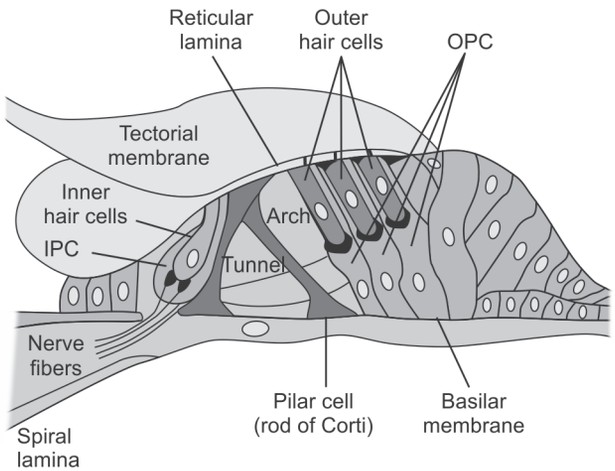



**Fig. 12.15:** Organ of corti

### ***Sound Transduction***

Sound waves which enter the cochlea gets transmitted along the scala vestibuli and spreads towards helicotrema. At the same time sound waves are also transmitted to fluid in other chambers. This will lead to vertical up and down movement of basilar membrane. This results in up and down and side to side movement of hair cells. The processes of hair cells project into the endolymph whereas the bases are bathed in perilymph.

### *Mechanism*

When tip links pull stercocilia the ion channels open, there is $K^{+}$ influx → receptor potential in hair cells → $Ca^{2+}$ influx causes depolarization → release of neurotransmitter (glutamate) into synaptic cleft between receptor cell and afferent sensory nerve → neurotransmitter binds with specific receptor on the sensory nerve → ligand gated ion channels open → action potential in cochlear division of 8th cranial nerve → auditory pathway.

## Auditory Pathway

The afferent fibers in the auditory division of the 8th cranial nerve is the 1st order neuron and it ends in dorsal and ventral coclear nucleus (Fig. 12.16). There are three sets of fibers from this level:

1. Dorsal cochlear nucleus → 2nd order fibers cross to opposite side → ascend and end in inferior colliculus (many collaterals given to reticular formation) → 3rd order neurons arise → end in medial geniculate body of same and opposite → 4th order neurons arise → end in auditory cortex (primary auditory area 41, association area 20, 21, 22).
2. Ventral cochlear nucleus → 2nd order fibers cross to opposite side → end in trapezoid body → 3rd order neuron arises → end in inferior colliculus → 4th order neuron arises → medial geniculate body (no relay) → end in auditory cortex.
3. Ventral cochlear nucleus → 2nd order fibers end in superior olive → 3rd order fibers arise → ends in medial geniculate body (collaterals to inferior colliculus and reticular formation → 4th order neurons arise → ends in auditory cortex.

### *Efferent Pathway*

Some fibers from cortex descend and ends in outer hair cells.

Neurotransmitter released is ACh, although these inhibitory fibers end in outer hair cells, they actually modify the activity of inner hair cells.

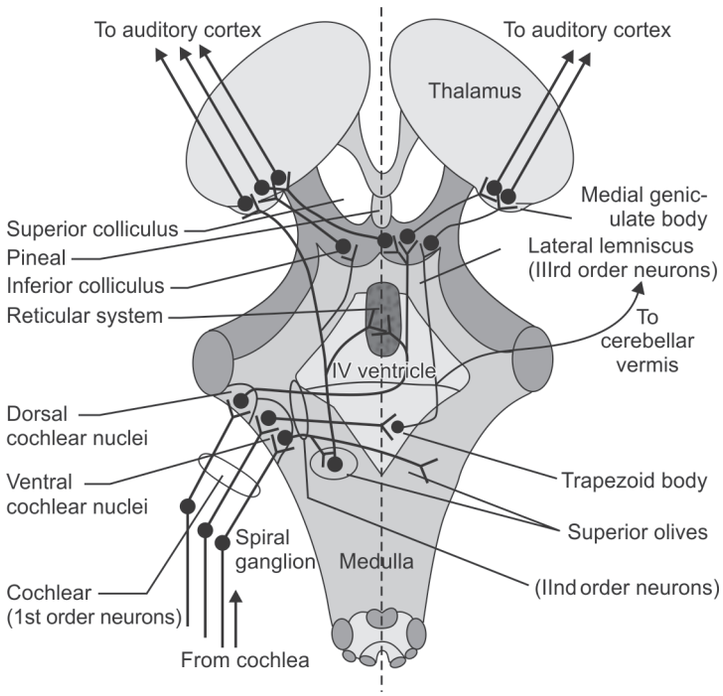



**Fig. 12.16:** Auditory pathway

***Salient features of the pathway***

a. Bilateral representation due to extensive crossing of fibers.
b. There is a descending pathway.
c. Integration of visual and auditory impulse occurs due to connection between superior and inferior colliculus.
d. General arousal as it gives collaterals to reticular formation.

## *Traveling Wave Theory/Place Theory*

The movement of foot plate of stapes set up a series of traveling waves in the perilymph of scala vestibule (Fig. 12.17). Basilar membrane is the mechanical analyzer of sound frequency. The basic pattern of movement of basilar membrane is like a traveling wave. High frequency sound waves produce maximum height at the oval window. Low frequency sound has maximum height near the apex. Correspondingly basilar membrane near the oval window vibrates in response to high frequency sound and basilar membrane near the apex vibrates in response to low frequency. That is different hair cells respond to different frequencies of sound depending upon their location on the basilar membrane. This is applicable to frequencies of 2000–20,000 Hz. Human ear can discriminate sound of frequency between 20–20,000 Hz (Fig. 12.18).

## *Volley's Principle/Frequency Theory*

Volley's principle is applicable for low frequency of sound (less than 2000 Hz). There is a relation between frequency of sound and action potential developed in sensory nerve endings. For low frequency sound, frequency of action potential is less. If greater frequency, a volley of action potential is produced.

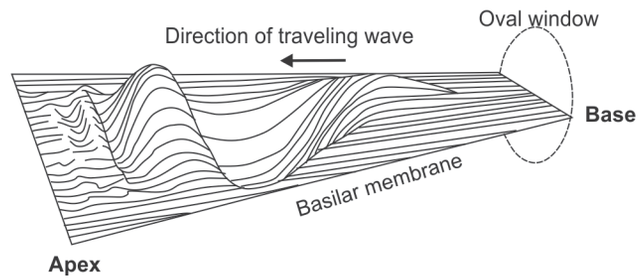



**Fig. 12.17:** Traveling wave theory

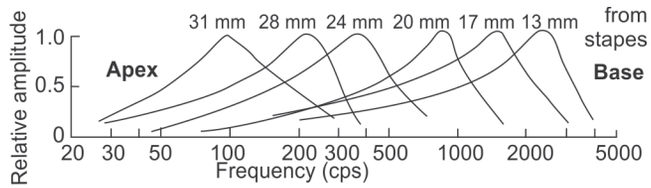



**Fig. 12.18:** Graphical representation of frequency of sound with the amplitude of vibrations in relation to distance from the stapes

## *Masking*

It is a phenomenon to produce inaudibility of one sound by the presentation of another. In audiometry one ear is kept busy while the other being tested by a sound.

## Deafness

Inability of an individual to hear either wholly or partially. Deafness is of two types:

### *Conductive Deafness*

Here the defect is in conduction of sound due to impaired sound transmission.

***Causes***

(a) ear wax, (b) defect in vibration of tympanic membrane, (c) infection of middle ear (otitis media), (d) auto sclerosis, (e) eustachian tube blocked due to common cold.

### *Nerve Deafness*

Due to damage to the hair cells or in the neural pathway.

***Causes***

(a) Hereditary, (b) injury to 8th CN, (c) drugs like streptomycin, (d) vascular cause, (e) industrial noise pollution.

### *Tests for Hearing*

1. Watch test
2. Tuning fork tests (Table 12.2)
3. Audiometry test

Auditory acuity (sharpness of hearing) can be measured with the help of an audiometer. This test helps to assess the degree of deafness and the frequency range in which deafness is most affected. The device consists of the following parts:

a. Electronic oscillator
b. Intensity dial
c. Head phone

***Note:*** *Vestibulo-ocular reflex:* It is actually a reflex that maintains visual fixation on stationary points while the body rotates. When rotation starts, the eyes move slowly in a direction opposite to the direction of rotation, maintaining visual fixation.

*Nystagmus:* The regular and rhythmic to and fro involuntary oscillatory movements of the eyes. Meniere's disease/endolymphatic hydrops. It is a disorder of the inner ear where the endolymphatic system is distented with endolymph.

*Endocochlear/Endolymphatic potential:* An potential difference of about +80 millivolts exists all the time between endolymph and perilymph, with positivity inside the scala media and negativity outside. It is generated by continual secretion of $K^+$ ions into the scala media by the stria vascularis.

## SENSATION OF TASTE

Taste buds are the sense organs for taste. Size of taste bud is about 50–70 μm and they are ovoid in shape with 40 mm diameter. Each taste bud is made of three types of cells (Fig. 12.19):

**Table 12.2: Tests of hearing**

| *Text* | *Method* | *Normal* | *Conductive deafness* | *Nerve deafness* |
|---|---|---|---|---|
| 1. Rinne test | Base of the vibrating tunning fork is placed on the mastoid process until subject no longer hears it (bone conduction), then it is held in the air, next to ear (air conduction). | Subject hears vibrations in air after bone conduction is over. Air conduction is better than bone conduction (Rinne's test positive). | Vibration in air not heard after bone conduction is over, that is bone conduction is better than air conduction (Rinne's test negative). | If partial nerve deafness. Rinne's test is positive. If complete nerve deafness, both air conducted and bone conducted sounds are not perceived. |
| 2. Weber test | Base of the vibrating tunning fork is placed on the vertex of skull in midline or over the mandible. | Both the ears 'hear' the sound equally well. | Sound is better heard in the affected ear. | The 'deaf' ear remains deaf to bone conducted sound and sound is thus better heard and perceived by the normal ear, i.e. 'lateralized' to healthy ear. |
| 3. Schwabach test | Bone conduction of the subject is compared with that of the examiner's assuming that the latter is normal. | Both the subject and examiner 'hear' the sound equally well. | Subject's bone conduction is better than the examiner's. | Subject's bone conduction is worse than the examiner's. |

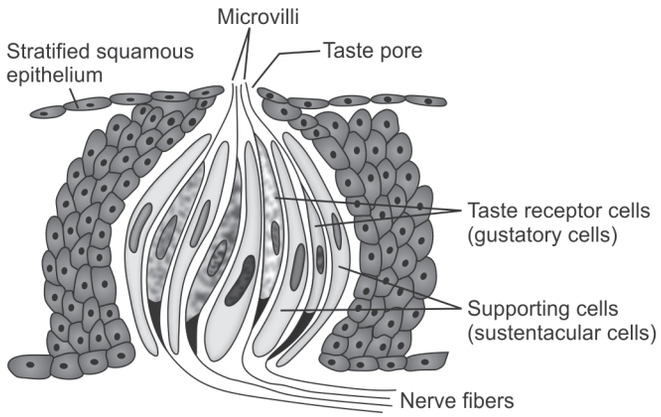



**Fig. 12.19:** Taste receptor (or taste bud)

a. Taste/gustatory cells-type 3 cells.
b. Supporting/sustentacular cells-type 1 and 2 cells.
c. Basal cells: They differentiate into new receptor cells.

Chemoreceptors are present in taste buds on walls of papilla. There are four types of papillae:

### *Fungiform*

They are rounded structures most numerous near the tip of the tongue. It contains five taste buds located on the tip of the papillae.

### *Filiform*

Small conical structures that cover the dorsum of the tongue. No taste buds are present on filiform papillae.

### *Foliate*

These are found occasionally upon the posterolateral surfaces of tongue.

### *Circumvallate*

They are prominent structures arranged in a V on the back of the tongue. They are 10-12 in number. Larger vallate papillae contains up to 100 taste buds located along the sides of the papillae.

Total number of taste buds is 10,000 and its number decreases with age. Taste bud is stimulated only at the tip as the necks of taste cells and sustentacular cells are connected to each other and to the surrounding epithelial cells by tight junctions so that only tip is exposed to oral fluids. At the base of taste bud, afferent nerve fibers are attached. Each taste bud is innervated by 50 nerve fibers.

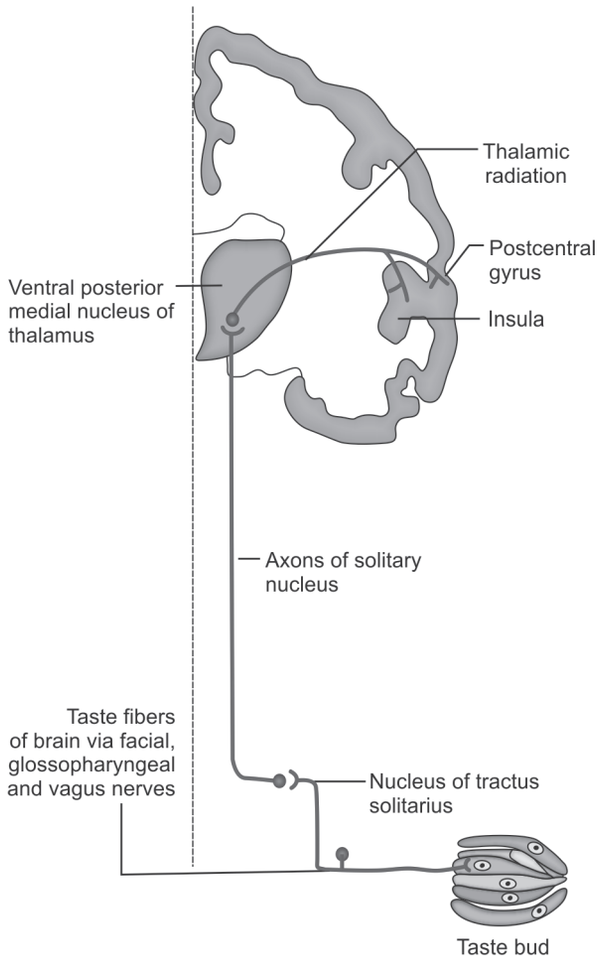



**Fig. 12.20:** Taste pathway

## Taste Pathway

It is a three orders uncrossed pathway (Fig. 12.20). 1st order neurons are:

a. Chorda tympani branch of 7th CN, which carries sensation from anterior 2/3rd of tongue.
b. 9th CN, which carries sensation from posterior 1/3rd of tongue.
c. 10th CN, which carries sensation from areas other than tongue, i.e. epiglottis, pharynx and palate.

From taste cells in taste bud, 1st order neurons arise → reach nucleus tractus solitarius of medulla → 2nd order neurons ascend ipsilaterally in medial lemniscus → end in thalamus (ventral posteromedial nucleus) → 3rd order neurons arise → end in face area of somatosensory cortex in postcentral gyrus. Some fibers end on anterior part of insula.

The basic taste modalities are:

a. Sweet: Receptor is G protein activated gustducin.
b. Bitter: Receptor same as sweet.
c. Salt: Receptors are E NaCs (i.e. epithelium $Na^+$ channels).
d. Sour: Receptors are E NaCs HCN (hyperpolarization activated cyclic nucleotide gated cation channels).
e. Umami (sweet pleasant taste evoked by monosodium glutamate): Receptor is mGluR4 receptor.

***Note:*** Miraculin-taste modifier protein which when applied to tongue makes acid taste sweet.

### *Abnormalities*

1. Ageusia: Absence of taste and it is commonly drug induced
2. Hypogeusia: Diminished taste sensitivity
3. Dysgeusia: Disturbed sense of taste.

## OLFACTION

The olfactory receptor cells are located in a specialized portion of the nasal mucosa, the yellowish pigmented olfactory mucous membrane. Olfactory mucous membrane is constantly covered by mucous which is produced by Bowman's cells, present under the basal lamina of the membrane. Receptors are bipolar neurons with lifespan of 60 days. In between the receptor cells, there are supporting cells and basal cells. Each neuron has a short and thick dendrite with expanded end called as olfactory rod, from these rods 10–20 cilia (unmyelinated process) project to the surface of the mucosa.

Odoriferous substances combine with receptors on surface of cilia. This will initiate G protein coupled reaction, finally leading to opening of $Ca^{2+}$ channels. $Ca^{2+}$ influx initiates receptor potential, then action potential develops which gets transmitted along olfactory nerve.

### *Olfactory Bulb*

Olfactory bulb is the part of cerebral hemisphere located at the base of cerebral cortex, just below the frontal lobe.

In the olfactory bulb, the axons of the receptors enter olfactory bulb via cribriform plate and synapse with primary dendrites of the mitral cells and tufted cells to form the olfactory glomeruli. In addition to mitral and tufted cells, it also contains inhibitory interneurons, i.e. granular and periglomerular cells. Each glomerulus receives information from 26,000 receptors but there are only 24 mitral cells and 68 tufted cells (Fig. 12.21).

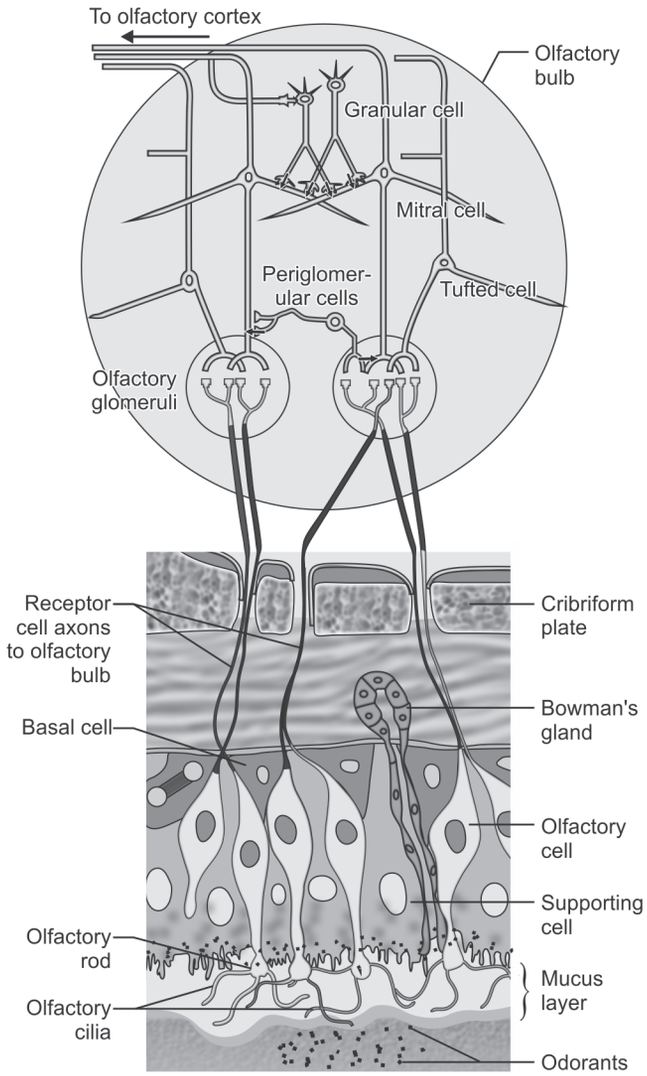



**Fig. 12.21:** Olfactory bulb

### Olfactory Pathway

Olfactory nerve → pierce cribriform plate of ethmoid → reach olfactory bulb → synapse with mitral and tufted cell → axons of mitral and tufted cells form olfactory stria. The olfactory striae are 3 in number (Fig. 12.22) They are:

a. Medial striae (formed by axons of tufted cells)-cross the midline in the anterior commissure to form synapses with granule cells in the opposite olfactory bulb.

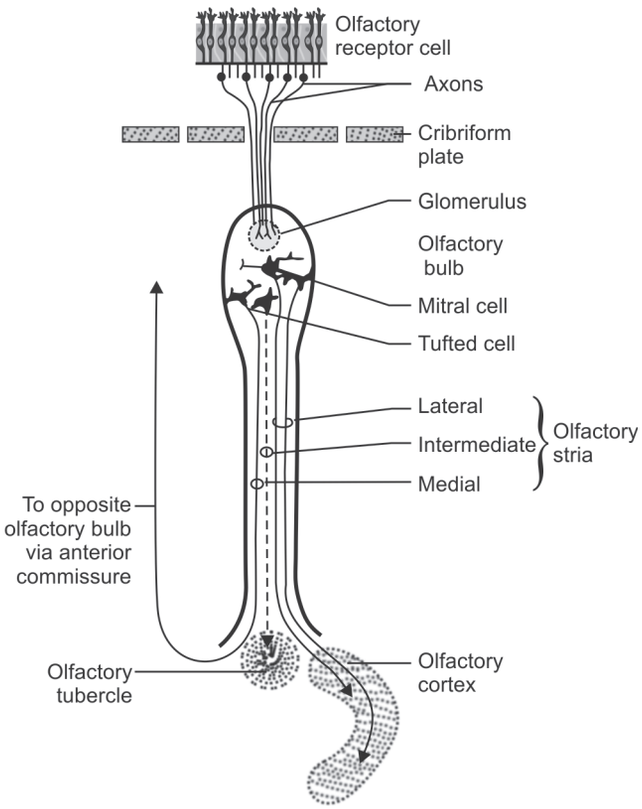



**Fig. 12.22:** Olfactory pathway

b. Lateral striae (formed by axons of mitral cells)-runs to the olfactory cortex on the same side. Olfactory cortex includes the part of limbic system, i.e. the anterior olfactory nucleus, piriform cortex, olfactory tubercle, amygdala and entorhinal cortex.
c. Intermediate striae (other fibers)-ends in olfactory tubercle, and hence with the limbic system.

### *Characteristics of Pathway*

a. No neocortical projections.
b. No relay in thalamus.
c. Receptors are directly in contact with atmosphere.
d. Receptors are tele and chemoreceptors.
e. Rapid and early adapting.

### *Abnormalities*

Anosmia: Complete absence of smell.
Parosmia: Change in character of smell.
Hyposmia: Diminished olfactory sensitivity.
Dysosmia: Distorted sense of smell.

# Section 2

# PRACTICALS

*Chapter*

# 13

# Hematology

## DETERMINATION OF ERYTHROCYTE SEDIMENTATION RATE

### Apparatus

Westergren's pipette, blood sample, Westergren's stand and 3.8% sodium citrate solution. Westergren's pipette is a narrow cylindrical glass tube of 300 mm length with a uniform bore of 2.5 mm. It is open at both ends and is graduated from 0 to 200 above downwards. The anticoagulant used is 3.8% sodium citrate solution in the ratio 4:1, i.e. 4 parts blood and 1 part anticoagulant.

### Principle

When a column of blood taken in narrow tube is kept vertically undisturbed, the red blood cells (RBC's) settle down due to higher specific gravity than plasma. Erythrocyte sedimentation rate (ESR) is the number of millimeters of clear plasma seen above the cell layer, and is expressed in millimeters at the end of 1st hour.

### Mechanism of ESR

Sedimentation occurs in three stages:

*Stage 1 (10 to 15 minutes):* Rouleaux formation (piling of RBC's) and aggregation occurs.

*Stage 2 (40 to 45 minutes):* Sinking of aggregates at constant speed.

*Stage 3 (10 to 12 minutes):* Aggregated cells pack at the bottom of the tube.

### Normal Values (Westergren's Method)

Adult male: 1 to 3 mm at the end of 1 hour
Adult female: 3 to 7 mm at the end of 1 hour
Infants : 0 to 0.5 mm at the end of 1 hour.

#### *Note*

Wintrobe's method can also be used for determination of ESR. However, it is used for determination of PCV. Value will be higher than that in Westergren's method.

*Adult male:* 0 to 9 mm at the end of 1 hour
*Adult female:* 0 to 20 mm at the end of 1 hour.

### Viva Questions

1. Why do the red cells settle down in a sample of anticoagulated blood?
   Since, the blood is not moving, the red cells settle down because they are heavier (sp. gr. = 1.095) than the plasma (sp. gr. = 1.032) in which they are suspended.
2. What is rouleaux formation?
   Rouleaux formation is the piling of RBC one on top of each other like a stack of coins. Fibrinogen neutralizes the negative charges imparted by sialic acid moieties on the cell membrane and thereby makes the RBCs sticky so that they tend to adhere to each other and form larger rouleaux.
3. Mention the factors responsible for rouleaux formation
   a. Concentration of fibrinogen, albumin and globulin.
   b. Bacterial proteins and toxins, products of inflammation and tissue destruction released into the blood neutralize the surface charges of red cells.
   c. Concentration of glycoprotein in plasma.
   d. Biconcave shape of red cells favors rouleaux formation.
   e. Number of red cells.
4. What are the factors influencing ESR?
   a. Rouleaux formation favors sedimentation.
   b. Increase in concentration of fibrinogen in plasma increases the rouleaux formation and hence increases ESR.
   c. Concentration of $\alpha$ and $\beta$ globulins increases ESR.
   d. Albumin decreases ESR.
   e. The biconcave disk shape of RBCs help in rouleaux formation. Variation in size of RBCs or anisocytosis and variations in shape of RBCs or poikilocytosis interferes with rouleaux formation and hence decreases ESR.
   f. *RBC count:* When the RBC count increases ESR decreases.
   g. ESR is influenced by viscosity of blood, specific gravity, acid-base balance, temperature, age of the blood since withdrawal and the anticoagulant used. Excess oxalate will slow sedimentation.

h. *Position of the tube:* Slanting position of the tube increases ESR.

5. Name the physiological and pathological variations of ESR.
   I. *Physiological*
      a. ESR is low in newborn.
      b. ESR is high in pregnancy, lactation and old age.
      c. ESR is more in females and less in males.
   II. *Pathological*
      ESR is increased in:
      a. Chronic infections like tuberculosis.
      b. Rheumatic fever.
      c. Collagen diseases.
      d. Malignancies like leukemias and multiple myeloma.
      e. Acute infections.
      f. Anemias except sickle cell anemia.

      ESR is reduced in:
      a. Allergic conditions.
      b. Sickle cell anemia.
      c. Afibrogenemia.
      d. Polycythemia.
6. What is the clinical significance of ESR?
   a. *To assess the prognosis of diseases:* ESR is a valuable prognostic tool in following the course of a disease, such as tuberculosis, rheumatoid arthritis, etc. while a patient is on treatment. If a weekly ESR shows a trend towards a decrease, it would indicate an improvement. But if the The ESR shows an increase, it would mean that the disease is deteriorating.
   b. As an indicator of bodily reaction to tissue injury and inflammation. The ESR values are not diagnostic, i.e. they will not tell the name of the disease that is causing a raised ESR. It is a sensitive indicator of tissue damage. The ESR is raised in all organic (pathological) conditions in contrast to functional disorders (anxiety neurosis, hypochondria).
7. Can you use oxalate mixture in Westergren method and citrate in Wintrobe method?
   No. The anticoagulants employed for each method have been standardized and cannot be interchanged.

   Sodium citrate cannot be used in Wintrobe method because the blood will be too much diluted as compared to the height of the tube; and this will give high false values for ESR.
8. What are the disadvantages of Wintrobe method?
   The disadvantage is that, this method is less sensitive because the column of blood is not as high as is desirable for good results and the chances of errors are high, especially when the ESR is increased, say to over 50 mm.

## PACKED CELL VOLUME (HEMATOCRIT)

### Apparatus

Wintrobe's tube, copper sulfate solution and double oxalate mixture. Double oxalate mixture consists of potassium and calcium oxalate. Here, the anticoagulant is used in the ratio 3:2, i.e. 3 parts blood mixed with 2 parts of anticoagulant.

Wintrobe's hematocrit tube is a cylindrical tube with a uniform bore and opens at the top. It is 11 cm long and is graduated from 0-10 cm from above downwards on one side and 10-0 cm on the other side. The diameter of the tube is 2.5 mm.

### Principle

When tube containing the blood sample is subjected to centrifugal forces, heavier RBCs settle at the bottom and the lighter elements remain above the RBC layer. RBC layer denotes the packed cell volume (PCV)/hematocrit.

### Observations

*The tube shows:*

1. An uppermost layer of clear plasma, it is straw colored.
2. A whitish and thin layer of platelets above and leukocytes below just below the plasma layer. This is called buffy coat and is 0.5 –1 mm thick.
3. A tall bottom layer of packed red cells. This red cell layer is separated from the buffy coat by the black line. This line is due to the presence of reduced Hb, present in the red cells lying adjacent to the white cells. This line marks the upper limit of red cell layer. Height of the red cell column varies from 4.2–4.7 cm. The packed cell volume percentage is obtained by multiplying the reading obtained by 10.

### Normal Value

*Adult male:* 46 ± 5%
*Adult female:* 42 ± 5%.

#### *Note*

1. Hematocrit value of blood in microcirculation vessels (meta arterioles, arterioles, capillaries) is lower than that of actual blood. In these small vessels, the red cells tend to move in the center of the bloodstream (axial flow). As a result, the blood along the sides of the vessels has a low hematocrit, and branches leaving at right angles may receive cell–poor blood. In capillaries, the effect is marked because the RBCs move in a single file in the middle of the

stream. This phenomenon called plasma skimming, may be responsible for the capillary blood hematocrit being about 25% lower than the whole body hematocrit.
2. The PCV of venous blood is slightly higher (3%) than that of arterial blood (refer page 43).

## Viva Questions

1. What is PCV?
   It is the volume of cellular elements per unit volume of whole blood. In a normal adult it is approximately 45%
2. What do you mean by hematocrit value ?
   It is the volume percentage of the packed RBC only (not all the formed elements) with respect to the whole blood. In a normal person, PCV and hematocrit are almost the same. But in conditions where there is abnormal proliferation of WBC (as in leukemia) the values can be different.
3. What is the importance of determining hematocrit?
   It is simple, but accurate method for determining the presence of anemia or polycythemia. It is also used for the screening of anemia.
4. What cells make up the buffy layer? Mention its clinical significance.
   The buffy layer consists of packed platelets and leukocytes. A rough estimate of WBC count may be made from the thickness of the buffy coat. A thickness of 1 mm corresponds to 10,000 WBC. The thickness increases in cases of leukemia, severe leukocytosis and primary thrombocytosis. Smears from buffy coat are useful when WBC count is very low and may be of use in detecting the LE cells in systemic lupus erythematosus, blast cells in aleukemic leukemia and plasma cells in multiple myeloma.
5. Briefly mention about the plasma column.
   It is normally straw colored. It is red in hemolysis, pale in anemia, yellow in jaundice, milky and opaque in lipemia.
6. What is the effect of a high hematocrit ?
   Increase in hematocrit increases the viscosity of blood which leads to an increase in peripheral resistance, and thus the blood pressure.
7. Name the conditions where PCV is increased and those where it is decreased.

***High PCV is Seen in:***

I. *Physiological conditions*
   a. Newborn
   b. High altitude
   c. After exercise
   d. Dehydration resulting from profuse sweating without adequate fluid intake.

II. *Pathological conditions*
   a. Polycythemia.
   b. Dehydration resulting from severe gastroenteritis.
   c. Burns leading to hemoconcentration.

***Low PCV is seen in:***

I. *Physiological conditions*
   a. During pregnancy due to hemodilution
   b. In females.

II. *Pathological conditions:* In various types of anemias.

8. What are the uses of Wintrobe's method?
   Estimation of PCV is the primary use. It is also used for the determination of ESR and demonstration of LE cells.
9. What is true hematocrit?
   Even under optimum conditions, it is impossible to completely pack the red cells together, and about 2% plasma remains trapped in between the red cells. This percentage is more if the red cells are abnormal in shape (e.g. spherocytosis, sickle cells). To compensate for trapped plasma, the true cell volume (true hematocrit) is obtained by multiplying observed hematocrit value by 0.98.

**Table 13.1: Difference between Westergren tube and Wintrobe tube**

| *Westergren tube* | *Wintrobe tube* |
|---|---|
| It is a long tube | It is a short tube |
| Total length 300 mm | Total length 110 mm |
| Diameter 2.5 mm | Diameter 3 mm |
| Both ends are open | Lower end is closed |
| Marking from top of the tube to the bottom, i.e.<br>Upper reading = 0 mm<br>Lower reading = 200 mm | Marking from top of the tube to the bottom and vice versa. Left side lower reading = 10 cm<br>Right side<br>Upper reading = 10 cm<br>Lower reading = 0 cm |
| For ESR only | For both ESR and PCV |

## ESTIMATION OF HEMOGLOBIN (SAHLI'S METHOD)

### Apparatus

Sahli's hemoglobinometer, N/10 HCl.

### Principle

Hemoglobin is converted to acid hematin. Then it is estimated by matching the color with a standard plate of the same derivative after diluting it with distilled water.

Preparation of the standard. The standard color in Sahli's hemoglobinometer is prepared by treating blood containing 14.4 gm of Hb with N/10 HCl and diluting the same with distilled water 100 times.

## Normal Values

*Adult male:* 14-8 gm%

*Adult female:* 12-16 gm%

*Newborn:* 18-23 gm%

The high value in the newborn is due to the increased RBC count. The newborn has been living in state of relative hypoxia, which is a very potent stimulus for the secretion of erythropoietin. The value decreases gradually and reaches the adult value by 16–18 months.

## Viva Questions

1. Can strong acids (such as nitric, sulfuric acid, concentrated HCl) or alkalies be used in place of decinormal HCl?
   The strong acids, which are very strong oxidizing agents and alkalies will cause disruption of Hb and thus cannot be used. Only N/10 HCl is used because standardization has been done for acid hematin.
2. Can tap water be used for diluting and color matching?
   No, it cannot be used because its soil may cause turbidity which will interfere with color matching.
3. Can N/10 HCl be used instead of distilled water for diluting and color matching?
   Yes, it can be used because it being transparent, it cannot further deepen the color once all the Hb has been converted into acid hematin.
4. What will happen if quantity of N/10 HCl is changed?
   The minimum quantity should be present so as to form complete acid hematin.
5. What are the disadvantages of Sahli's method?
   a. The method estimates only oxy Hb and reduced Hb, other forms such as carboxyHb and met Hb are not estimated.
   b. In the long-term use, the standard coloration on the hemoglobinometer may fade and become lighter. This will lead to wrong result.
6. What are the other methods of Hb estimation?
   a. Spectrophotometric methods
      - Cyanmethemoglobin method
      - Oxyhemoglobin method
      - Haldane's carboxyHb method
      - Wu's alkaline hematin method.

   b. Tallqvist method
   c. Copper sulfate falling drop method
7. Name some derivatives of hemoglobin.
   - Oxyhemoglobin
   - Reduced hemoglobin (deoxygenated Hb)
   - Carbaminohemoglobin
   - Carboxyhemoglobin
   - Methemoglobin
   - Sulfhemoglobin
   - Cyanmethemoglobin (hemoglobincyanide).
8. Why is it required to allow the solution to stand for 10 minutes before dilution?
   This time is required for complete hemolysis of RBCs and maximum conversion of hemoglobin in blood to form acid hematin.
9. What are the functions of hemoglobin?
   - Carriage of $O_2$
   - Carriage of $CO_2$
   - Homeostasis of pH (buffer action of Hb)
   - It preserves iron in the body.
10. How is heme synthesized from the body?
    Heme portion of Hb is synthesized from glycine and succinyl CoA. Heme is synthesized by cells of erythroid series in red bone marrow.
11. Name the physiological and pathological variations of Hb content in RBC.
    I. *Physiological*
       a. *Age:* Hb% is more in newborn.
       b. *Sex:* Higher in males.
       c. *At high altitudes:* Hb% is increased at high altitudes as hypoxia stimulates erythropoiesis which in turn increases Hb count.
       d. *Exercise:* Hb content is increased after exercise.

    II. *Pathological*
       Hb content is increased in polycythemia and decreased in all types of anemias.
12. What would happen if Hb were present freely in the plasma instead of in the red cells?
    Normally, only a very small amount is present in the plasma (about 3 mg/dL), most of it being confined to red cells. If it were present in the plasma, it would increase the viscosity (thus raising BP), and the osmotic pressure of blood (thus affecting fluid exchanges). It would also be excreted in the urine, besides being taken up and rapidly destroyed by the reticuloendothelial system.
13. Calculate the oxygen carrying capacity of blood.
    Normal oxygen carrying capacity of blood per gram of Hb is 1.34 ml. For 15.79 gm/dL of Hb, the oxygen carrying capacity becomes $15.79 \times 1.34 = 20.2$ ml/dL of blood.
14. Discuss the differences between adult Hb and fetal Hb. (Table 13.2).
15. What is anemia and how it is graded to Hb concentration?
    Refer Page no. 16.
16. What are the normal variants of hemoglobin ?
    Refer Page no. 12.
17. What is the fate of Hb?
    Refer Page no. 13.
18. What is the structure of Hb, where is it synthesized?
    Refer Page no. 13.

**Table 13.2: Adult and fetal Hb compared**

| *Adult hemoglobin* | *Fetal hemoglobin* |
|---|---|
| 1. Contains 4 polypeptide chains (2 alpha and 2 beta) | 1. The 2 beta chains replaced by gamma chains |
| 2. Appears in red cells of the fetus in 5th month. At birth 20% of total Hb is Hb A | 2. HbF at birth makes up 80% of total Hb disappear by 5th month after birth |
| 3. Lifespan long—120 days | 3. Lifespan short—about 2 weeks |
| 4. It has the usual affinity for oxygen | 4. It has greater affinity for oxygen as it binds 2,3 DPG less avidly |
| 5. Percentage saturation at $pO_2$ of 20 mm Hg = 30-35% | 5. Percentage saturation at $pO_2$ of 20 mm Hg = 70% |

## RBC COUNT

### Apparatus

Improved Neubauer's counting chamber, RBC pipette, RBC diluting fluid (Hayem's fluid).

### Composition of Hayem's Fluid

1. *Sodium sulfate:* To prevent rouleaux formation.
2. *Sodium chloride:* To maintain isotonicity of fluid (RBC remains suspended in solution).
3. *Mercuric chloride:* Act as preservative (antifungal and antibacterial).
4. *Distilled water:* As a solvent.

### Normal Values

*Males:* 4.5–6.5 million/cu mm

*Females:* 3.9–5.6 million/cu mm

*Newborn:* 6–7 million/cu mm

### Viva Questions

1. How is diluting factor calculated?
   0.5 part of blood is mixed 100.5 part of Hayem's fluid in pipette. Blood mixes with diluting fluid only in the bulb. So, 1 part diluting fluid that remains in the stem does not mix with the blood, i.e. 0.5 part blood and 99.5 part diluting fluid in blood, to form 100 part of solution.

$$\text{Dilution factor} = \frac{\text{Final volume}}{\text{Original volume}} = \frac{100}{0.5} = 200$$

2. What is the function of bead in the bulb?
   a. Bead act as stirrers.
   b. Free rotation of bead in the bulb signifies pipette is dry
   c. Beads are distinguishing feature - Red bead for RBC pipette, white bead for WBC pipette.
3. Would not the bead decrease the dilution due to its own volume?
   The volume of bead is taken into consideration during manufacture of the pipette.
4. Why the fluid in the stem is discarded?
   The fluid from the stem portion of the pipette is discarded because the actual mixing is taking place only in the bulb and stem contains only the diluting fluid.
5. Since, the mature red cells do not contain 'nuclei, are they dead cells?
   The RBCs, though without nuclei, are not dead in the usual sense. Since there are no mitochondria (and other organelles), energy is not available from oxidative phosphorylation (Kreb's cycle). However, they contain a number of enzymes which control important functions. The cells contain all enzymes necessary for energy supply from anaerobic glucose metabolism via the Embden-Meyerhof pathway (hexose monophosphate shunt). (Glucose enters RBCs by an active process which is insulin-independent).
6. What are the uses of Neubauer's chamber?
   It helps in finding out: RBC count, WBC count, platelet count and also cells in CSF, peritoneal, pleural fluids, etc.
7. What are the physiological and pathological variations in RBC count?

*Increase in RBC Count*

   a. Physiological-males, high altitude, high temperature, low $O_2$ tension, after exercise, infants.
   b. Pathological-polycythemia vera, hyperthyroidism, Cushing's syndrome, dehydration, chronic lung disease, congenital cyanotic heart disease.

*Decrease in RBC Count*

Seen in all types of anemia.

8. What is the site of RBC formation during fetal life and after birth?
   Refer Page no. 14
9. What is the lifespan and fate of red cells?
   Refer Page no. 13
10. What is erythropoiesis and what are the stages of differentiation and maturation of red cells?
    Refer Page no. 14, 15
11. How is erythropoiesis regulated?
    Refer Page no. 15, 16
12. Mention the sites of erythropoietin formation.
    Refer Page no. 15
13. What is polycythemia?
    Refer Page no. 17

## WBC COUNT

### Apparatus

Improved Neubauer's counting chamber, WBC diluting fluid (Turk's fluid).

### Composition of Turk's Fluid

a. Glacial acetic acid-lyses membrane of RBC, platelets and causes swelling of nucleus of WBC.
b. Gentian violet-stains nucleus of WBC.
c. Distilled water-as a solvent.

### Calculation of Dilution Factor

$$DF = \frac{\text{Final volume}}{\text{Original volume}} = \frac{10}{0.5} = 20$$

### Normal Values

*Adults:* 4000 -11000/cu mm

*Newborn:* 10000 -25000/cu mm

*Children up to 4 years:* 18000 cells/cu mm (count decreases after 4 years).

### Viva Questions

1. What are the other uses of WBC pipette?
   The WBC pipette can be used for diluting the blood much less for counting RBCs in cases of severe anemia, or for counting platelets. It can also be used for counting sperms and bacteria.
2. Why are the red cells not seen when counting the leukocytes?
   The red cells are not seen because they are hemolyzed by glacial acetic acid in the WBC diluting fluid, i.e. Turk's fluid. The remnants of red cells membranes are faintly visible, the so called ghost cells.
3. How you differentiate a WBC pipette from a RBC pipette (Table 13.3).
4. Are WBCs also lyzed while doing WBC count ?
   Yes. WBCs are also lyzed, this is to destroy the plasma membrane to expose the nucleus for staining. So while counting we actually count the nucleus of WBC and not WBC as a whole.
5. What are the physiological and pathological variations in WBC count?
   Increase in leukocyte count>11000/cu mm is called leukocytosis. It generally refers to an increase in neutrophils and hence it is synonymous with neutrophilia.

**Table 13.3: RBC and WBC pipette compared**

| *RBC pipette* | *WBC pipette* |
|---|---|
| 1. Calibrations are 0.5 and 1.0 below the bulb, and 101 above the bulb. | 1. Calibrations are 0.5 and 1.0 below the bulb, and 11 above it. |
| 2. The capillary bore is narrow, thus it is a slow speed pipette. | 2. The capillary bore is wider, hence it is a fast speed pipette. |
| 3. Bulb is larger and has a red bead. | 3. Bulb is smaller and has a white bead. |
| 4. The volume of the bulb is 100 times the volume contained in stem | 4. The volume of the bulb is 10 times the volume contained in stem. |
| 5. The dilution can be 1 in 100 or 1 in 200. | 5. The dilution can be 1 in 10 or 1 in 20. |

*Increase in TLC*

a. *Physiologically*
   i. *Diurnal variations:* The count is lowest in the morning and rises during miday. It is the highest in the evening. Count is lowest after rest.
   ii. *After exercise:* Count is increased after strenuous muscular exercise. It is probably due to redistribution of cells and it becomes normal within 1 hour.
   iii. Count is higher in newborns and infants.
   iv. Count is increased in pregnancy and is highest during labor. It is also increased in menstruation.
b. *Pathologically*
   i. Leukocytosis is seen in acute bacterial infections like boils, abscesses, pneumonia, etc.
   ii. It is increased in allergic conditions like asthma, hay fever, etc.
   iii. Hemorrhage, burns and malignant disease also show leukocytosis.

*Decrease in TLC*

Leukopenia is the reduction in leukocyte count below normal. It is pathological and occurs in:
   a. Certain bacterial infections like typhoid and paratyphoid.
   b. Viral infections like influenza, measles and smallpox.
   c. Protozoan infections like malaria and kala-azar.

6. What is leukopoiesis? Where does it occur?
   Leukopoiesis, i.e. production of WBCs occurs both in the bone marrow and lymphatic tissues. The two major lines of WBCs myeloid (for granulocytes and monocyte) and lymphoid (for lymphocyte) arise from pleuripotent hemopoietic stem cells in the bone marrow.

7. What is the lifespan of leukocyte?
   Normally, the lifespan of granulocytes is about 8-10 hours or a few days. But the lymphocytes recirculate between blood and lymphoid tissue and may survive for months.
8. What is meant by the term agranulocytosis, leukocytosis, leukopenia and leukemia?

*Agranulocytois*: Decrease in the number of granulocytes.

*Leukocytosis*: Increase in the number of WBC beyond 11,000/mm$^3$ irrespective of the type of cells (granulocytes, monocytes, leukocytes).

*Leukopenia*: Decrease in the number of white cells below 4000/mm$^3$.

*Leukemia*: It is a group of malignant neoplasms of WBC forming organs–bone marrow and lymphoid tissue. The TLC is generally above 40,000 - 50,000/mm$^3$ or even a few lakhs.

## DLC

### Apparatus

Glass slide, Leishman's stain, Cedar wood oil.

### Composition of Leishman's Stain

*Eosin:* Acidic dye, stains positively charged particles. For example, nuclei of RBC's, granules of eosinophils.

*Methylene blue:* Basic dye, stains negatively charged particles. For example, nuclei of WBC's, granules of basophils.

*Acetone free methyl alchohol:* Fixative and preserves cells. The methyl alcohol should be acetone free to prevent shrinkage, crenation and lysis of cells.

### Points of Identification

1. *Neutrophil*
   - Multilobed nucleus
   - Fine pink granules
2. *Eosinophil*
   - Bilobed spectacle shaped nucleus
   - Coarse brick red granules
3. *Basophil*
   - Roughly S-shaped nucleus
   - Coarse bluish black granules which may even mask the nucleus

4 *Monocyte*
   - Large kidney-shaped nucleus
   - Cytoplasm more

5. *Lymphocyte*
   - Unlobed nucleus (sometimes it may be indented)
   - Thin rim of cytoplasm.

### Comparison with RBC Size

a. Neutrophil, eosinophil, basophil, large lymphocyte: Double the size of RBC.
b. *Monocyte:* Double /triple the size of RBC.

### Viva Questions

1. Discuss the significance of DLC.
   The differential count is done to find if there is an increase or decrease of a particular type of WBC. Knowing the TLC, the absolute number of each type can be calculated. This information is important in detecting infection or inflammation, allergic and parasitic infections, and effects of chemotherapy and radiation therapy.
2. Why is Leishman's stain diluted after 1–2 minutes? What happens to the blood film during this period?
   During the fixation period of 1–2 minutes, the pure absolute alcohol serves two purposes:
   a. It precipitates the plasma proteins, which act as glue and attach (fix) the blood cells on to the glass slide.
   b. It preserves the shape and chemistry of cells to as, near the living state as possible.

The cells are not stained during this time, because the stain particles cannot enter the cells in their unionized state. Their ionization occurs only when water is added to the salts in the undiluted stain. (If diluted stain were added to start with, the blood smear itself would be washed away. Diluted Leishman's stain can be used if the blood film is first fixed in absolute alcohol).

3. Mention the absolute count, percentage and size (diameter) of various leukocytes?
   *Neutrophil:* 2000–7500/mm$^3$, 40–75%, 10–14 m.
   *Eosinophils:* 4–440/mm$^3$, 1–6% , 10–14 m
   *Basophil:* 0–100/mm$^3$, 0–1%, 10–14 m
   Monocyte: 500–800/mm$^3$, 2–10%, 10–18 m
   *Lymphocytes:* 1300–3500/mm$^3$, 20–45%, 10–14 m (large), 7–10 m (small).
4. What are the functions of various leukocytes?
   Refer Page no. 18, 19
5. Enumerate the conditions that cause neutrophilia and neutropenia, eosinophilia and eosinopenia, basophilia and basopenia, monocytosis and monocytopenia, lymphocytosis and lymphocytopenia.
   Refer Page no. 18, 19

6. Mention the steps of phagocytosis.
   Refer Page no. 19
7. What is Arneth count ?
   Refer Page no. 20

## DETERMINATION OF BLOOD GROUP

### Apparatus

Antisera A, B and D (Rh), 0.9% NaCl/3.8% sodium citrate solution, capillary dropper.

### Principle

Surfaces of red cell membrane contain genetically determined antigens-agglutinogens while plasma contains antibodies Red cells allowed to react with commercially available antisera with agglutinins. Clumping/hemolysis as a result of antigen-antibody reaction.

### Viva Questions

1. What is agglutination?
   Clumping and hemolysis of red cells during antigen - antibody interaction.
2. What are the different blood group systems?
   Different blood group systems include ABO, Rh, M and N, Kell and Duffy, MNS, Lutheran, etc.
3. How will you differentiate agglutination from rouleaux formation?
   Dilution with saline disperses rouleaux, but agglutinated cells are not dispersed.
4. What is Bombay blood group?
   This blood type is a rare phenomenon in which the H antigen is absent. Since there is no H antigen, there is no antigen A or antigen B on the red cells. However, the plasma contains anti-A, anti-B and anti-H antibodies. As a result, such a person can receive blood only from a person having Bombay blood type.
5. What is reverse blood typing?
   The blood grouping (typing) procedure in which the red cells of a person (whose blood type is to be determined) are tested against anti-A and anti-B sera, is called "blood typing" or "forward blood typing".
   In another but related procedure called "reverse blood typing" (also called "serum typing" or "backward blood typing") the serum of the would-be recipient is tested against red cells containing known antigens, i.e. red cells from persons with blood types A, B, AB, and O. It agglutination occurs with A and AB red cells, the blood type is B; if agglutination occurs with B and AB red cells, the blood type is A; if agglutination occurs with A, B, and AB red cells, the blood type is O and if there is no agglutination in any RBCs the blood type is AB. [In AB blood type there are no antibodies in the plasma (serum).
6. What are cold and warm antibodies?
   Refer Page no. 29
7. What is Landsteiner's law?
   Refer Page no. 24
8. What is cross matching?
   Refer Page no. 25
9. What is Rh factor and what is its clinical significance?
   Refer Page no. 25
10. How can HDN be prevented? What is its treatment?
    Refer Page no. 25
11. What are the indications of blood transfusion?
    Refer Page no. 25
12. What are the hazards of blood transfusion?
    Refer Page no. 25, 26
13. How is donated blood stored?
    Refer Page no. 26

## RETICULOCYTE COUNT

### Apparatus

Microscope, Petri dish, blotting paper, reticulocyte stains (supravital stains).

### Reticulocyte Stains

a. *Brilliant cresyl blue:* 1g of this dye is dissolved in 100 ml of citrated saline (1 volume of 3.8% sodium citrate and 4 volumes of normal saline).

*Uses*

i. Brilliant cresyl blue stains the RNA of reticulocytes.
ii. Citrate prevents the clotting of blood.
iii. Normal saline provides tonicity.

b. *New methylene blue:* It stains the reticulum of reticulocytes unlike brilliant cresyl blue. It is chemically different and stains more deeply and uniformly. One gram of this dye is dissolved in 100 ml of citrated saline.

### Theory of Reticulocyte Staining

The basophilic remnants of RNA and ribosomes in the cytoplasm of reticulocytes is stained by brilliant cresyl blue. The dye enters the cells and stains the basophilic material to form bluish precipitates of dots, short strands and filaments. This reaction can occur only in supravitally (vitally) stained cells, i.e. in 'unfixed' and 'living' cells. The more the immature cells, greater is the amount of precipitable material present in them.

### Points of Identification of Reticulocytes

Reticulocytes are non-nucleated cells and are slightly larger (diameter-8 μm) than RBCs (7.5 μm). They also stain lighter

than the red cells, and contain dots, strands and filaments of bluish-stained material.

### Normal Values

1. *Newborn:* 30–40% (no: decreases to 1–2% during 1st week of life).
2. *Infants:* 2–6%
3. *Children and adults:* 0.2–1%

### Viva Questions

1. What is a reticulocyte?
   Reticulocytes are the non-nucleated immediate precursors of red cells that develop in the red marrow from the PHSCs. They contain large amounts of remnants of RNA and ribosomes. They are present in large numbers in bone marrow and small numbers in blood.
2. What are the indications of doing reticulocyte count?
   - Assessment of erythroid activity of bone marrow.
   - It can also help in assessing the effectiveness of a drug used in the treatment of anemia.
3. What is the importance of reticulocytes count?
   An increase in the reticulocyte count is indicative of regeneration of red cells.
4. How do you differentiate between a reticulocyte and RBC?
   a. Size of reticulocyte: 8 $\mu m^3$ and size of erythrocyte is 6.7-7.7 $\mu m^3$ (reticulocyte is bit larger than RBC).
   b. DNA: Reticulocyte has central core of RNA have takes up basic stains. RBC's do not have a central core of RNA.
   c. Cytoplasm of reticulocyte is coarse and appears to contain granules (ribosomes) while that of RBC does not.
5. What is reticulocytosis? Name the conditions in which it occurs.
   Increase in the number of reticulocytes in blood is referred to as reticulocytosis. The conditions in which reticulocytes count is high are:
   - Recovery from anemia.
   - After acute hemorrhage.
   - Proliferation of bone marrow.
     Physiologic conditions: In newborn; hypoxic conditions (high altitude); menstruation.
     Pathological conditions: Hemolytic anemia, sickle cell anemia; polycythemia.
6. What is vital and supravital staining?
   The term "vital" suggests that this method has to do with living cells. Vital staining is a special method of staining employed for unfixed, "living cells" (or as nearly living as possible), including tissue cultures. There are two types of vital staining:

*Supravital staining:* It is *in vitro* method where the living cells are stained by immersing them in a dye solution.

*Intravital staining:* It is *in vivo* method where a dye is injected into a living organism for selective staining.

7. What are the characteristics of reticulocyte?
   - Size is 7.2 $\mu m^3$.
   - Uniform light-bluish violet–due to presence of RNA
   - A reticulum is formed within the cell when RNA is precipitated with a basic dye.

## PLATELET COUNT

There are two methods for platelet counting:
a. Direct method
b. Indirect method

### Direct Method

#### *Apparatus*

Microscope, RBC pipette, counting chamber with cover slip, Rees-Ecker diluting fluid or freshly prepared 1% ammonium oxalate solution. Ammonium oxalate destroys red cells but preserves platelets; it also acts as an anticoagulant.

- Rees-Ecker diluting fluid contains the following:
- Brilliant cresyl blue (0.1 g) – Stains platelets
- Sodium citrate (3.8 g) – Prevents clotting and makes the fluid isotonic.
- Formalin – Prevents fungal growth and lyses RBCs.

### Calculation of Platelet Count

With the knowledge of platelet count, and the RBC count, the actual number of platelets per $mm^3$ blood can now be calculated. Normal platelet count is 2,50,000–5, 00,000/$mm^3$.

#### *Automated Method*

It is a very accurate method. It is carried out on an Eleccell counter. The red cells and platelets in the diluted blood sample pass through an aperture. The particles between 2 and 10 $\mu m^3$ are counted as platelets.

### Viva Questions

1. What are the physiological variations of platelet count?
   Minor variations in platelet count occurs in the following conditions:
   a. Increased counts may be seen after severe exercise, and sometimes at high altitudes.
   b. Decreased counts, near the lower side of the normal, may be seen in the newborns and in females, during menstruation.
2. What are the different types of granules present in the platelets?
   Alpha-granules, dense granules and glycogen granules.
3. What are megakaryocytes ?
   Platelets are produced from the giant cells which are called megakaryocytes in the bone marrow. Diameter is about 100 μm.

4. What is meant by the terms thrombocytopenia and thrombocytosis?
   Thrombocytopenia: The term refers to a decreased count 'of platelets. It may be due to decreased production or increased destruction.
   Thrombocytosis: The term refers to an increase in platelet count above 4, 50,000/mm$^3$ of blood.
5. Mention the causes of thrombocytopenia.
   a. Deficient production, hypoplastic and aplastic anemia, various drugs and antibiotics.
   b. Thrombocytopenic purpura.
   c. Pernicious anemia.
6. Mention the causes of thrombocytosis.
   a. Following hemorrhage, severe injury or any major surgical operation.
   b. Removal of spleen.
   c. Chronic myeloid leukemia.
   d. Polycythemia vera.
7. How is hemostais brought about by platelets?
   a. Increased tendency to aggregation
   b. Vasoconstriction by serotonin and norepinephrine causing closure of ruptured blood vessels.
8. What is the normal platelet count? Describe their site of formation, lifespan and functions.
   Refer Page no. 20
9. How does aspirin act as an antiplatelet agglutinating agent and what is its clinical value?
   Refer Page no. 21

## BLEEDING TIME AND CLOTTING TIME

### Bleeding Time

It is the time taken from the puncture of the blood vessels to the stoppage of bleeding. It can be found by two methods - Duke's method and Ivy's method. Normal time: 2–6 minutes (according to the Duke's method).

### Clotting Time

It is the time taken from the puncture of blood vessels to the formation of the fibrin thread. It can be found by two methods. Capillary glass tube method and Lee and White method. Normal values: 3–8 minutes at 37°C.

### Viva Questions

1. What is the clinical importance of doing bleeding time (BT) and clotting time (CT)?
   BT and CT are important in the following situations:
   a. History of frequent and persistent bleeding from minor injuries, or spontaneous bleeding into tissues.
   b. Before every minor and major surgery (tooth extraction, etc).
   c. Before taking biopsy, especially from bone marrow, liver, kidney, etc.
   d. Before and during anticoagulant therapy.
   e. Family history of bleeding disorders.
2. What are the factors on which BT and CT depend?

*Bleeding time depends on:* Breadth and depth of the wound, degree of hyperemia of the skin puncture site, number of platelets and their functional status, functional status of the blood vessels, temperature (in cold weather, low temperature promotes vasoconstriction and thus shorten BT).

*Clotting time depends on:* Nature of contact surface (glass in this case: siliconized surface would prolong the CT, presence or absence of clotting factors, temperature (low temperature may prolong the CT).

3. Name the conditions in which BT is prolonged?
   Deficiency of vitamin C, thrombocytopenic purpura.
4. Name the conditions in which CT is prolonged.
   Hemophilia (due to lack of factor VIII), liver disease, lack of Christmas factor (factor IX), vitamin K deficiency.
5. What is hemophilia? Mention the changes of BT and CT in hemophilia.
   Hemophilia is a disorder in which clotting time is prolonged. In 85% of cases, it is due to deficiency of factor VIII and in about 15% patients it is due to deficiency of factor IX. BT is normal in hemophilic person; only CT is prolonged.
6. How does BT differ from CT? What is the interrelation between them, and which aspects of hemostasis are tested by them?
   Both BT and CT are done together in all disorders of hemostasis. They are interrelated in the sense that platelets are involved in both tests. The BT tests the platelet plug formation and the condition of the microvessels (arterioles, capillaries, venules), while CT tests the formation of the clot. Increase in BT (e.g. in purpura), or CT (e.g. in hemophilia) usually occur independently of each other.
7. Name the conditions in which only the BT is prolonged while the CT is normal.
   Low platelet count (thrombocytopenia), functional platelet defects, vessel wall defects.
8. What is purpura? Mention the changes of BT and CT in purpura.
   Refer Page no. 24

## ABSOLUTE EOSINOPHIL COUNT

The absolute count of eosinophils can be done by two methods:

a. *Direct method:* The cells are counted directly by employing hemocytometry.
b. *Indirect method:* Here the percentage of eosinophils is determined from a blood smear counting of leukocytes.

From the TLC value, the absolute eosinophil count can be calculated. For example, If TLC = 8000/mm$^3$ and eosinophils are 2% in DLC, then the absolute count = 2/100 × 8000 = 160/mm$^3$ of undiluted blood.

In this experiment, the direct method of hemocytometry will be used.

*Principle:* Blood is diluted 10 times in a WBC pipette using Pilot's diluting fluid that lyses RBCs and leukocytes other than eosinophils. The stained cells are then counted in a counting chamber.

## Apparatus

Microscope, counting chamber, WBC pipette, Pilot's diluting fluid (for eosinophil counting).

## Composition

### *Stock Solutions*

a. Propylene glycol
b. *Phloxine:* 1% solution in water (0.5% eosin may be used but phloxine is superior)
c. *Sodium bicarbonate:* 10% solution in water

*Working solution*: It is made by mixing and filtering the following:

a. Propylene glycol = 50 ml
b. Phloxine (1%) = 10 ml
c. Sodium bicarbonate (10% ) = 1 ml
d. Heparin = 100 units
e. Distilled water = 40 ml

***Note:*** The diluting fluid is freshly prepared from stock solution when required. Propylene lyses the red cells, phloxine stains the eosinophil granules and sodium carbonate solution lyses all leukocytes except eosinophils.

Normal absolute eosinophil count: 10-400/mm$^3$ (Eosinophil count of capillary blood is usually 10–15% higher).

## Viva Questions

1. What is the clinical significance of absolute eosinophil count?

   Formerly, eosinophil count was considered as an index of ACTH activity in the blood. When ACTH is injected into a person with normal adrenocortical function, there is a drastic reduction in the absolute eosinophil count. This test, called "Thorn's test" used to be employed to assess adrenocortical function. However, with better hormone assay tests, this test is no longer employed. However, the absolute count helps in diagnosing various allergic and parasitic conditions.

Chapter

# 14 Amphibian Experiments

## GASTROCNEMIUS MUSCLE AND SCIATIC NERVE PREPARATION OF FROG

### Composition of Amphibian Ringer Solution

a. 0.65% NaCl: Isotonic with the amphibian plasma.
b. 0.14% KCl: Maintaining membrane potential.
c. 0.012% $CaCl_2$: Maintaining membrane potential.

The amphibian Ringer solution stimulates ATPase activity. The optimal pH is about 0.02% $NaHCO_3$.

***Note***

i. The tissues used to demonstrate the properties of skeletal muscles are sciatic nerve, gastrocnemius muscle of frog.
ii. Stimulus is defined as a sudden change in external or internal environment of a tissue due to which a response is obtained.
iii. The different types of stimuli used to stimulate a tissue are electrical, mechanical, chemical and thermal.
iv. Of these different stimuli electrical stimuli is preferred because we can adjust the strength of current, also the duration and frequency of the stimulus can be varied. Current does not damage the tissue.

## RECORDING OF A SIMPLE MUSCLE CURVE

Simple muscle curve is recording of simple muscle twitch. Total muscle twitch of frog's gastrocnemius muscle-0.1 second.

### Simple Muscle Twitch

Simple muscle twitch (Fig. 14.1) is the contraction and relaxation of muscle following a single stimulus.

The different phases of simple muscle curve are described below.

#### *Latent Period (LP)*

It is the period between the point of stimulus and the onset of contraction. *Normal duration:* 0.01–0.012 second.

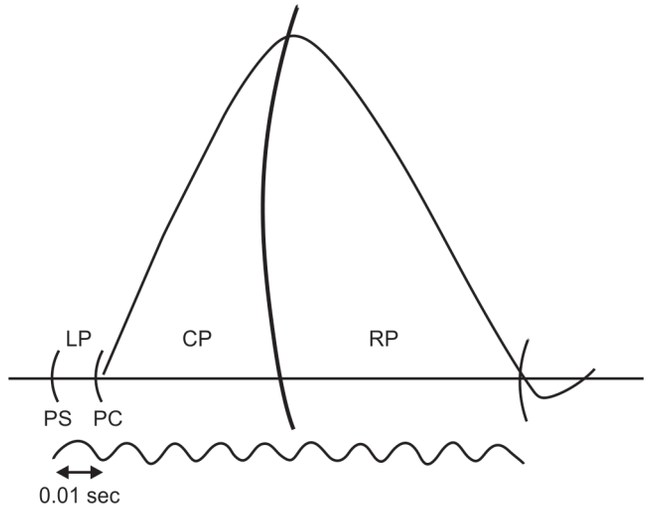



**Fig. 14.1:** Simple muscle twitch

**Table 14.1: Differences between isometric and isotonic muscle contraction**

| *Isometric* | *Isotonic* |
|---|---|
| The muscle is not allowed to shorten, i.e. contraction of muscle without shortening | The muscle shortens in length depending upon the load |
| There is no change in LP, but the CP and RP increases | There is no change in LP, but the CP and RP decreases |
| The tension developed is greater and depends upon the strength of stimulus | The tension developed is relatively less and depends on load applied |
| The muscle does no work | The muscle does the work |
| Heat produced is more | Heat produced is less |
| For example, contraction of the postural muscles against gravity | For example, lifting up a weight with hand, there is shortening of biceps |

***Causes for LP***

i. Time taken for the generation of impulse.
ii. Time taken for the transmission of impulse along the nerve fiber.
iii. Neuromuscular delay.
iv. Time taken for release of $Ca^{2+}$ in muscle fiber (excitation contraction coupling time)
v. Inertia of lever.

***Factors influencing LP***

i. Stimulating near the vertebral end increases the LP and if at the muscle end the LP decreases.
ii. *Temperature:* High temperature decreases LP.
iii. Fatigue increases LP.
iv. Increase in pH increases the LP.

### Contraction Period (CP)

It is the period between the point of contraction and to point of maximum contraction. *Normal duration:* 0.04 second

***Factors influencing CP***

i. *Temperature:* Increase in temperature increases speed of contraction , therefore decreases CP and vice versa.
ii. *Fatigue:* When muscle is at fatigue, CP increases.

### Relaxation Period (RP)

It is the period between the point of maximum contraction to the point of relaxation of muscle. *Normal duration:* 0.05–0.06 second.

***Factors influencing RP***

i. *Temperature:* As temperature increases, RP also increases
ii. *Fatigue:* As fatigue increases, RP also increases.

## EFFECT OF TWO SUCCESSIVE STIMULI ON SKELETAL MUSCLE

This experiment is meant to study the refractoriness of skeletal muscle. Skeletal muscle is refractive only during LP.

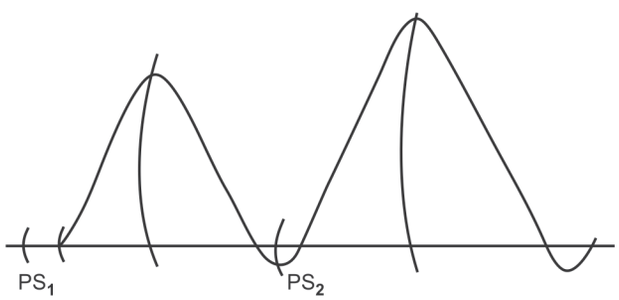



**Fig. 14.2:** Effect of second stimulus after relaxation period on muscle contraction

### Beneficial Effect

When the 2nd stimulus is applied after the relaxation period of the first one, the 2nd curve obtained is of higher amplitude (Fig. 14.2). This is called beneficial effect.

### Causes of Beneficial Effect

1. Increase in temperature due to metabolic reactions.
2. Increase in elasticity of muscle due to decrease in the viscosity of muscle protein.
3. Decrease in the pH due to conversion of glycogen to lactic acid and there by muscle contracts more rapidly.

### Superposition

When the 2nd stimulus falls during the relaxation period, the 2nd curve obtained is superimposed on the first. The 2nd contraction will be of higher amplitude (Fig.14.3).

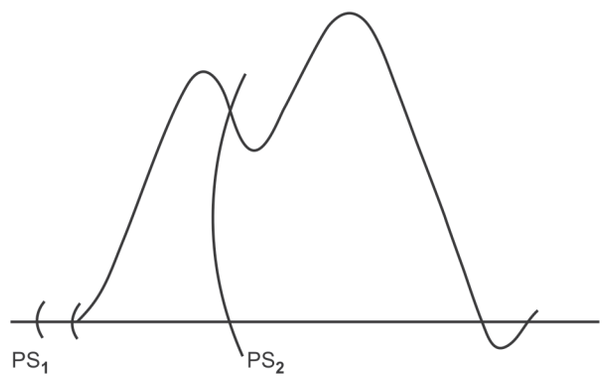



**Fig. 14.3:** Effect of second stimulus during relaxation period on muscle contraction

### Summation

This results when the 2nd stimulus falls during the contraction period of the first one. Here the effects of the two stimuli are fused together and leads to a forceful contraction. The curve has higher amplitude and a broader base than the normal curve and also it has two points of stimulation (Fig. 14.4).

***There are two types of summation:***

a. Wave/temporal summation
b. Multifiber/quantal summation.
a. *Wave/temporal summation:* The stimuli are of same strength, but the frequency of stimuli are increased and the contractions are fused.
b. *Multifiber/quantal summation:* The strength is increased, so that the number of motor units contracting is increased.

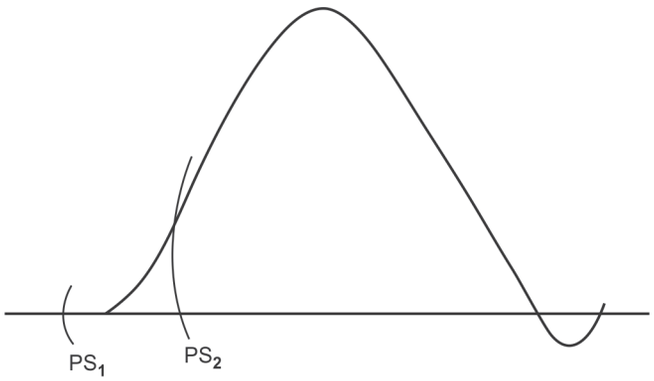



**Fig. 14.4:** Effect of second stimulus during contraction period on muscle contraction

## Refractory Period

Refractory period is the period after the application of the 1st stimulus during which a 2nd stimulus of adequate strength fails to produce a response. In skeletal muscle the refractory period is less than 0.005 second and is represented by the early part of LP in the simple muscle twitch.

*It has two phases:*

i. *Absolute refractory period:* It is the period during which a 2nd stimulus will not produce a response, whatever be the intensity of the stimulus.
ii. *Relative refractory period:* It is the period during which a second stimulus of stronger intensity can produce a response.

***Inference***

In skeletal muscle, the 2nd stimulus is effective during relaxation period and contraction period, but ineffective during latent period (Fig. 14.5).

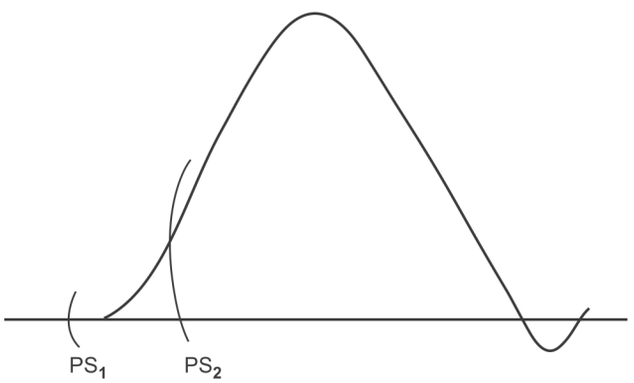



**Fig. 14.5:** Graph showing the importance of refractory period on muscle contraction

## EFFECT OF TEMPERATURE ON SIMPLE MUSCLE TWITCH

**a. Effects of warm Ringer's solution (Figs 14.6A and B)**

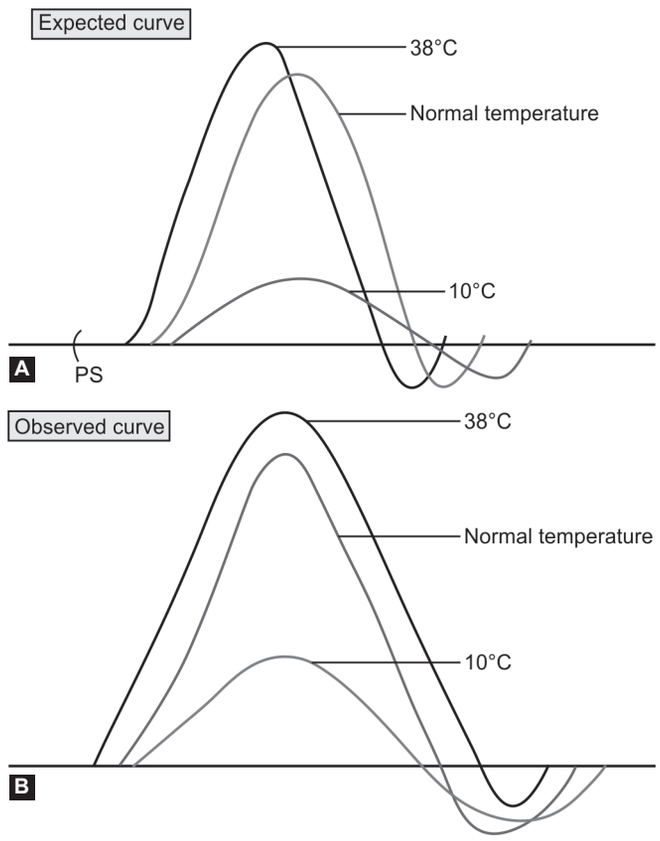
i. Decrease in LP.
ii. Decrease in CP and RP.
iii. Increase in amplitude or strength of muscle contraction.

### Causes for These Changes

i. Increase in enzymatic and metabolic processes.
ii. Increase in velocity of nerve conduction and transmission.
iii. Decrease in viscosity of muscle protein.

### *Heat Rigor*

At temperature above 42°C, the muscle proteins coagulate causing a condition known as heat rigor, which is an irreversible process.




**Figs 14.6A and B:** (A) Expected curve of effect of temperature on muscle contraction; (B) Observed curve of effect of temperature on muscle contraction

**b. Effects of cold Ringer's solution (Figs 14.6A and B)**

i. Increase in LP.
ii. Increase in contraction and relaxation period.
iii. Decrease in amplitude or strength of muscle contraction.

***Causes for these changes***

i. Decrease in enzymatic and metabolic processes.
ii. Decrease in velocity of nerve conduction and transmission.
iii. Increase in viscosity of muscle protein.

### *Cold Rigor*

With very low temperature the muscle fails to contract and there will be no response to stimulus, which is a reversible process.

## GENESIS OF FATIGUE

### Fatigue

Fatigue is defined as the inability of muscle to respond to a stimulus following repeated stimulation. Neuromuscular junction is the site of fatigue in muscle nerve preparation.

When a muscle is repeatedly stimulated the first few contractions increase in amplitude due to beneficial effect. When further stimulated, amplitude decreases and there is incomplete relaxation, ultimately the muscle does not respond to any stimulation (Fig. 14.7A).

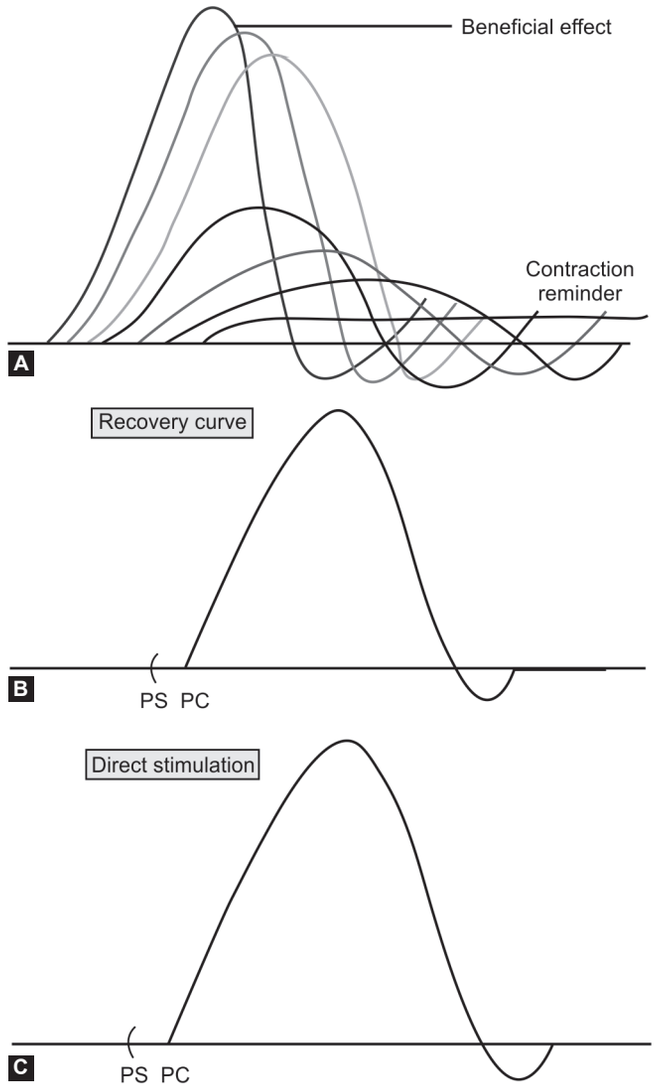
### *Causes of Fatigue*

1. Anoxia.
2. Accumulation of metabolic waste products like lactic acid. Small amounts of lactic acid increases excitability, but high concentration decreases it.
3. Depletion of acetylcholine.
4. Shortage of energy producing substances like glycogen, creatine phosphate.
5. Failure to re-establish the electrical potential due to repeated stimulation.

Synapse is the site of fatigue in an intact animal. Neuromuscular junction is the site of fatigue in an isolated preparation. Fatigue is reversible which is proved by the recovery curve (Fig. 14.7B).

***Factors affecting fatigue***

a. Fatigue is enhanced by:
   1. Increasing the frequency of stimulation.
   2. By application of load.
   3. Increase in temperature.
   4. Lack of $O_2$.
b. Factors favoring recovery:
   1. Giving rest
   2. Giving $O_2$




**Figs 14.7A to C:** (A) Phenomenon of fatigue; (B) Recovery curve; (C) Effect of direct stimulation on muscle contraction

***Inference***

Repeated stimulation causes fatigue of muscle. Site of fatigue is the neuromuscular junction in an isolated gastrocnemius-sciatic preparation (Fig. 14.7C). Fatigue is a reversible process.

## EFFECT OF AFTERLOAD AND FREE-LOAD ON MUSCLE CONTRACTION

### Afterload

It is the load acting on the muscle after it starts contracting. It has no effect on the muscle before it contracts and so there is no initial stretching of the muscle fiber (Fig. 14.8).

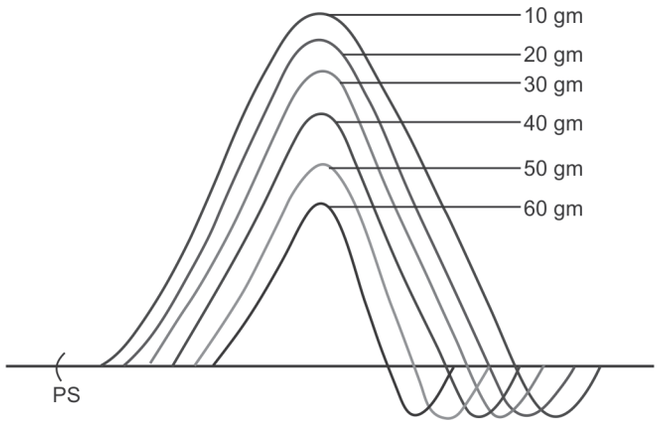



**Fig. 14.8:** Effect of afterload on muscle contraction

## Free-load

It is the load acting on the muscle even before it starts contracting. It will stretch the muscle fiber before it contracts.

### *Observation*

With increase in load, the amplitude decreases. In free-load, the contraction obtained for a given weight is of higher amplitude than that obtained for the same weight in afterload. This is because in free-load, the initial length of the muscle is increased. So there is increase in force of contraction. This proves Starling's law. This law is also applicable to cardiac muscle. When venous return to the heart is increased. So there is an increase in the initial length of the muscle fiber and force of contraction is increased.

For example for free-load: Throwing the ball in shot put.

For example for afterload: Lifting a weight from the ground.

***Calculation of work done***

Force applied to move an object through a given distance is called work done.

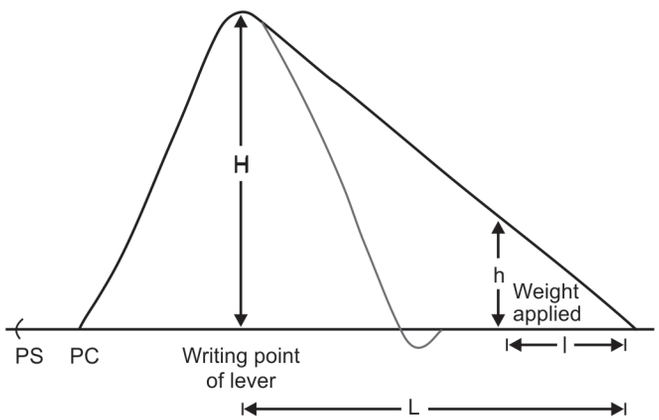



**Fig. 14.9:** Schematic diagram for the calculation of work done

$$W = F \times h$$

$$\text{From the Figure 14.9, } h = \frac{H \times I}{L}$$

where,

W= Work done

F = Force applied

H= Apparent height of contraction for each weight applied

h = Actual height to which weight is lifted

l = Distance between fulcrum of lever and weight applied

L = Distance from the fulcrum and the writing point of the lever.

## GENESIS OF TETANUS

It is incomplete tetanus where subsequent stimuli fall during relaxation period of the previous one. So the curves obtained will have a wavy appearance. This occurs at a frequency of 20 vib/sec, there is partial fusion of individual contractions which is due to incomplete relaxation and curves do not touch baseline. This is called clonus.

## Tetanus

It is a smooth sustained contraction due to mechanical fusion of curves. Here subsequent stimuli fall during contraction period of previous one, but electrical properties are separate.

The minimum frequency at which tetanus occurs is called ***critical fusion frequency***. In frog it is 25 vib/sec. The critical fusion frequency depends on duration of contraction period. It is inversely proportional to the contraction period of the muscle. Conditions which increase the contraction period such as cold, fatigue, etc. will decrease the critical fusion frequency.

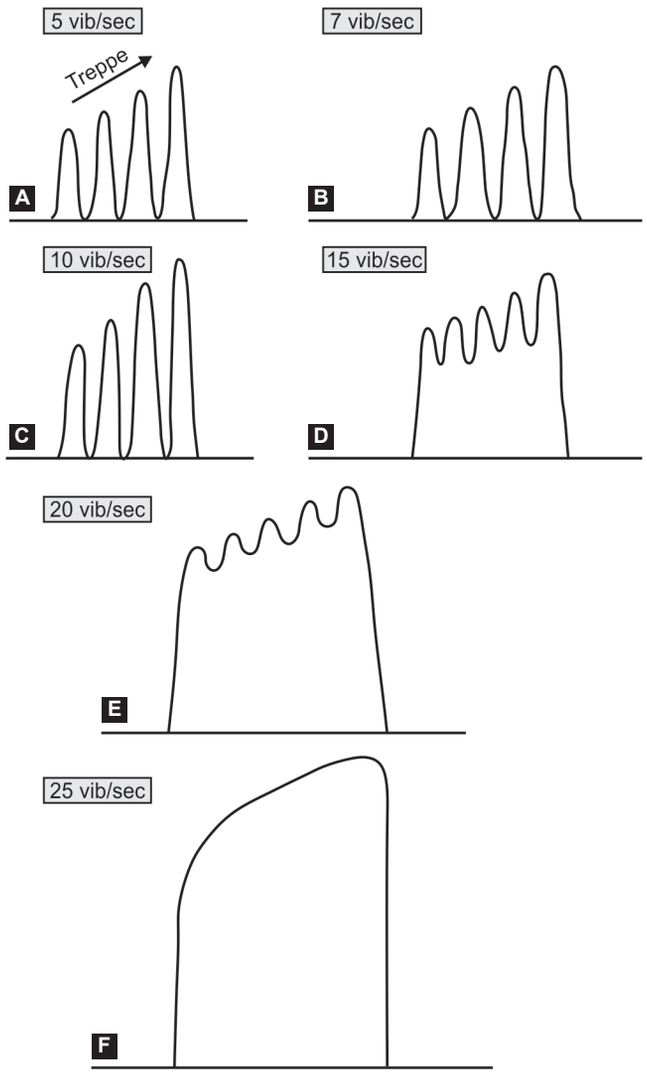
At a frequency of 30 vib/sec complete fusion of contractions take place, thereby producing a smooth sustained contraction called tetanus (Figs 14.10A to F).

### *Tetany*

It is a clinical condition where there is a spasm of muscle due to hypocalcemia, alkalosis.

***Factors affecting the genesis of fatigue***

a. *Type of muscle:* In fast white muscle, tetanizing/critical fusion frequency is small compared to slow red muscle.
b. *Temperature:* When temperature decreases, tetanus occurs at lower frequency of stimuli.
c. *Fatigue:* A fatigued muscle undergoes tetanus with low frequency of stimulus.
d. *Refractory period:* In skeletal muscle, refractory period is very short therefore they can undergo tetanus very easily. Cardiac muscle cannot be tetanized because of its long refractory period.




**Figs 14.10A to F:** Genesis of tetanus. The approximate rate of stimulation is indicated above each set of recording

***Note:*** The duration of one simple muscle twitch is 0.1 second so we do not get fusion of frequency up to a frequency of 10 vib/second.

## VELOCITY OF NERVE IMPULSE

$$\text{Velocity} = \frac{\text{length in meters}}{\text{time in seconds}}$$

This experiment shows that the conduction of nerve impulse is not an instantaneous phenomenon. Under similar electrical and chemical changes the difference in LP is due to the time taken for transmission of nerve impulse from vertebral end to muscle end (Fig. 14.11).

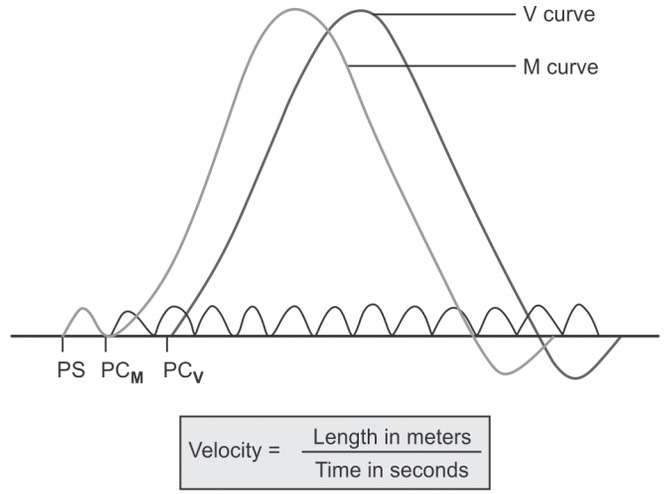



**Fig. 14.11:** Velocity of transmission of nerve impulse when stimulated from vertebral end and muscle end

### Factors which Increase Velocity

1. *Diameter of the nerve:* Thicker fibers conduct at a faster rate than thinner fibers. Velocity of nerve impulse is 5 m/s per micrometers diameter.
2. *Myelination of the nerve:* In myelinated fiber the impulse jump from 1 node of Ranvier to another, process called saltatory conduction. In myelinated fibers of frog velocity is 20–30 m/s.
3. *Temperature:* Increase in temperature increases velocity.

### Factors which Decrease Velocity

1. Mechanical pressure.
2. Narcotic drugs.
3. Fatigue.
4. Cold.

## AMPHIBIAN HEART EXPERIMENTS

### Normal Cardiogram of Frog

Frog's heart is three chambered with two auricles and one ventricle. in addition there is a sinus venosus that drains in to the auricles and the bulbous arteriosus which drains the ventricle. Difference between frog's heart and mammalian heart is given in Table 14.2

### Composition

#### *Ringer's Solution*

NaCl : 0.65 g%, it maintains rhythmicity
KCl : 0.014 g%, necessary for relaxation

| Table 14.2: Differences between frog's heart and mammalian heart | |
|---|---|
| *Frog's heart* | *Mammalian heart* |
| Three chambered | Four chambered |
| Sinus venosus is the pacemaker of heart | SA node is the pacemaker |
| Nutrition of heart is from the surrounding tissue fluid | Nutrition is from the coronary blood vessels which supply the heart |
| Chamber perfusion | Coronary perfusion |
| Specialized conducting system is absent | Specialized conducting system is present |
| Ringer's solution is used in the experiment | Ringer's lock solution is used. |
| Oxygen, pressure and temperature need not be maintained | Oxygen,temperature and pressure have to be maintained |

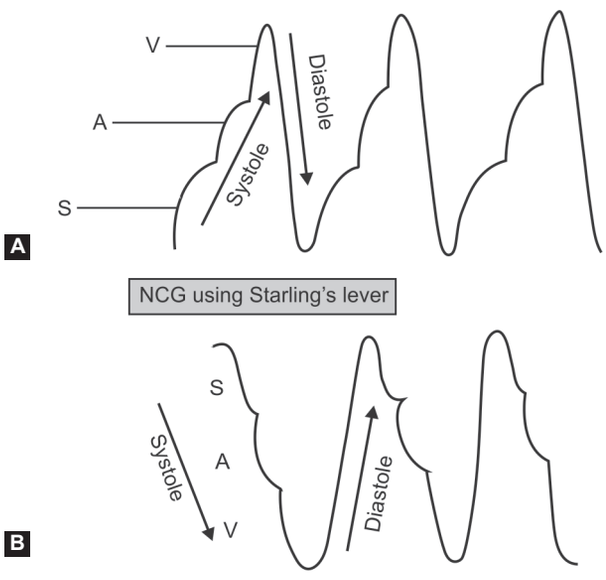
$CaCl_2$ : 0.012 g%, necessary for relaxation
$NaHCO_3$ : 0.02 g%, it acts as a buffer
Distilled water: 100 ml

### *Ringer Lock's Solution*

NaCl : 0.9 g%
KCl : 0.042 g%
$CaCl_2$ : 0.02 g%
$NaHCO_3$ : 0.02 g%
Glucose : 0.1 g%

***Note:*** When normal cardiogram (NCG) is recorded using a simple lever (Figs 14.12A and B), the upstroke indicates systole and the downstroke indicates diastole.

There are three waves in the systole S, A, V as shown in Figures 14.12A and B. 'S' wave is due to contraction of sinus venosus. 'A' wave is due to contraction of atria and 'V' wave is due to contraction of ventricle. The contraction of ventricle is followed by relaxation. These are the sequences of events occurring in the heart and it indicates the rhythmicity if the heart. It also helps to determine the heart rate with the help of time tracing below the NCG.




**Figs 14.12A and B:** (A) Record of normal cardiogram of frog using simple lever; (B) Record of normal cardiogram of frog using Starling's lever

## Bulbus Arteriosus

On the ventral aspect of the frog's heart there is an initial dilated portion of the aorta called as bulbus arteriosus.

White crescentic lie on the dorsal aspect of the frog's heart. The auricles and the sinus venosus are separated by white crescentic line which represents the parasympathetic nerve ganglion.

## Effect of Temperature on Frog's Heart

The effect of temperature (heat and cold) on frog's heart can be studied separately under:

a. Effect on sinus venosus
b. Effect on ventricle

**a. Effect on sinus venosus**

***i. Effect of heat on sinus venosus (Fig. 14.13A)***

Two effects are seen:

1. *Increase in heart rate (1° effect):* Sinus venosus is the pacemaker in the frog's heart. Application of warm saline increases the rate at which impulse is generated. Therefore the heart rate is increased.
2. *Force of contraction of heart decreases (2° effect):* This is because increase in the heart rate will decrease the diastolic pause. Therefore ventricular filling decreases. So EDV decreases, so there is decreased stretching of ventricular muscle fibers, so force of contraction decreases (Frank-Starling law).

***ii. Effect of cold on sinus venosus (Fig. 14.13B)***

Two effects are seen:

1. *Decrease in heart rate (1° effect):* This is due to decrease in the rate of impulse generation at sinus venosus.

2. *Force of contraction of heart increases(2° effect):* When cold saline is applied on sinus venosus the heart rate decreases, but the diastolic pause increases. Therefore, there will be increased diastolic filling, which increases the EDV. Hence there will be increased stretching of ventricular muscle fibers, thereby increasing the force of contraction (according to Frank-Starling law of cardiac muscle).

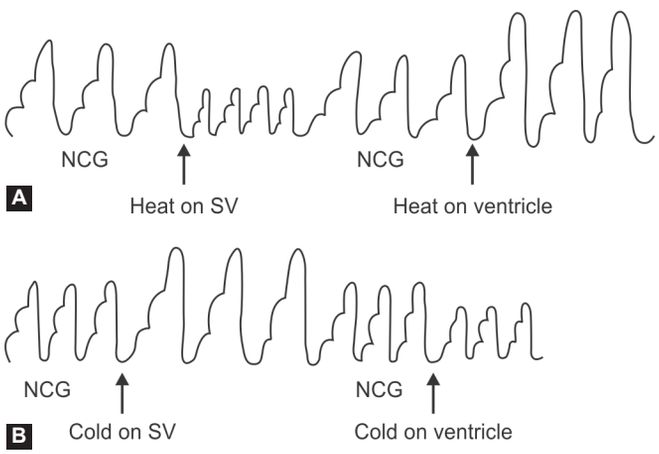
**b. Effect on ventricles**

***i. Effect of heat on ventricles (Fig. 14.13A)***

1. No change in heart rate
2. Force of contraction of heart increases.
   There is no change in heart rate as ventricle is not the pacemaker of the frog's heart. Further the force of contraction increases because of increase in metabolism of the ventricle and also there is decrease in the viscosity of muscle protein.

***ii. Effect of cold on ventricles (Fig. 14.13B)***

1. No change in heart rate (HR)
2. Force of contraction of heart decreases
   There is no change in HR as ventricle is not the pacemaker of the frog's heart. The force of contraction decreases because of decrease in metabolism of the ventricle and also there is increase in the viscosity of muscle protein.




**Figs 14.13A and B:** (A) Effect of heat on sinus venosus and ventricles of frog's heart; (B) Effect of cold on sinus venosus and ventricles of frog's heart

## Effect of Stannius Ligature on Frog's Heart

Application of ligature is an attempt to block the transmission of cardiac impulse from sinus venosus to auricles in the 1st ligature and from atria to ventricles in the 2nd ligature.

1. **Effect of 1st Stannius ligature (Fig. 14.14)**
   1st Stannius ligature is applied on the white crescentic line between sinus venosus and the atria.

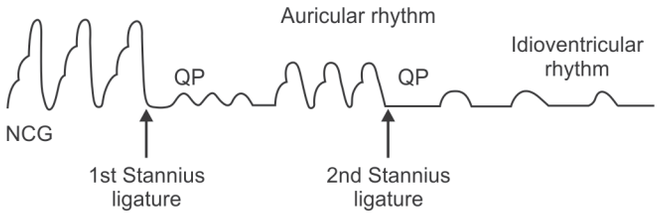



**Fig. 14.14:** Effect of Stannius ligature on frog's heart

   a. After the 1st ligature, the heart stops except at the sinus venosus due to blockage of impulses coming from the sinus venosus. Therefore sinus venosus will continue to beat on its own because it is the pacemaker of the heart. This is called ***sinus rhythm.***
   b. The atria and ventricle stop beating in diastole. But after some time the atria initiate their own impulse and start beating on their own at a slower rate independent of the sinus rhythm. This is called ***auricular rhythm.*** The impulse from the atria reach the ventricle and they also start beating.

2. **Effect of 2nd Stannius ligature (Fig. 14.14)**
   2nd Stannius ligature is applied on the atrio-ventricular groove between two atria and the ventricle in the frog's heart.

   When the 2nd Stannius ligature is applied, the auricles stop contracting whereas the ventricles continue to contract at its own rhythm. This is the ***idioventricular rhythm.***

   a. Average rate of impulse production (human heart)
      SA node = 72/min
      AV node = 50/min
      Ventricle = 30/min
   b. Velocity of conduction (human heart)
      SA node = 0.05m/s
      AV node = 0.05m/s
      Atrial and ventricular musculature=1m/s
      Bundle of His = 1m/s
      Purkinje fibers = 4 m/s
      *In frog's heart*
      Heart rate = 50–60/min
      Auricular rhythm = 20–30/min
      Idioventricular rhythm = <10/min

## Refractory Period and Extrasystole in Frog's Heart

Refractory period is a brief period during which cardiac muscle does not respond to restimulation. It has two phases:

1. **Absolute refractory period:** It is the period during which a 2nd stimulus will not produce any response whatever be the intensity of the stimulus. In cardiac muscle, it extends

throughout contraction period (systole) and early part of relaxation period (diastole) and is about 0.25–0.3 sec.

2. **Relative refractory period:** It is the period during which a 2nd stimulus of stronger intensity can produce a response. The rest of diastole is in the relative refractory period and is about 0.05 second.

***Note:*** Summation and tetanus are not possible in cardiac muscle because whole of contraction is in absolute refractory period. A long refractory period is due to prolonged repolarization in cardiac muscle.

### *Functional Significance of Long Refractory Period*

1. It maintains the normal rhythm of heart.
2. Summation and tetanus are not possible in heart muscle.
3. Under normal condition it would not produce any extrasystole.
4. If extrasystole occurs the compensatory pause helps to regain the normal rhythm.

Normally the impulse passes from atria to ventricle in an orderly sequence. When the ventricle is stimulated in the later part of diastole, an extrasystole is produced because the heart is in the relative refractory period. During this time a normal impulse from SA node reaches the ventricle but it fails to produce a contraction because the heart is in the absolute refractory period of extrasystole. This missing of 1 beat produces the compensatory pause. Only when the next normal impulse from SA node reaches the ventricle it will respond. So the total duration of extrasystole, preceding contraction and compensatory pause equals to two normal cardiac cycle.

***Extrasystole (Fig. 14.15)***

It is the response of myocardium to a stimulus other than one from the normal pacemaker. It can be auricular, nodal or ventricular in man.

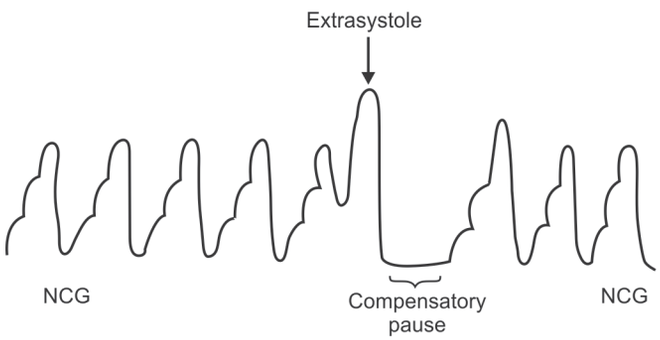



**Fig. 14.15:** Graph showing extrasystole and compensatory pause in frog's heart

*Causes of extrasystole*

1. Physiological
   a. Excessive consumption of alcohol, coffee and smoking
   b. Occasionally in pregnancy.
2. Pathological
   a. Digitalis toxicity
   b. Ischemic heart disease
   c. Rheumatic carditis
   d. Thyrotoxicosis.

## Effect of Vagal Stimulation on Frog's Heart

With weak stimuli, the heart may beat faster and more forcefully due to the excitation of sympathetic fibers present in the vagal trunk. With increase in the strength of stimuli the heart beat becomes slower and weaker. Finally the heart stops in diastole. This is called ***vagal inhibition.*** With continued stimulation of the vagus (do not increase the strength of current), the heart starts beating at a slower rate inspite of the stimulation,which is the idioventricular rhythm. This phenomenon is called the ***vagal escape*** **(Fig. 14.16).** Then when the stimulus is stopped the heart beats normally.

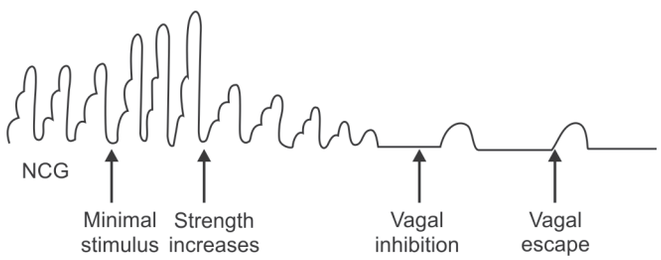



**Fig. 14.16:** Effect of vagal stimulation on frog's heart

### *Vagal Escape*

It is the escape of the heart from the inhibitory effect of vagus.

***Cause of vagal escape***

1. Depletion of acetylcholine due to continous stimulation.
2. Idioventricular rhythm: The lower 2/3rd of the ventricle is not supplied by the vagus. So it starts contracting on its own even while the vagus is being stimulated.
3. Stimulation of sympathetic fibers present in the vagal nerve.

## Effect of Adrenaline, Acetylcholine on Frog's Heart

1. **Adrenaline:** Adrenaline is stimulatory to frog's heart.

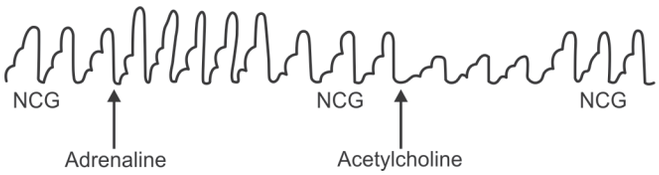



**Fig. 14.17:** Effect of adrenaline, acetylcholine on frog's heart

### *Actions of Adrenaline*

It increases:
a. *Rate of contraction:* +ve chronotropic effect
b. *Force of contraction:* +ve inotropic effect
c. *Velocity of contraction:* +ve dromotropic effect
d. *Irritability:* +ve bathmotropic effect.

***Explanation***

Adrenaline increases the heart rate due to its effect on sinus venosus (Fig. 14.17). Increase in the force of contraction is due to its direct effect on ventricular contraction. Action of adrenaline in heart is mediated through β-receptors.

**2. Acetylcholine:** It is inhibitory to frog's heart.

***Actions of acetylcholine***

It decreases:
a. *Rate of contraction:* –ve chronotropic effect
b. *Force of contraction:* –ve inotropic effect
c. *Velocity of contraction:* –ve dromotropic effect.

## Perfusion of Frog's Heart and Effect of Ions on it

### *Frog's Heart is Perfused with Ringer's Solution*

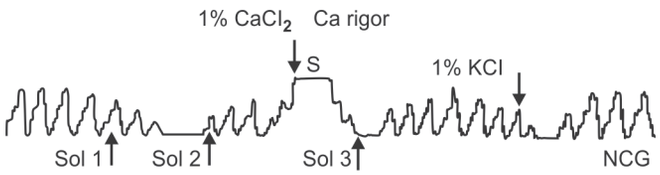



**Fig. 14.18:** Effect of perfusion of frog's heart and effect of ions on it

***Solution I:*** Contains 0.65% NaCl . The heart beats rhythmically but becomes weaker and weaker and finally stops in diastole. Solution I is removed and solution II is added (Fig. 14.18).

***Solution II:*** Contains 0.012% $CaCl_2$ in addition to NaCl. The heart regains rhythmicity but contractions become slow and sustained. Relaxation becomes less and less. Now when 1 drop of 1% $CaCl_2$ is added the heart stops in systole. This is called *calcium rigor.* Solution II is removed and solution III is added.

***Solution III:*** Contains 0.014% KCl in addition to the above ions. The heart relaxes quickly and gradually begins to beat normally. But after sometime the amplitude falls. Now when 1 drop of 1% KCl is added heart stops in diastole. This is called *$K^+$ inhibition.* Now when the solution is removed and Ringer's solution is added, heart regains its normal amplitude and rhythm.

***Discussion***

**1. Action of NaCl**
   $Na^+$ ions are essential for:
   a. Excitation of heart
   b. Maintaining rhythmicity.

**2. Action of $Ca^{2+}$**
   a. Maintain contractibility
   b. For sliding action of actin and myosin $Ca^{2+}$ is necessary.

*Causes of calcium rigor*

When contraction increases more ATP is utilized and complete loss of ATP occurs. Relaxation depends on ATP, which when lost relaxation is ultimately inhibited. Excess of $Ca^{2+}$ causes heart to go into spastic contractions and the heart stops in systole.

**3. Action of $K^+$:** Necessary for relaxation

*$K^+$ inhibition*

When excess of $K^+$ is present in ECF, it causes heart to become extremely dilated and flaccid. The heart is slowed and stops in diastole.

Chapter

# 15 Clinical Examinations (Reporting Pattern)

## CLINICAL EXAMINATION PROFORMA

Name :
Age :
Sex :
Occupation :
Address :

### General Examination

| | | |
|---|---|---|
| Built and nourishment | : | Moderately built and adequately nourished |
| Height | : | |
| Weight | : | |
| Pallor | : | No pallor |
| Jaundice /Icterus | : | Not jaundiced |
| Cyanosis | : | Not cyanosed |
| Clubbing | : | No clubbing of fingers or toes. |
| Lymphadenopathy | : | No significant lymph node enlargement |
| Edema | : | No edema |
| Skin and hair | : | Skin and hair healthy |
| Pulse | : | 72/min regular, normal in volume, character and tension, no thickening of vessel walls, all peripheral pulsations are felt equally and normally on both sides and there is no brachio femoral delay. |
| Blood pressure | : | 120/80 mm Hg in the right upper limb in supine position. |
| JVP | : | Not raised |
| Respiratory rate | : | 14/min, regular |
| Body temperature | : | 37°C |

### Impression

On general examination, the subject appears to be normal.

***Note***

1. *Pallor:* It gives a rough assessment of degree of anemia of the patient. It is looked for by retracting the lower eyelids and observing the color of palpebral conjunctiva. It is normally red in color. Pallor is also noted by color of skin, especially of palms, nail bed, mucosa of tongue and oral cavity.
2. *Jaundice/Icterus:* It is the yellowish discoloration of skin, sclera and mucous membrane due to deposition of bilirubin in tissues. Clinically obvious when serum bilirubin exceeds 2 mg/dl. Jaundice is looked for in upper sclera by asking the patient to lower his eyeballs.
3. *Cyanosis:* It is the bluish discoloration of the skin and mucous membrane due to an increase in amount of reduced Hb in blood above 5 gm%. Peripheral cyanosis is looked for at fingertips, ear lobes, tip of nose, etc. and central cyanosis at tongue and lips.
4. *Clubbing:* It is the thickening of tissues at base of nail associated with obliteration of angle between nail base and adjacent skin of the finger and increase in convexity of the nail. Clubbing is seen in cardiovascular diseases like cyanotic congenital heart disease, infective endocarditis; pulmonary diseases like bronchiectasis, chronic interstitial lung disease, chronic lung infection, lung abscess, lung cancer and other causes like cystic fibrosis, cirrhosis of liver, inflammatory bowel disease.
5. *Lymphadenopathy:* Different groups of lymph nodes are palpated. For example, cervical, axillary, inguinal, etc.
6. *Edema:* Presence of dependent edema in ambulant persons is usually detected by applying sustained firm pressure with the thumb against medial malleolus or shaft of tibia (for about 30 sec) and see for pitting or depression at pressure point.

## HUMAN ARTERIAL BLOOD PRESSURE

In clinical medicine, blood pressure is the lateral pressure exerted by the flowing blood in the systemic arteries.

### Apparatus

Sphygnomanometer and stethoscope
Sphygnomanometer has three important parts :
1. A mercury manometer
2. A rubber bag with linen cuff
3. An air pump.

### Definitions

1. Systolic blood pressure (SBP): It is the highest BP recorded during systole of cardiac cycle.
2. Diastolic blood pressure (DBP): It is the lowest BP recorded during diastole of cardiac cycle.
3. Pulse pressure (PP) = SBP-DBP
4. Mean arterial BP is the weighted mean pressure of blood. Mean arterial BP = DBP + 1/3PP.

### Procedure

Measurement is done by two methods:

#### *Palpatory Method*

Here the radial pulse is palpated. Pressure in the cuff is elevated until the pulse disappears. The cuff is then slowly deflated. Reading at which the pulse reappears corresponds to the systolic BP.

#### *Auscultatory Method*

Here brachial artery is auscultated during the measurement. Cuff is inflated 20–30 mm Hg above the systolic BP got by palpatory method. Slowly deflate the cuff and observe the manometer reading when a first tapping sound is heard. This corresponds to systolic BP. Now the cuff is slowly deflated listening to serial changes in the sound. The manometer reading when the sound completely disappears corresponds to diastyolic BP. Series of sound heard during deflation are called Korotkoff's sound and they are divided into five phases :

- *Phase I:* Sudden reappearance of a clear tapping sound. It becomes louder during 10–15 mm Hg fall of pressure.
- *Phase II:* Sound becomes soft and murmuring in the next 10–15 mm Hg fall of pressure.
- *Phase III:* Murmuring character continues but becomes louder and clear in the next 5–7 mm Hg fall of pressure.
- *Phase IV:* Sound becomes soft and muffled.
- *Phase V:* Sound completely disappears.

### Basis of Korotkoff's Sounds

Normal blood flow is laminar and stream lined and is always silent. Flow through a partially occluded vessels produces turbulence, hence a sound is produced. There is no sound in a completely occluded vessel. When the vessel is partially occluded by the pressure cuff there is turbulence. These sounds of vibration are transmitted and heard by auscultation. Appearance and disappearance of sounds are observed which corresponds to systolic and diastolic BP respectively.

### Auscultatory Gap and its Significance

In some patients of hypertension, there may be a gap in the Korotkoff sound. As the Hg is lowered, a few faint sounds are heard which soon disappear only to reappear once again at a lower pressure. This brief interruption, which may range from 40–60 mm Hg is called the 'auscultatory' or 'silent' gap. If the Hg column is raised to this gap and then the pressure lowered, one may miss the first appearance of sounds, which indicate systolic pressure, and thus record a false low systolic pressure.

To avoid this mistake, the BP should always be recorded by the palpatory method first. Then during auscultatory method, the Hg column must be raised 30–40 mm Hg above the level found by palpatory method. If we record BP only by auscultatory method, systolic BP may be underestimated due to the presence of auscultatory gap (particularly in HT individuals). But, during palpatory method this gap is not seen so there will be an idea of actual BP so, palpatory method is done before auscultatory method to get an approx value of systolic BP.

### Normal Values

*Systolic BP:* 100–140 mm Hg.
*Diastolic BP:* 60–90 mm Hg.

### Results

BP by palpatory method (systolic BP)
BP by auscultatory method
a. Sitting :
b. Standing :
c. Recumbent :
d. After exercise :

## EXAMINATION OF RESPIRATORY SYSTEM

Name :
Age :
Sex :
Occupation :
Address :

### General Examination

Built and nourishment : Moderately built and adequately nourished
Height :
Weight :
Pallor : No pallor
Jaundice /Icterus : Not jaundiced

| | | |
|---|---|---|
| Cyanosis | : | Not cyanosed |
| Clubbing | : | No clubbing of fingers or toes. |
| Lymphadenopathy | : | No significant lymph node enlargement |
| Edema | : | No edema |
| Skin and hair | : | Skin and hair healthy |
| Pulse | : | 72/min regular, normal in volume, character and tension, no thickening of vessel walls, all peripheral pulsations are felt equally and normally on both sides and there is no brachio femoral delay. |
| Blood pressure | : | 120/80 mm Hg in the right upper limb in supine position. |
| JVP | : | Not raised |
| Respiratory rate | : | 14/min, regular |
| Body temperature | : | 37°C |

### Systemic Examination

#### *Inspection*

Nostrils and throat normal
Trachea central
Shape of the chest normal bilaterally symmetrical.
Apex beat visible below and medial to the nipple.
Respiratory movements: Equal on both sides
Respiratory rate: .... /min. Rhythm: regular/irregular. Type: Abdomino thoracic or thoraco abdominal
No dilated veins or visible pulsations over the chest
No localized prominence/depression/intercostal edema

#### *Palpation*

Respiratory rate, rhythm, type of respiration
Trachea central
Apex beat-palpable (note the site also)/not palpable.
Respiratory movements equal over corresponding areas.
Chest expansion-cms
Vocal fremitus normal and equally present over corresponding areas.

#### *Percussion*

Percussion note is equally resonant over all corresponding areas except over the cardiac and liver dullness.

#### *Auscultation*

Normal vesicular breath sounds heard over all lung fields
Bronchial breath sounds heard over trachea
*Added sounds:* Nil (Rhonchi, crepititions, pleural rub)
Vocal resonance is normal and equal over all corresponding areas.

#### *Impression*

The respiratory system of the given subject appears to be normal.

***Note:*** For the purpose of physical examination and description of findings, the chest wall is divided into different areas bilaterally, i.e.

*In front*

- Supraclavicular area
- Clavicular area
- Infraclavicular area
- Mammary area
- Inframammary area.

*Sides*

- Axillary area
- Infra-axillary area.

*Behind*

- Suprascapular area
- Scapular area
- Interscapular area
- Infrascapular area.

## EXAMINATION OF CARDIOVASCULAR SYSTEM

| | | |
|---|---|---|
| Name | : | |
| Age | : | |
| Occupation | : | |
| Address | : | |

### General Examination

| | | |
|---|---|---|
| Built and nourishment | : | Moderately built and adequately nourished |
| Height | : | |
| Weight | : | |
| Pallor | : | No pallor |
| Jaundice /Icterus | : | Not jaundiced |
| Cyanosis | : | Not cyanosed |
| Clubbing | : | No clubbing of fingers or toes. |
| Lymphadenopathy | : | No significant lymphnode enlargement |
| Edema | : | No edema |
| Skin and hair | : | Skin and hair healthy |
| Pulse | : | 72/min regular, normal in volume, character and tension, no thickening of vessel walls, all peripheral pulsations are felt equally and normally on both sides and there is no brachio femoral delay. |
| Blood pressure | : | 120/80 mm Hg in the right upper limb in supine position. |

JVP : Not raised
Respiratory rate : 14/min, regular
Body temperature : 37°C

### Systemic Examination

#### *Inspection*

*Shape of precordium:* Normal, no bulging/deformity
*Apex beat:* Visible below and medial to the left nipple
*Jugular venous pulse:* Just visible/not visible.
*Other visible pulsations:* Suprasternal, carotid and epigastric pulsation not visible.

#### *Palpation*

Apex beat is felt in the 5th left intercostal space 1 cm medial to the midclavicular line.
*Thrills:* No thrills
*Left parasternal heave:* No LPH.

#### *Percussion*

The upper border of the liver percussed out in the 5th space in the midclavicular line, 7th space in the midaxillary line and 9th space in the scapular line on the right side. The right border of the heart corresponds with in the right border of the sternum and left border corresponds with the apex beat.

#### *Auscultation*

Mitral area : S1 and S2 sounds heard-normal intensity (S1 louder)
No additional sounds
No murmur/click/pericardial rub
Tricuspid area : S1 and S2 sounds heard-normal intensity (S1 louder)
No additional sounds
No murmur
Pulmonary area : S1 and S2 sounds heard-normal intensity (S2 louder)
No additional sounds
No murmur
Aortic area : S1 and S2 sounds heard-normal intensity (S2 louder)
No additional sounds
No murmur

#### *Impression*

The cardiovascular system of the subject appears to be normal.

***Note:*** For the sake of auscultation, the precordium is divided into the following areas:

- *Mitral area:* 5th intercostals space 1 cm medial to the midclavicular line
- *Tricuspid area:* Lower end of the sternum to the left side
- *Aortic area:* 2nd right intercostal space close to the sternum
- *Pulmonary area:* 2nd left intercostal space close to the sternum

## EXAMINATION OF HIGHER FUNCTIONS AND SENSORY SYSTEM

Name :
Age :
Occupation :
Address :

### General Examination

Built and nourishment : Moderately built and adequately nourished
Height :
Weight :
Pallor : No pallor
Jaundice /Icterus : Not jaundiced
Cyanosis : Not cyanosed
Clubbing : No clubbing of fingers or toes.
Lymphadenopathy : No significant lymph node enlargement
Edema : No edema
Skin and hair : Skin and hair healthy
Pulse : 72/min regular, normal in volume, character and tension, no thickening of vessel walls, all peripheral pulsations are felt equally and normally on both sides and there is no brachio femoral delay.
Blood pressure : 120/80 mm Hg in the right upper limb in supine position.
JVP : Not raised
Respiratory rate : 14/min, regular
Body temperature : 37°C

### Higher Functions

General appearance and behavior : Normal
Level of consciousness : Conscious
Mental and emotional state : Cooperative
Delusions and hallucinations : No hallucinations or delusions
Orientation in place and time : Well oriented in time place and person
Memory : Normal
Intelligence : Normal
Sleep : Normal

Gait : Normal
Speech : Normal

### Sensory System (Table 15.1)

Stereognosis :
Sense of position :
Passive movements :
Report of sensory cranial nerves :
Paraesthesia :

***Impression:*** The higher functions and sensory system of the subject appears to be normal.

## EXAMINATION OF MOTOR SYSTEM

Name :
Age :
Sex :
Occupation :
Address :

### General Examination

Built and nourishment : Moderately built and adequately nourished
Height :
Weight :
Pallor : No pallor
Jaundice /Icterus : Not jaundiced
Cyanosis : Not cyanosed
Clubbing : No clubbing of fingers or toes.
Lymphadenopathy : No significant lymph node enlargement
Edema : No edema
Skin and hair : Skin and hair healthy
Pulse : 72/min regular, normal in volume, character and tension, no thickening of vessel walls, all peripheral pulsations are felt equally and normally on both sides and there is no brachiofemoral delay.
Blood pressure : 120/80 mm Hg in the right upper limb in supine position.
JVP : Not raised
Respiratory rate : 14/min, regular
Body temperature : 37°C

### Higher Functions

General appearance and behavior :
Emotional state :
Delusions and hallucinations :
Sleep :
Orientation in place and time :
Level of consciousness :
Memory :
Intelligence :
Gait :
Speech :

### Motor System (Examine both Upper Limb and Lower Limb)

1. Bulk of the muscle

| Left | Right |
|---|---|
| | |

2. Tone of the muscle
3. Strength (power) of the muscle

**Table 15.1: Examination of sensory system**

| *Sensation* | | *Trunk* | | | | *Limbs* | | | | *Face* | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *Front* | | *Back* | | *Upper* | | *Lower* | | *Rt* | *Lt* |
| | | *Rt* | *Lt* | *Rt* | *Lt* | *Rt* | *Lt* | *Rt* | *Lt* | | |
| **Touch** | | | | | | | | | | | |
| Fine touch | | | | | | | | | | | |
| Crude touch | | | | | | | | | | | |
| Tactile localization | | | | | | | | | | | |
| Tactile discrimination | | | | | | | | | | | |
| Vibration sense | | | | | | | | | | | |
| **Pain** | | | | | | | | | | | |
| Superficial pain<br>Pressure pain | | | | | | | | | | | |
| Pressure pain | | | | | | | | | | | |
| Temperature | Heat | | | | | | | | | | |
| | Cold | | | | | | | | | | |

### *Muscles of Upper Limb*

a. Abductor pollicis brevis :
b. Opponens brevis :
c. Dorsal interossei :
d. Interossei and lubricals :
e. Flexors of the fingers :
f. Flexors of the wrist :
g. Extensors of the wrist :
h. Brachioradialis :
i. Biceps, triceps, supraspinatus

| Left | Right |
|---|---|
| | |

j. Deltoid, infraspinatus :
k. Pectoralis :
l. Serratus anterior :
m. Latissimus dorsi :

### *Muscles of the Trunk*

a. Muscles of the abdomen :

| Left | Right |
|---|---|
| | |

b. Erector spinae and muscles of back :
c. Trapezius :
d. Diaphragm :

### *Muscle of the Lower Limb*

a. Intrinsic muscles of foot :
b. Flexors and extensors of toes and foot :
c. Flexors of the knee :
d. Extensors of the knee :
e. Extensors of thigh :
f. Flexors of thigh :
g. Adductors of thigh :
h. Abductors of thigh :
i. Rotators of the thigh :

4. Reflexes
5. Coordination of movements

### *Upper Limb*

- Finger-nose test
- Finger to finger test

### *Lower Limb*

- Straight line test
- Heel-knee test
- Romberg's test

6. Gait
7. Motor cranial nerves
8. Involuntary movements

***Impression:*** The motor system of the subject appears to be normal.

## EXAMINATION OF CRANIAL NERVE

Name :
Age :
Sex :
Occupation :
Address :

### General Examination

Built and nourishment : Moderately built and adequately nourished
Height :
Weight :
Pallor : No pallor
Jaundice /Icterus : Not jaundiced
Cyanosis : Not cyanosed
Clubbing : No clubbing of fingers or toes.
Lymphadenopathy : No significant lymphnode enlargement
Edema : No edema
Skin and hair : Skin and hair healthy
Pulse : 72/min regular, normal in volume, character and tension, no thickening of vessel walls, all peripheral pulsations are felt equally and normally on both sides and there is no brachio femoral delay.
Blood pressure : 120/80 mm Hg in the right upper limb in supine position.
JVP : Not raised
Respiratory rate : 14/min, regular
Body temperature : 37°C

### Higher Functions

Conscious
Cooperative
Well oriented in time, place and person
Memory and intelligence : normal
No hallucinations, delusions/illusions
Speech and articulation: normal
Sleep : normal
Right handed person/Left handed person
Gait : normal

## Cranial Nerves Examination

### 1. Olfactory Nerve

Test for sense of smell

| Left | Right |
|---|---|
| | |

### 2. Optic Nerve

a. Visual acuity
   - Distant vision (using snellen's chart)
   - Near vision (using Jager's chart)
b. Field of vision (confrontation test)
c. Color vision (using Ishihara chart)

### 3. Occulomotor 4. Trochlear 6. Abducent nerves

a. Presence of squint, nystagmus and ptosis

| Left | Right |
|---|---|
| | |

b. Size and shape of pupil
c. Ocular movements
d. Light reflex
   - Direct
   - Indirect (consensual)
e. Accomodation reflex

***Note:*** Both light reflex and accommodation reflex are included under pupillary reflexes.

### 5. Trigeminal

| Left | Right |
|---|---|
| | |

***Test for sensory functions***

a. Sensations over face
b. Corneal reflex
c. Conjunctival reflex
d. Jaw jerk

***Test for motor functions***

a. Ask the patient to clench his teeth
b. Ask the patient to open his mouth

### 7. Facial Nerve

***Test for sensory functions***

| Left | Right |
|---|---|
| | |

a. Taste sensation over anterior 2/3rd of tongue

***Test for motor functions***

a. Look for wrinkle over forehead
b. Ask subject to close his eyes tightly and then tell him to open it against resistance
c. Look for nasolabial folds on both sides
d. Ask the subject to smile
e. Ask the subject to inflate both cheeks (Inflation test)
f. Ask the subject to whistle

### 8. Vestibulocochlear Nerve

| Left | Right |
|---|---|
| | |

a. Watch test
b. Rinne's test
c. Weber's test
d. Schwabach's test
e. Barany's test

### 9. Glossopharyngeal Nerve

***Test for sensory functions***

| Left | Right |
|---|---|
| | |

a. Taste sensation over posterior 1/3rd of tongue
b. Sensations in mucous membrane of soft palate and palate

***Test for motor functions***

a. Pharyngeal reflex (Gag reflex)
b. Palatal reflex
c. Nasal twang
d. Nasal regurgitation
e. Dysphagia and dysphonia

### 10. Vagus Nerve

a. Nasal twang
b. Nasal regurgitation
c. Test palatal arch during phonation (by saying 'Ah')
d. Deviation of uvula
e. Pharyngeal reflex (Gag reflex)
f. Palatal reflex

### 11. Accessory Nerve (Spinal)

| Left | Right |
|---|---|
| | |

a. Ask the subject to shrug his shoulders against resistance
b. Ask the subject to turn his head against resistance with a hand on side of face

### *12. Hypoglossal Nerve*

| Left | Right |
|---|---|
| | |

a. Look for any deviation on protrusion of tongue
b. Movements of the tongue
c. Look for any fasciculation, wasting and tremors of tongue
d. Look for protrusion of cheek on pushing with tongue

***Impression:*** The cranial nerves of the subject appears to be normal.

## EXAMINATION OF REFLEXES

Name :
Age :
Sex :
Occupation :
Address :

### General Examination

Built and nourishment : Moderately built and adequately nourished
Height :
Weight :
Pallor : No pallor
Jaundice /Icterus : Not jaundiced
Cyanosis : Not cyanosed
Clubbing : No clubbing of fingers or toes.
Lymphadenopathy : No significant lymphnode enlargement
Edema : No edema
Skin and hair : Skin and hair healthy
Pulse : 72/min regular, normal in volume, character and tension, no thickening of vessel walls, all peripheral pulsations are felt equally and normally on both sides and there is no brachio-femoral delay.
Blood pressure : 120/80 mm Hg in the right upper limb in supine position.
JVP : Not raised
Respiratory rate : 14/min, regular
Body temperature : 37°C

### Examination of Reflexes

#### *Superficial Reflexes*

Conjunctival

| Left | Right |
|---|---|
| | |

Corneal
Palatal
Pharyngeal
Abdominal
Cremasteric
Plantar

### Deep Tendon Reflexes

Jaw Jerk
Biceps Jerk
Triceps Jerk
Supinator
Knee Jerk
Ankle Jerk

### Viceral Reflexes

Micturition
Defecatrion
Sexual Function

### Note

#### *Superficial Reflexes*

***Conjunctival reflex***

Afferent : Ophthalmic division of trigeminal nerve.
Efferent : Facial nerve.
Center : Pons

***Corneal reflex***

Afferent : Ophthalmic division of trigeminal nerve.
Efferent : Facial nerve.

***Palatal reflex***

Afferent : Glossopharyngeal nerve.
Efferent : Vagus nerve.

***Superficial abdominal reflex***

Spinal segment: $T_7$–$T_{12}$

***Plantar reflex***

Spinal segment: $L_5$, $S_1$

***Deep reflexes***

Knee jerk : $L_2$–$L_4$
Ankle jerk : $S_1$, $S_2$
Triceps jerk : $C_6$, $C_7$
Biceps jerk : $C_5$, $C_6$
Supinator jerk : $C_5$, $C_6$

# Section 3

## RAPID FIRE

*Chapter*

# 16

# Multiple Choice Questions

## GENERAL PHYSIOLOGY

**1. Glucose is transported into the cell by:**
a. Simple diffusion
b. Primary active transport
c. Facilitated diffusion
d. Endocytosis

**2. Resting membrane potential develops mainly due to:**
a. $K^+$ efflux
b. $Cl^-$ influx
c. $Ca^{2+}$ influx
d. $Na^+$ efflux

**3. Part of action potential that coincides with absolute refractory period is:**
a. Depolarization
b. Hyperpolarization
c. Depolarization and 1/3 of repolarization
d. After repolarization

**4. Decrease in colloidal osmotic pressure leads to:**
a. Dehydration
b. Edema
c. No change in the body fluid
d. Acidosis

**5. One of the following is not a second messenger:**
a. NO
b. cGMP
c. IP3
d. cAMP

**6. Na-K pump contribution to RMP in excitable tissue is:**
a. 4 mV
b. 15 mV
c. 60 mV
d. 10 mV

**7. Depolarization in an excitable tissue may be due to the following factors except:**
a. $Na^+$ influx
b. $Ca^{2+}$ influx
c. Associated with increased membrane permeability to $Na^+$ in nerves and striated muscle
d. $K^+$ influx

**8. Gap junctions are present in one of the following tissues:**
a. Skeletal muscles
b. Neurons
c. Cardiac muscle
d. Epithelial tissue

**9. Isotonic fluids should contain:**
a. 300 mOsm/L
b. 350 mOsm/L
c. 10 mOsm/L
d. 400 mOsm/L

**10. Minimum strength of stimulus required to elicit an impulse when applied for long duration is:**
a. Chronaxie
b. Rheobase
c. Utilization time
d. Threshold stimulus

**11. Cell shape and motility are provided by:**
a. Microfilament
b. Microtubules
c. Golgi apparatus
d. Both a and b

**12. A unique characteristics of smooth muscle is that:**
a. It can sustain a contraction for prolonged periods
b. Calcium is not required for contraction
c. Repetitive contractions are not possible
d. Myosin filaments are not required

**13. The ionic channels in excitable membrane are lined by:**
a. Cephalins
b. Proteins
c. Lipids
d. Carbohydrates

**14. ECF volume is measured by using:**
a. Insulin
b. Inulin
c. Evans blue
d. $D_2O$

**15. Cyclic AMP acts a second messenger in the secretion of all except:**
a. FSH
b. Estrogen
c. Glucagon
d. Epinephrine

**16. The most important buffer in the extracellular fluid is:**
a. Hemoglobin
b. Protein
c. Phosphate
d. $H_2CO_3$: $HCO_3^-$

**17. The substance essential for the transfer of fatty acids across mitochondrial membrane:**
a. Creatine
b. Creatinine
c. Carnitine
d. Co-enzyme A

**18. Which of the following does not act intracellularly to produce physiological effects:**
a. Triiodothyronine
b. Inositol triphosphate
c. Aldosterone
d. Cyclic AMP
e. Dopamine

**19. $Ca^{2+}$ binding proteins are involved in excitation-contraction coupling in:**
a. Skeletal muscle
b. Smooth muscle
c. Both
d. Neither

**20. Aquaporin channels transport mainly:**
a. $H_2O$
b. $Na^+$
c. $Ca^{2+}$
d. Glucose

**21. Exocytosis requires**
a. $Na^+$
b. $K^+$
c. $Ca^{2+}$
d. $Mg^{2+}$

**22. Microfilaments are made up of:**
a. Calmodulin
b. Myosin
c. Actin
d. Titin

**23. Gated ion channels open or close by:**
a. Alteration in membrane potential
b. Binding to an internal ligand
c. Binding to an external ligand
d. Depending upon lipid solubility of an ion

## CIRCULATING BODY FLUIDS

**1. Hemophilia B (Christmas disease) is produced by deficiency of coagulating factor:**
a. VII
b. V
c. IX
d. X

**2. Which of the plasma protein is not synthesized primarily in the liver:**
a. Angiotensinogen
b. Fibrinogen
c. Gamma globulin
d. Prothrombin

**3. Normal lifespan of RBC:**
a. 1 hour
b. 1 day
c. 1 week
d. 120 days

**4. Colloidal osmotic pressure contributed mainly by:**
a. Albumin
b. Fibrinogen
c. Thrombin
d. Prothrombin

**5. Humoral antibody formation response is shown by:**
a. Neutrophil
b. T lymphocytes
c. B lymphocytes
d. Monocytes

**6. The following are present in circulating blood except:**
a. Fibrinogen
b. Prothrombin
c. Thrombin
d. Albumin

**7. Erythropoietin is secreted by:**
a. Stomach
b. Adrenal cortex
c. Kidney
d. Bone marrow

**8. Adult hemoglobin has:**
a. 2 alpha and 2 delta chains
b. 2 alpha and 2 beta chains
c. 4 alpha chains
d. 2 alpha chains

**9. The conversion of fibrinogen to fibrin is caused by:**
a. Prothrombin
b. Thrombin
c. Plateletes
d. Fibrin stabilizing factor

**10. Plasma osmolality in a normal adult (in mOsm/L) is:**
a. 250
b. 310
c. 280
d. 320

**11. Cyanosis occurs when the reduced Hb level in the blood is:**
a. More than 5 g/100 ml
b. Less than 5 mg/100 ml
c. Less than 5 g/100 ml
d. More than 5 mg/100 ml

**12. Conversion of prothrombin to thrombin requires:**
a. Factor X
b. Factor VII, X, V, $Ca^{2+}$
c. Factor V
d. $Ca^{2+}$, Va, phospholipid and factor Xa

**13. This is not a vitamin K dependent blood clotting factor:**
a. Factor I
b. Factor II
c. Factor VII
d. Factor X

**14. Kernicterus is a condition characterized by:**
a. Bilirubin deposition in basal ganglia
b. Excessive greed to eat meat
c. Severe anemia
d. Mild anemia

**15. Megaloblastic anemia is not a feature of the:**
a. Vitamin $B_{12}$ (cyanocobalamine)
b. Folic acid
c. Iron
d. Gastric juice secretion

**16. With regard to blood transfusion:**
a. Transfusion cannot be done with one's own blood
b. ABO group antigens are present in the cytoplasm of the RBCs
c. ABO antigens are not present in any other tissue of the body
d. Cross matching is necessary before transfusion

**17. The total blood protein in 100 ml of blood is about:**
a. 7.3 gm
b. 23 gm
c. 45 gm
d. 23 mg

**18. Megaloblastic anemia is due to the deficiency of:**
a. Vitamin C
b. Iron
c. Vitamin E
d. Vitamin $B_{12}$

**19. The biggest cell in the bone marrow is:**
a. Reticulocytes
b. Megakaryocytes
c. Erythrocytes
d. Metamyelocytes

**20. Which of the following is true about stored blood:**
a. Decrease in intracellular Na
b. Increase in intracellular Na
c. Decrease in plasma K
d. None of the above

**21. Microcytic hypochromic RBCs are seen in:**
a. Hemorrhagic anemia
b. Folic acid deficiency anemia
c. Pernicious anemia
d. Iron deficiency anemia

**22. Normal reticulocyte count in adult is _____ % of normal RBC count:**
a. 0.1–0.2
b. 1–2
c. 5–10
d. 10–12

**23. Decreased MCHC is found in:**
a. Microcytic hypochromic anemia
b. After acute hemorrhage
c. Vitamin $B_{12}$ deficiency
d. Aplastic anemia

**24. von Willebrand factor has role in:**
a. Platelet adhesion against injured vascular surface
b. Activation of clotting factor
c. Clot lysis
d. Vasoconstriction

**25. Dicoumarol therapy inhibits synthesis of all the following factors except:**
a. Factor IX
b. Factor II
c. Factor VII
d. Factor I

**26. The fragility of RBC is decreased in all the following except:**
a. Thalassemia
b. Sickle cell anemia
c. Spherocytic anemia
d. Microcytic hypochromic anemia

**27. Macrophages are involved in the function of:**
a. Destroying senescent red cells and catabolism of hemoglobin
b. Phagocytosis of the organisms
c. Releasing chemicals which are toxic to the larvae of the parasites
d. Production of antibodies

**28. Lymphatics:**
a. Collects and transports proteins and lipids from the intestinal spaces
b. Exhibits bidirectional flow due to absence of valves
c. Do not have any role to play in the defense of the body
d. Drains directly into the arterial system

**29. Interleukins are secreted mainly by the:**
a. RBCs
b. Macrophages
c. Hepatic cells
d. Platelets

**30. Blood group of father being AA and mother BO, the child can belong to:**
a. A and B
b. B and AB
c. O and A
d. A and AB

**31. Citrate is useful anticoagulant because of its ability to:**
a. Bind vitamin K
b. Chelate calcium
c. Bind factor XII
d. Both a and b

**32. Increased erythrocyte production will occur in persons who:**
a. Live at high altitude
b. Have chronic pulmonary disease
c. Experience hemorrhage
d. All

**33. The integral membrane glycoprotein of human RBC is:**
a. Porrin
b. Ankyrin
c. Spectrin
d. Glycophorin

**34. Blood group antigens are:**
a. Attached to plasma proteins
b. Attached to hemoglobin molecule
c. Found in saliva of all persons
d. None

**35. Thromboxane A2 is released mainly by the:**
a. Platelets
b. Vascular endothelium
c. Liver
d. Muscles

**36. Reticulocytes are stained with:**
a. Brilliant cresyl blue
b. Sudan black
c. Indigo carmine
d. None

**37. Arneth count is:**
a. Counting the lymphocytes
b. Counting the lobes in the neutrophil
c. Counting the granules in the eosinophil
d. WBC counting in the bone marrow

**38. Iron is stored in the body in the following except:**
a. RE system
b. Spleen
c. Gallbladder
d. Bone marrow

**39. What prevents blood loss after rupture of small blood vessels:**
a. Vasoconstriction
b. Formation of fibrin threads
c. Formation of platelet plug
d. Production of hematoma to increase perivascular pressure
e. All of the above

**40. Neutropenia is seen in all except:**
a. Pernicious anemia
b. Bone marrow depression
c. Trauma
d. Megaloblastic anemia

**41. The best screening test for hemophilia is:**
a. BT
b. PT (prothrombin time)
c. CT
d. CRT

**42. Hemoglobin is a buffer because of its:**
a. Histidine residue
b. Glycoprotein nature
c. Weak acidic nature
d. Iron molecule

**43. Mean life of RBC in transfused blood is (in days):**
a. 120
b. 100
c. 60
d. 90

**44. Lifespan of neonatal RBC is:**
a. 120 days
b. 100 days
c. 6 months
d. 1 year

**45. Heparin, an anticoagulant, is manufactured by:**
a. Plasma cells
b. Mast cells
c. Lymphocytes
d. Blood platelets

**46. When infection occurs in tissue, what type of WBC is first attracted from the blood into the tissue by the process of chemotaxis:**
a. Neutrophils
b. Monocytes
c. Eosinophils
d. Basophils
e. Plasma cells

**47. Which of the following reflects glycemic control in diabetics:**
a. HbA
b. HbA2
c. HbA1C
d. HbC

**48. For what aspect of blood cell production is vitamin-$B_{12}$ essential:**
a. Formation of hemoglobin
b. Extrusion of the nucleus from the normoblasts
c. Formation of DNA
d. Activation of erythropoietin
e. Promotion of iron absorption from the intestinal tract

**49. Blood group antigens are:**
a. Unconjugated proteins
b. Glycoproteins
c. Amino acid derivatives
d. Steroidal hormones

**50. The cell membrane of human erythrocyte is more permeable to:**
a. $Cl^-$ than $K^+$
b. $K^+$ than $Na^+$
c. $K^+$ than urea

**51. Aggregation of platelet is inhibited by:**
a. $Ca^{2+}$
b. ADP
c. Thrombin
d. Prostacyclin

**52. Neutrophil count tends to fall in all except:**
a. Bacterial infection
b. Pernicious anemia
c. Drugs depressing bone marrow

**53. Intrinsic factor is secreted by:**
a. Liver
b. Chief cells of stomach
c. Parietal cells of stomach
d. Beta cells of pancreas

**54. Stuart prower factor is factor:**
a. VIII
b. IX
c. X
d. XII

**55. Lymphocyte is how much % of white cell count:**
a. 1–2%
b. 80%
c. 20–40%
d. 10%

**56. Total blood volume is _____ % of body weight:**
a. 8
b. 20
c. 40
d. 80

**57. Human cell membrane is composed of:**
a. Protein molecules
b. Carbohydrate and phospholipid
c. Lipoprotein mainly
d. Amino acid residues

**58. Patients with anemia tend to have:**
a. Decrease in cardiac output
b. Low oxygen tension in the arterial blood
c. Pallor of the mucous membrane

**59. Iron deficiency anemia is:**
a. More common in male than female
b. Caused by large pale erythrocytes
c. Followed by chronic blood loss from the body

**60. Factor used in the extrinsic pathway of blood coagulation is:**
a. V
b. VIII
c. Tissue factor
d. X

**61. Hemostasis is normally accomplished by or associated with:**
a. Polymerization of plasma fibrinogen molecule
b. Blood coagulation
c. Vascular spasm
d. Formaton of platelet plug
e. All of the above

**62. Anticoagulants that prevent coagulation when placed in a blood sample outside the body include all except:**
a. Citrate
b. Oxalate
c. Heparin
d. Coumarins

**63. Increased amounts of erythropoietin might be released from the kidneys in all cases except when the:**
a. Arterial $pO_2$ is normal and arterial $O_2$ content is reduced
b. Arterial $pO_2$ and arterial $O_2$ content are reduced
c. Arterial $pO_2$ is low and the saturation of hemoglobin with $O_2$ is much reduced
d. Tissue $pO_2$ and renal blood floe are both increased

**64. Which of the plasma protein has got the highest molecular weight:**
a. Fibrinogen
b. Albumin
c. Globulin

**65. What is the most important event in trival injury:**
a. Blood coagulation
b. Formation of platelet plug
c. Vascular spasm
d. Formation of thromboplastin
e. Formation of prothrombin activator

**66. Which is true about serum albumin:**
a. Contributes maximally to plasma oncotic pressure
b. It is anionic
c. Freely filterable in renal filter
d. Not synthesized in liver

**67. Decreased MCHC is found in:**
a. Microcytic hypochromic
b. Megloblastic anemia
c. Sideroblastic anemia
d. Vitamin $B_{12}$ deficiency

**68. Blood clotting can be prevented by the use of potassium oxalate. It is due to:**
a. Checking of conversion of fibrinogen into fibrin
b. Inactivation of all factors for blood coagulation
c. Neutralization of acidic medium
d. Removal of free $Ca^{2+}$ ion

**69. Histocompatibility complexes are the:**
a. Groups of proteins set to recognize antigen, by specific genes
b. Nonspecific antigen
c. Aggluntination product of antibody-antigen reaction
d. Colonies of B and tumor cells

**70. Which one of the following is related to vasoconstriction produced by blood platelets during hemorrhage:**
a. 5HT
b. Histamine
c. Thrombothenin
d. Bradykinin

**71. After hemorrhage, restoration of blood volume is due to:**
a. Arterial constriction
b. Shift of intracellular fluid to extracellular space
c. Increased venous return
d. Intravenous infusion

**72. Structure of Hb is normal but decreased in amount in:**
a. Chronic blood loss
c. Sickle cell anemia
c. Hemolytic anemia
d. Thalessemia

**73. T lymphocyte differentiate into all except:**
a. Helper cells
b. Plasma cells
c. Cytotoxic cells
d. Suppressor cells

**74. Abnormality of hereditary spherocytosis lies in:**
a. Spectrin molecule
b. CD4 Cells
c. Amino acid
d. Hb

## RESPIRATORY SYSTEM

**1. Compared with the apex of the lung, the base of the lung has:**
a. Same V/P ratio
b. A higher pulmonary capillary $pO_2$
c. A lower V/P ratio
d. A higher pulmonary capillary $pCO_2$

**2. Normal value of functional residual capacity is:**
a. 250 cc.
b. 500 cc.
c. 1200 cc.
d. 2200 cc.

**3. $CO_2$ is carried in venous blood mostly in the form of:**
a. Carbonic acid
b. Bicarbonate
c. Dissolved $CO_2$
d. Carbamino Hb

**4. Most potent respiratory stimulant is:**
a. Oxygen
b. $CO_2$
c. $K^+$
d. $H^+$

**5. Type II pulmonary epithelial cells secrete:**
a. Mucus
b. Polypeptide
c. Serotonin
d. Surfactant

**6. Which of the following change does not occur in high altitude acclimatization:**
a. Reticulocytosis
b. Increased serum cortisol
c. Increased rate of respiration
d. Decreased serum erythropoietin.

**7. Compliance of lungs is decreased in all conditions except:**
a. Fibrosis of lungs
b. Pulmonary edema
c. Emphysema
d. IRDS

**8. Alveolar ventilation is increased in:**
a. In rapid shallow breathing
b. In slow deep breathing
c. While breathing under the sea with SCUBA apparatus.
d. Immediately after hyperventilation

**9. The difference of amount of oxygen present in 100 ml of arterial blood and 100ml of venous blood at rest is equal to:**
a. 20 ml
b. 5 ml
c. 19.4 ml
d. 14.4 ml

**10. The lung volume which cannot be measured by using spirometer is:**
a. Residual volume
b. Vital capacity
c. Inspiratory reserve volume
d. Tidal volume

**11. Oxygen content of saturated arterial blood is:**
a. 11.2 ml/100 ml
b. 25 ml/100 ml
c. 19 ml/100 ml
d. 14.5 ml/100 ml

**12. CA is found in:**
a. Leukocytes
b. Erythrocytes
c. Plasma
d. Lymphocytes

**13. The $pO_2$ of alveolar air is:**
a. 40 mm Hg
b. 158 mm Hg
c. 104 mm Hg

**14. The respiratory center:**
a. Is located in hypothalamus
b. Is activated during swallowing
c. Sends out regular rhythmic impulses to the respiratory muscle at rest

**15. Under normal respiratory conditions greatest resistance to air flow occurs in:**
a. Alveolar duct
b. Nose
c. Large bronchi
d. Terminal bronchiole

**16. In stagnant (ischaemic) hypoxia and histotoxic hypoxia, which of the following is abnormal:**
a. Arterial $pO_2$
b. Arterial $O_2$ content
c. Arterial %-$O_2$ saturation of Hb
d. A-V $pO_2$ difference

**17. Which of these are not lung capacities:**
a. Inspiratory capacity
b. TLC
c. MVV
d. FRC

**18. In restrictive type of lung diseases, VC:**
a. Increases
b. Decreases
c. Normal
d. May increase or decrease

**19. Which of the following shifts oxy-Hb dissociation curve to the left:**

a. Increase in body temperature
b. Increase in pH
c. Increase in $CO_2$
d. Increased 2,3 DPG

**20. The type of adrenergic receptor present in the smooth muscle of bronchi is:**

a. Beta 1
b. Beta 2
c. Alpha 1
d. Alpha 2

**21. Oxygen:**

a. Carriage by fetal and adult hemoglobin does not differ in their capacity
b. Transport increases if administered at high pressure
c. Molecular combination with hemoglobin occurs with the same ease
d. Is indicated for therapy in histotoxic hypoxia

**22. What is the primary function of pneumotaxic center located in the pons:**

a. To limit the duration of inspiration
b. Inhibition by vagal afferents
c. To initiate basic rhythm of respiration

**23. Which of the following statement about pulmonary blood flow during exercise is true:**

a. It increases by the same amount as systemic blood flow
b. It increases less than systemic blood flow
c. It decreases
d. It does not change

**24. The dead space is what percent of the tidal volume:**

a. 10%
b. 1%
c. 30%
d. 50%

**25. Volume of air inspired and expired in each breath in normal respiration is called:**

a. Total lung capacity
b. Tidal volume
c. Residual volume
d. Inspiratory capacity

**26. Inherent rhtymicity of respiration is controlled by neurons located in the:**

a. Carotid body
b. Lungs
c. Reticular formation in the medulla
d. Pneumotaxic center

**27. $O_2$ therapy is not effective in:**

a. Histotoxic hypoxia
b. Ischemic hypoxia
c. Anemic hypoxia
d. Hypoxic hypoxia

**28. Respiratory quotient of fat, protein and carbohydrate are respectively:**

a. 0.7, 0.8, 1
b. 0.8, 0.7, 1
c. 0.8, 1, 0.7
d. 1, 0.8, 0.7

**29. During starvation, the nonprotein RQ value is close to:**

a. 1
b. 0.5
c. 0.25
d. 0.75
e. 0

**30. Bohr effect is:**

a. Effect of Zn on carbonic anhydrase activity
b. Effect of $pCO_2$ on oxyhemoglobin dissociation
c. $HCO_3^-$ leaving the RBC in exchange of Cl
d. $H^+$ leaving RBC for each $CO_2$ that inters

**31. Haldane effect is:**

a. Binding of $O_2$ to Hb-favors exalation of $CO_2$
b. Binding of $CO_2$ to Hb-favors release of $O_2$
c. Important mechanism of $O_2$ trasport in body
d. All of the above

**32. J receptors are situated in:**

a. Heart
b. Blood vessels
c. Alveolar interstitium
d. Carotid body

**33. Stimulation of baroreceptor leads to:**

a. Increase in BP and heart rate
b. Decrease in BP and rise in heart
c. Increased intracranial tension
d. Decreased intracranial tension

**34. Respiratory acidosis can cause:**

a. Decreased $pCO_2$ and decreased pH
b. Increased $pCO_2$ and decreased pH
c. Increased $pCO_2$ and increased pH
d. Decreased $pCO_2$ and increased pH

**35. The most important factor in transport of $CO_2$ as bicarbonate is:**
a. Affinity to Hb
b. Basic nature of $HCO_3$
c. Increased solubility of $CO_2$
d. Carbonic anhydrase in RBC

**36. Normal value of FEV1 % in an adult male is:**
a. 80%
b. 95%
c. 65%
d. 50%

**37. Sympathetic vasoconstrictor tone is diminished in response to increased activity of:**
a. Carotid body chemoreceptors
b. Carotid sinus pressor receptors
c. Pain receptors
d. Medullary chemoreceptors.

**38. Structures through which $O_2$ must diffuse in passing from alveolar lumen to hemoglobin:**
a. Surfactant containing liquid
b. Alveolar membrane, basement membrane
c. Capillary endothelium, plasma and RBC membrane
d. All of the above

**39. An increase in ventilation occurs in all situations except:**
a. Fall in plasma bicarbonate
b. Sleep
c. Fall in pH of CSF
d. Rise in blood adrenalin level

**40. During the initial part of inspiration which of the following does not occur:**
a. Intrapulmonary pressure falls
b. Intrathoracic pressure rises
c. Intra-abdominal pressure rises
d. The partial pressure of $O_2$ in dead space rises

**41. When the atmospheric pressure is halved which of the following is not likely to develop:**
a. An increase in pulmonary ventilation
b. A fall in arterial $pO_2$
c. A fall in arterial pH
d. A rise in cerebral blood flow

**42. The most important substance controlling alveolar ventilation is:**
a. $O_2$
b. $CO_2$
c. $H_2O$
d. None of the above

**43. The diffusing capacity for $CO_2$ compared to that for oxygen is:**
a. 20 times
b. 10 times
c. 5 times
d. 2 times

**44. Total vital capacity is decreased but timed vital capacity is normal in:**
a. Bronchial asthma
b. Scoliosis
c. Chronic bronchitis
d. All of the above

**45. Compliance of lung is decreased in all conditions except:**
a. Fibrosis of lung
b. Emphysema
c. Pulmonary oedema
d. Kyphosis

**46. Arterial $pO_2$ is reduced in:**
a. Anemia
b. KCN poisoning
c. Pulmonary hypoventilation
d. CO-poisoning

**47. Maximum voluntary ventilation is:**
a. 20–50 L /min
b. 50–75 L /min
c. 75–125 L /min
d. 125–170 L /min

**48. In cigarette smoking, surfactant is:**
a. Increased
b. Decreased
c. Increased following decrease
d. Unaltered

**49. $CO_2$ affects respiratory center via:**
a. CSF $H^+$ concentration
b. Carotid body
c. Inflation and deflation receptors
d. Aortic body

**50. Hyperbaric oxygenation is useful in all except:**
a. Congenital heart disease
b. Gas gangrene
c. CO-poisoning
d. Nitrogen toxicity

**51. Chemoreceptor mechanism is not triggered in:**
a. Anemic hypoxia
b. Hypoxic hypoxia
c. Stagnant hypoxia
d. Histotoxic hypoxia



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**52. Which of the following statements is correct:**

a. Breathing and respiration are the same
b. Breathing results in intake of $O_2$ and removal of $CO_2$ from lungs
c. Breathing provides energy to the body

**53. Exchange of gases between blood and alveolar air in the lungs occur by:**

a. Simple diffusion
b. Osmosis
c. Active transport
d. All of these

**54. In a normal adult, the ratio of physiological and anatomical dead space is:**

a. 2 : 1
b. 1 : 3
c. 3 : 1
d. 1 : 1

**55. $O_2$ transported from lung to tissues is:**

a. 70%
b. 86%
c. 91%
d. 97%

**56. When $CO_2$ is removed from the lungs which of the following also occur:**

a. Efflux of $HCO_3^-$ from RBC
b. Efflux of $CI^-$ from RBC
c. Efflux of $O_2$ and influx of $CO_2$

**57. When $CO_2$ in inspired air increases beyond 10% at atmospheric pressure it causes:**

a. Decreased ventilation
b. Depression of CNS
c. Diminished sensory acuity
d. All of the above

**58. Destruction of pneumotaxic center in pons causes:**

a. Apnea
b. Forceful respiration
c. Apneustic respiration
d. Accelerated respiration

**59. When under certain conditions the P50 value of hemoglobin rises, the affinity of the pigment for combining with $O_2$ will:**

a. Remain the same
b. Fall
c. Rise
d. First rise, then fall

**60. If under certain conditions the P50 value of hemoglobin rises to 100 mm Hg, a person will die of $O_2$ deficiency because the pigment:**

a. Is not loading enough oxygen in the lungs
b. Can load enough oxygen in the lungs but cannot unload it in tissues
c. Can neither load or unload oxygen
d. Suffers degradation and cannot function normally

**61. Work during normal respiration is mainly done for overcoming:**

a. Lung elasticity
b. Respiratory air passages
c. Alveolar air spaces
d. Creating negative pleural pressure

**62. Hypoxia may be characterized by:**

a. Low arterial $pO_2$
b. Intense chemoreceptor response
c. Favorable response to 100% oxygen
d. All of the above

**63. Oxygen therapy has significant value in all of the following types of hypoxia except:**

a. Atmospheric hypoxia
b. Hypoventilation hypoxia
c. Hypoxia due to pulmonary edema
d. Hypoxia due to decreased hemoglobin in the blood
e. Histotoxic hypoxia due to cyanide poisoning.

**64. Combination of hemoglobin with $O_2$ in the lungs can be promoted by:**

a. Decreasing $O_2$ concentration in blood
b. Increasing $O_2$ concentration in blood $O_2$
c. Increasing $CO_2$ concentration in blood
d. Introducing $CO_2$ into the blood

**65. Alveolar hyperventilation causes:**

a. Respiratory acidosis
b. Respiratory alkalosis
c. Metabolic acidosis
d. Metabolic alkalosis

**66. The partial pressure of oxygen in the arterial blood is normally lower than that of alveolar gas primarily because:**

a. Lungs use oxygen
b. Blood moves through the lungs too fast
c. Oxygen requires a pressure gradient to diffuse into blood
d. Some portions of the lungs are ventilated but not perfused
e. Some portion of the lungs are perfused but not ventilated

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**67. Contraction of which of the following muscles is most important for causing forceful expiration:**
a. Internal intercostal
b. Diaphragm and abdominal muscles
c. External intercostal
d. Sternocleidomastoid

**68. For cyanosis to be manifested the amount of reduced hemoglobin in blood should be:**
a. 1 gm%
b. 3 gm%
c. 5 gm%
d. 7 gm%

**69. Respiratory movements are under control of:**
a. Cerebral hemispheres
b. Cerebellum
c. Crura cerebri
d. Medulla oblongata

**70. Which of the following can be measured by using the helium dilution method:**
a. Functional residual capacity
b. Tidal volume
c. Dead space
d. Total lung volume

**71. $O_2$ is transported from alveoli into blood in the pulmonary capillaries by:**
a. Filtration
b. Secondary active transport
c. Facilitated diffusion
d. Passive diffusion

**72. During quiet breathing which of the following discharge spontaneously:**
a. Inspiratory neurons
b. Neurons in apneustic center
c. Expiratory neurons
d. Stretch receptors in the lungs

**73. $O_2$ therapy is not effective in:**
a. Hypoxic hypoxia
b. Anemic hypoxia
c. Ischemic hypoxia
d. Histotoxic hypoxia

**74. Normal anatomical dead space is:**
a. 250 ml
b. 150 ml
c. 175 ml
d. 200 ml

**75. Respiration during exercise is regulated by:**
a. Cerebral cortex
b. Hypoxia at muscles
c. Joint proprioceptors
d. All the above

**76. The normal intrapleural pressure:**
a. Is less negative during inspiration
b. Helps lung expansion
c. Reduces venous return to heart
d. Both a and b are correct

**77. $O_2$ therapy is of significance in:**
a. Pulmonary fibrosis
b. Cyanide poisoning
c. Sever anemia
d. Right to left shunt in heart

**78. Pulmonary fibrosis would be expected to produce:**
a. Histotoxic hypoxia
b. Stagnant hypoxia
c. Decreased vital capacity
d. Cyanosis
e. Emphysema

**79. Airway resistance:**
a. Is increased if the lungs are removed and inflated with saline
b. Does not affect the work of breathing
c. Is increased in paraplegic patients
d. Makes up 80% of work of breathing

**80. Surfactant deficiency is the primary cause for:**
a. Acute respiratory distress syndrome
b. Emphysema
c. Chronic bronchitis
d. Bronchial asthma

**81. p50 is decreased by:**
a. Fever
b. Increase in blood pH
c. Exercise
d. Acclimatization to high altitude

## CARDIOVASCULAR SYSTEM

**1. T wave of ECG occurs:**
a. At the beginning of atrial contraction
b. After atrial contraction
c. At the beginning of ventricular contraction
d. At the end of ventricular contraction

**2. The QRS complex of ECG represents:**
a. Atrial depolarization
b. Atrial repolarization
c. Ventricular depolarization
d. Ventricular repolarization



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**3. Cardiac index is cardiac output:**
a. Per unit body weight
b. Per unit surface area
c. Per unit body volume
d. Per unit time

**4. The most important cardiac and vasomotor center are located in:**
a. Pons
b. Medulla
c. Hypothalamus
d. Cerebellum

**5. The region of heart having the lowest inherent rhythmicity is:**
a. SA node
b. AV node
c. Atrial muscle
d. Ventricular muscle

**6. Parasympathetic stimulation:**
a. Increases heart rate
b. Decreases heart rate
c. No effect on heart rate
d. Initiates heart rate

**7. If all the nerves to the heart are cut, then heart will:**
a. Beat rhythmically
b. Stop
c. Beat arrythmically
d. Shrink

**8. In a healthy adult male, the diastolic pressure is:**
a. 120 mm Hg
b. 100 mm Hg
c. 90 mm Hg
d. 80 mm Hg

**9. The increase in vascular permeability responsible for 'wheal' formation in triple response is due to:**
a. Serotonin
b. Acetyl choline
c. Histamine
d. Adrenaline

**10. Closure of semilunar valves occurs at the onset of which phase of cardiac cycle:**
a. Isovolumetric contraction
b. Isovolumetric relaxation
c. Rapid ejection
d. Rapid filling

**11. A heart attack occurs when blockage takes place in artery carrying blood to:**
a. Lungs
b. Kidneys
c. Heart
d. Brain

**12. Maximum peripheral resistance is offered by:**
a. Blood capillaries
b. Arteries
c. Arterioles
d. Venules

**13. Negative bathmotrophic effect can be produced by:**
a. Stimulation of vagus
b. Section of vagus
c. Stimulation of sympathetic chain
d. Increasing the temperature

**14. Maximum blood flow in the left coronary artery occurs during:**
a. Early ventricular systole
b. Late ventricular systole
c. Early ventricular diastole
d. Late ventricular diastole

**15. ECG:**
a. Helps in the diagnosis of serum $K^+$ abnormalities
b. Is the direct recording of the ventricular muscle action potentials
c. Is the recording of the SA nodal pace maker potentials
d. Mean electrical axis is >110 degree in left axis deviation

**16. Cardiac output:**
a. Can be measured by using echocardiography
b. Is dependent on the length of the muscle fiber
c. Decreases after adrenaline infusion
d. Is not altered in digitalis administration

**17. When pulse rate is 100 per minute, R-R interval in ECG will be:**
a. 0.8 sec
b. 0.8 minutes
c. 0.6 sec
d. 1 sec

**18. During ventricular diastole blood pressure in the blood capillary is:**
a. About 80 mm Hg
b. About 120 mm Hg
c. About 30 mm Hg
d. About 100 mm Hg

**19. Thrombus means:**
a. Increase in thrombocyte count
b. Blood clot in a test tube
c. Decreased thrombocyte count
d. Blood clot inside a blood vessel

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**20. Capacitance vessels are:**
a. Aorta
b. Large veins
c. Capillaries
d. Arterioles

**21. Normal coronary blood flow is:**
a. 70 mL/min
b. 250mL /min
c. 5000 mL /min
d. 1250 mL /min

**22. The Jugular venous:**
a. Pulse can't be seen in the people with normal heart
b. Pressure is typically raised in right ventricular failure
c. Pulse is not exaggerated in patients suffering from tricuspid incompetence

**23. First HS occurs with:**
a. Closure of aortic and pulmonary valves
b. Rapid ventricular filling
c. Closure of AV valves

**24. Which of the following is NOT a property of cardiac muscle:**
a. Excitability
b. Rhythmicity
c. Short refractory period

**25. When the HR is 100 beats/min, the cardiac cycle time is:**
a. 0.8 sec
b. 0.8 min
c. 0.6 sec
d. 1 sec

**26. The EDV of ventricle increases when:**
a. The person is upright
b. There is increase in venous tone
c. There is increase in intrapericardial pressure
d. There is decrease in ventricular compliance

**27. Incisura in the aortic pressure curve is:**
a. Because of increased aortic pressure
b. Associated with third HS
c. Rapid peripheral emptying
d. Backward flow of blood from aorta to ventricle

**28. Fast response action potential is seen in:**
a. SA node
b. AV node
c. Ventricular muscle
d. All the above

**29. In which of the following, the blood flow is least during exercise:**
a. Brain
b. Heart
c. Skeletal muscle
d. GIT

**30. ST segment elevation in the ECG indicates:**
a. 1° heart block
b. 2° heart block
c. 3° heart block
d. Acute MI

**31. Tall T waves of ECG are associated with:**
a. Hypernatremia
b. Hypokalemia
c. Hyperkalemia
d. Hyponatremia

**32. The catecholamine useful for increasing the systolic pressure while treating circulatory shock is:**
a. Dopamine
b. Noradrenaline
c. Adrenaline
d. Glutamine

**33. Hypertension is a common complication of all of the following conditions except:**
a. Anaphylaxis
b. Pregnancy
c. Cushing's syndrome
d. Posterior pituitary fossa tumor
e. Pyelonephritis

**34. PR interval in an electrocardiogram is measured by finding the interval between the:**
a. Beginning of the P wave and the beginning of the R wave
b. Beginning of the P wave and the beginning of QRS complex
c. End of P wave and end of QRS complex
d. End of P wave and beginning of the QRS complex

**35. Stroke volume is increased by:**
a. Digitalis in failing heart
b. Sympathetic stimulation
c. Stretched cardiac muscle fibers
d. Decreased systemic blood pressure

**36. PR segment in the ECG corresponds to:**
a. Time interval between onset of atrial contraction and onset of ventricular contraction
b. Time delay in the AV node
c. SA nodal conduction time
d. Ventricular depolarization

**37. The first reactive change to occur after hemorrhage is:**
a. Vasoconstriction
b. Tachycardia
c. Raised cortisol
d. Raised epinephrine



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**38. Blood flow through left coronary artery is:**
a. Regulated by sympathetic vasodilator nerves
b. Increased when myocardial hypoxia is present
c. Greater during early systole
d. Decreased in reflex response to fall in blood pressure

**39. Dicrotic notch in aortic pressure curve is:**
a. Magnified by aortic regurgitation
b. Absent in arterioscle: rosis
c. Of no diagnostic value
d. Coincident with 2nd heart sound

**40. What is not true of jugular venous pulse:**
a. Pressure typically raised in right ventricular failure
b. Pressure typically raised in partial obstruction of SVC
c. Commonly visible in normal persons
d. Pulsations exaggerated in tricuspid incompetence

**41. Capacitance is least in the following vascular segment:**
a. Pulmonary artery
b. Systemic artery
c. Systemic vein
d. Pulmonary vein

**42. What prevents blood loss after rupture of a very small blood vessel:**
a. Vasoconstriction
b. Formation of fibrin threads
c. Formation of platelet plug
d. All of the above

**43. Work performed by the left ventricle is greater than that performed by the right ventricle due to differences in:**
a. Blood velocity
b. Stroke volume
c. Arterial pressure
d. Atrial pressure

**44. The arterial pulse pressure in the femoral artery is normally:**
a. Slightly less than the pulse pressure in the upper aorta
b. Greater than the pulse pressure in the upper aorta
c. Equal to the peak pressure in the upper aorta
d. One of the above

**45. The Purkinje fibers:**
a. Are myelinated axons
b. Do not have a very high conduction velocity
c. Have action potentials which has a long duration
d. All of the above

**46. In athletes bradycardia is because of:**
a. Decreased sympathetic tone
b. Increased vagal tone
c. Cardiac output
d. Low venous return

**47. Velocity of transmission is fastest through following part of the heart:**
a. AV node
b. Bundle of His
c. Atria
d. Purkinje fibers

**48. Plateau phase of action potential curve of cardiac tissue is due to:**
a. Opening of sodium channels
b. Opening of potassium channels
c. Opening of slow calcium channels
d. Closing of sodium channels

**49. Tachycardia at the onset of exercise is due to stimulation of**
a. Chemoreceptors
b. Baroreceptors
c. Stretch receptors
d. Joint proprioceptors

**50. Left ventricular systole corresponds to:**
a. Auricular diastole
b. Auricular systole
c. ST wave of ECG
d. P wave of ECG

**51. During exercise, blood flow does not decrease in:**
a. Cutaneous circulation
b. Hepatosplanchnic circulation
c. Coronary circulation
d. Renal circulation

**52. Difference of pulmonary microcirculation from systemic is:**
a. Resistance low; pulsatile flow
b. Resistance low; capillary pressure low
c. Capillary pressure high; pulsatile flow
d. None of the above

**53. Heart rate is under the control of:**
a. Vagus nerve
b. Autonomic nervous system
c. Both
d. None

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**54. Tricuspid valve is present between:**
a. Right atrium and right ventricle
b. Two atria
c. Two ventricles
d. Left atrium and ventricle

**55. When sympathetic nerve supply to heart is cut off, the heart rate will:**
a. Increase
b. Decrease
c. Show no change
d. None

**56. If heart is stimulated through its vagus supply, heart rate will:**
a. Decrease
b. Increase
c. Show no change
d. None

**57. The dicrotic notch on the aortic pressure curve is caused by:**
a. Closure of aortic valve
b. Closure of tricuspid valve
c. Closure of pulmonary valve
d. Closure of mitral valve

**58. PR interval is said to be prolonged if it exceeds:**
a. 0.2 sec
b. 0.25 sec
c. 0.30 sec
d. 0.35 sec

**59. Total blood volume is _____% of body weight:**
a. 8
b. 20
c. 40
d. 80

**60. Blood volume is greater in:**
a. Aorta
b. Capillaries
c. Arteries and Arterioles
d. Venules and Veins

**61. Blood brain barrier is made up of:**
a. Astrocytes
b. Oligodendrocytes
c. Oligodendroglia
d. Microglia

**62. Cerebrospinal fluid:**
a. Has a pressure which is slightly lower than venous pressure in the recumbent position (5 cm $H_2O$)
b. Has the main function of protecting the brain from injury when the head is struck
c. Is an ultrafiltrate of plasma
d. Both a and b

**63. Shock always involves:**
a. External hemorrhage
b. Internal hemorrhage
c. Central nervous system
d. Decreased tissue perfusion

**64. Plateau phase of plateau type of action potential is mainly caused by:**
a. Sustained $K^+$ efflux
b. $Ca^{2+}$ influx
c. $Na^+$ influx
d. $Na^+$-$K^+$ pump

**65. Mean blood pressure is:**
a. Systolic blood pressure + diastolic blood pressure /2
b. Systolic blood pressure–diastolic blood pressure
c. Systolic blood pressure + 1/3 pulse pressure
d. Diastolic blood pressure + 1/3 pulse pressure

**66. Normal adult lumbar CSF pressure in mm CSF is:**
a. 5–100
b. 70–180
c. 100–200
d. 200–280

## GASTROINTESTINAL SYSTEM

**1. Vitamin $B_{12}$ is absorbed primarily in:**
a. Stomach
b. Duodenum
c. Jejunum
d. Ileum

**2. Following statement about colon is incorrect:**
a. Movement include segmentation contraction
b. Mass peristalsis present
c. Net absorption of $K^+$ occurs
d. Net secretion of $HCO_3^-$ occurs

**3. The following are some of the gastrointestinal hormones except:**
a. Secretin
b. VIP
c. Trypsin
d. Villikinin

**4. Which one of the following statement is correct:**
a. Salivary secretion per day is about 1500 ml
b. Gastric secretion per day is about 2500 ml
c. Bile secretion per day is about 500 ml
d. All the above are correct



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**5. Which of the following is not an enzyme of digestive system:**
a. Enterokinase
b. Amylase
c. Trypsin
d. Streptokinase

**6. Intrinsic factor is secreted in:**
a. Intestine
b. Pancreas
c. Stomach
d. Liver

**7. Chymotrypsin acts upon:**
a. Starch in duodenum
b. Proteins in stomach
c. Proteins in duodenum in alkaline medium
d. Proteins in duodenum in acidic medium

**8. Gallbladder is stimulated by:**
a. Enterogastrone
b. Secretin
c. CCK
d. Enterokinase

**9. Dysphagia means:**
a. Loss of speech
b. Inhibition of breathing
c. Difficulty in breathing
d. Difficulty in swallowing

**10. The major mediator for gastric acid HCl secretion during cephalic phase is:**
a. Histamine
b. Gastrin
c. Somatostatin
d. ACh

**11. Vomiting is NOT associated with the following event:**
a. Contraction of the lower esophageal sphincter
b. Deep breath
c. Closure of glottis
d. Elevation of the soft palate

**12. All are pancreatic enzymes except:**
a. Chymotrypsinogen
b. Trypsinogen
c. Amylase
d. Insulin

**13. The inhibition of gastric juice secretion is brought about by:**
a. Food
b. Cholecytokinin
c. Acetylcholine
d. Gastrin

**14. Parietal cell is stimulated by all the following except:**
a. Insulin
b. Gastrin
c. Stretch of stomach wall
d. Histamine

**15. This is the main function of large intestine:**
a. Absorption of proteins
b. Digestion of proteins
c. Absorption of water and electrolytes
d. Digestion and absorption of fats

**16. Which salivary gland contributes to maximum quantity of saliva secreted:**
a. Parotid
b. Submandibular
c. Sublingual

**17. The potent choleretic agent is:**
a. Gastrin
b. Secretin
c. Bile salts
d. Glucagon

**18. Submandibular glands are:**
a. Serous gland
b. Mucous gland
c. Mixed gland
d. Predominating mucous gland

**19. Liver bile and gallbladder bile have the respective pH as:**
a. 6.4–7.2 and 8.6–9.4
b. 8.2–9.0 and 4.2–6
c. 6–7 and 8-9
d. 7.8–8.6 and 7.0–7.4

**20. In which of the following jaundice do we see biphasic reaction to Van Den Bergh test:**
a. Prehepatic jaundice
b. Hemolytic jaundice
c. Hepatic jaundice
d. Posthepatic jaundice

**21. Urinary bilirubin is absent in which type of jaundice:**
a. Hepatic jaundice
b. Hemolytic jaundice
c. Obstructive jaundice
d. Prehepatic jaundice

**22. Stimulation of the parasympathetic nerve to the salivary glands cause:**
a. Profuse secretion of watery saliva
b. Xerostomia
c. Profuse secretion of mucinous saliva
d. Produces no change

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**23. Potent stimulus for bile secretion:**
a. Bilirubin
b. Biliverdin
c. Secretin
d. Bile salts

**24. Which of the following is seen in obstructive jaundice:**
a. Excess of urobilinogen
b. Excess of unconjugated serum bilirubin
c. Excess of bile salts in the urine
d. All of the above

**25. The enzyme primarily responsible for protein degradation in stomach is:**
a. Trypsin
b. Pepsin
c. Chymotrypsin

**26. Antiperistalsis may sometimes be seen in:**
a. Stomach
b. Ileum
c. Colon
d. None

**27. Glycogenolysis in muscle does not raise blood sugar level due to lack of:**
a. Lactate dehydrogenase
b. Pyruvate kinase
c. G-6-phosphatase
d. Argininosuccinase

**28. Infant's gastric juice pH is:**
a. Generally high
b. Generally low

**29. The rate of absorption of sugars by small intestine is highest for:**
a. Disaccharides
b. Polysaccharides
c. Hexoses
d. Pentose

**30. Which of the following is not secreted by the pancreas:**
a. Procarboxypeptidases
b. Trypsinogen
c. Phospholipase A
d. Pepsinogen

**31. Which of the following is found in conjunction with bile acids:**
a. Cholic acid
b. Pregnenolone
c. Glycine
d. Cholyl acetyl CoA

**32. Alpha amylase acts on which bond**
a. Alpha 1- 4 bond
b. Alpha 1- 6
c. Beta 1- 4
d. Beta 1- 6

**33. The gastric phase of gastric secretion is brought about by:**
a. Neural factors
b. Hormonal factors
c. Gastric distension
d. Presence of proteins in the stomach
e. All of the above

**34. Gastric secretion is stimulated by all of the following except:**
a. Secretin
b. Gastric distension
c. Gastrin
d. Vagal stimulus

**35. Most potent stimulus for secretion of secretin is:**
a. Dilatation of intestine
b. Acid chyme
c. Protein
d. Fat

**36. Gastric emptying is decreased, by all except:**
a. Fatty meal
b. Hyperosmolarity in duodenum
c. Distension of the duodenum
d. Vagal stimulation

**37. Vagal stimulation following intake of food does not affect secretion of:**
a. Stomach
b. Pancreas
c. Parotid gland
d. Gallbladder

**38. Brunner's glands are located in:**
a. Mucosa of duodenum
b. Stomach
c. Pancreas

**39. Small intestinal peristalsis is controlled by:**
a. Myenteric plexus
b. Meissner's plexus
c. Vagus nerve
d. Parasympathetic system
e. Both a and b

**40. Fat is maximally absorbed in:**
a. Ileum
b. Colon
c. Stomach
d. Jejunum



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**41. The enzyme that acts on milk is:**
a. Rennin
b. Renin
c. Lipase
d. Amylase

**42. Which of the following is not produced from intestine:**
a. Gastrin
b. Enterogastrone
c. Secretin
d. Pancreozymin

**43. Emulsification of fat by bile occurs in:**
a. Liver
b. Pancreas
c. Duodenum
d. Stomach

**44. Digestion of fats, proteins and carbohydrates is completed in:**
a. Liver
b. Large intestine
c. Stomach
d. Small intestine

**45. Fat splitting enzyme is not present in:**
a. Saliva
b. Pancreatic juice
c. Succus entericus
d. Gastric

**46. Which cells of gastric mucosa secrete pepsinogen:**
a. Parietal cells
b. Argentaffin cells
c. Goblet cells
d. Zymogen (chief) cells

**47. A large greasy smelly stool usually indicates failure of digestion of:**
a. Carbohydrates
b. Fats
c. Proteins
d. Peptones

**48. Pancreatic juice takes part in digestion of:**
a. Proteins, carbohydrates
b. Proteins and fats, carbohydrates
c. Proteins and fats
d. Proteins only

**49. Trypsin differs from pepsin in that:**
a. It digests proteins in alkaline medium and not in acid medium
b. It digests proteins in acidic medium and not in alkaline medium
c. Both of these
d. None of these

**50. Stored fat is usually transported from one part of the body to another in the form of:**
a. Triglyceride
b. Free fatty acids
c. Glycerol
d. Neutral fat
e. Cholesterol

**51. Emulsification of fats is brought about by:**
a. Bile pigments
b. Bile salts
c. Vitamin $B_{12}$
d. HCI

**52. Removal of entire colon would be expected to cause:**
a. Malnutrition
b. Megaloblastic anemia
c. Jaundice
d. None.

**53. Vomiting center is situated in the:**
a. Hypothalamus
b. Amygdala
c. Pons
d. Medulla

**54. Which is essential for absorption of glucose from complex carbohydrates:**
a. Salivary amylase
b. Enterokinase
c. $Na^+$- $K^+$ ATPase
d. Secretin

**55. Wharton's ducts are associated with:**
a. Parotid glands
b. Submaxillary gland
c. Sublingual glands

**56. Paneth cells are found in:**
a. Crypts of Lieberkuhn
b. Peyer's patches
c. Organ of Corti
d. Islet of Langerhans

**57. Conversion of starch into maltose is brought about by:**
a. Invertase
b. Diastase
c. Zymase
d. Lipase

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**58. Obstructive jaundice is caused by:**
a. Defective pancreas
b. Impacted -gallstone in common bile duct
c. Liver deficiency
d. When bile is not removed from the blood

**59. Fatty acids can be absorbed only in the presence of:**
a. Glycerol
b. Lipase
c. Bile salts
d. Bile pigments

**60. Products of digestion that enter the lacteals of villi of small intestine are poured into:**
a. Jugular vein
b. Left jugular vein
c. Lymphatic vessels
d. Hepatic portal vein

**61. Products of digestion that enter the capillaries of villi of small intestine are carried to the liver via:**
a. Jugular vein
b. Left jugular vein
c. Lymphatic vessels
d. Hepatic portal vein

**62. Glycerol is one of the digestive products of:**
a. Carbohydrates
b. Fats
c. Proteins
d. Nucleic acids

**63. The inactive trypsin is converted to active trypsin by:**
a. HCl
b. Enterokinase
c. a and b
d. None of these

**64. Peristaltic waves are integrated by:**
a. Meisner's plexus
b. Auerbach's plexus
c. Circular muscle fraction is
d. Longitudinal muscle fibers

**65. Pancreozymin stimulates increase of:**
a. Pancreatic juice rich in bicarbonate
b. Pancreatic juice rich in enzymes
c. Gastric juice
d. Bile from liver

**66. The primary contractile pattern of small intestine during digestive period is:**
a. Segmentation
b. Peristalsis
c. Retropulsion
d. Pendular movements

**67. Gallbladder function does not include:**
a. Storage of bile
b. Acidification of bile
c. Concentration of bile
d. Secretion of bile

**68. The GIT secretion without hormonal regulation is:**
a. Bile
b. Saliva
c. Small intestinal juice
d. Gastric hydrochloric acid

**69. Mass peristalisis is seen in:**
a. Stomach
b. Rectum
c. Colon
d. Small intestine

## RENAL PHYSIOLOGY

**1. Sodium reabsorption from distal tubule will be increased if there is an increase in:**
a. Plasma potassium concentration
b. Plasma volume
c. Mean arterial pressure
d. Urine flow rate

**2. Glomerular filtration rate is decreased by the following:**
a. An increase in glomerular capillary pressure
b. A decrease in plasma oncotic pressure
c. A decrease in intrarenal pressure
d. An increase in plasma protein concentration

**3. Renal plasma flow is:**
a. 125 ml/min
b. 700 ml/min
c. 500 ml/min
d. 1250 ml/min

**4. Assuming GFR is 125 ml/min and plasma glucose level is 100 mg%, the amount of glucose filtered by glomerular membrane in 10 min would be:**
a. 125 mg
b. 1.25 g
c. 2 g
d. 2.5 g

**5. Which of the following statements about the PCT is false?**
a. About 60% of water is reabsorbed here
b. Glucose is completely reabsorbed here
c. Hydrogen ions are secreted here
d. The fluid leaving the PCT is hypotonic



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**6. More than two-thirds of the salt and water from the glomerular filtrate in the kidney is absorbed from:**
a. PCT
b. Loop of Henle
c. DCT
d. Collecting duct

**7. When dialysis is done in a patient with renal failure, the dialyzing fluid will contain:**
a. Creatinine
b. Urea
c. No creatinine or urea
d. RBCs

**8. Which of the following is not an example for osmotic diuretic:**
a. Urea
b. Glucose
c. Chlorthiazide
d. Mannitol

**9. The normal inulin clearance is about:**
a. 126 ml/min
b. 80 ml/min
c. 650 ml/min
d. 1.5 liters

**10. ADH acts on:**
a. PCT
b. Urinary bladder
c. Collecting ducts
d. Loop of Henle

**11. Renal threshold for glucose is:**
a. 160 mg/100 ml of blood
b. 120 mg/100 ml of blood
c. 180 mg/100 ml of blood
d. 375 mg/100 ml of blood

**12. Net filtration pressure in kidney:**
a. 20 mm Hg
b. 10 mm Hg
c. 30 mm Hg
d. 15 mm Hg

**13. Severe diarrhea leads to:**
a. A decreased $K^+$ contents of the body fluid
b. Alkalosis
c. Increased $Na^+$ contents of the body

**14. The substance used to measure GFR should be:**
a. Freely filtered
b. Should be reabsorbed
c. Should be secreted
d. Both a and c are correct

**15. The normal RBF is:**
a. 1400 ml/min
b. 1273 ml/min
c. 1500 ml/min
d. 1000 ml/min

**16. Inulin is used to measure:**
a. RBF
b. RPF
c. Urinary volume
d. GFR

**17. ADH secretion is induced by all the following except:**
a. Stress
b. Dehydration
c. Hypovolemia
d. Hyponatremia

**18. Which one of the following is not suitable for the substance used in measuring GFR:**
a. Will be stored in kidney
b. It should not be toxic and biologically inert
c. It should not have an effect on filtration rate
d. It should not be metabolized in the body

**19. TmG in male is:**
a. 375 mg/min
b. 200 mg/min
c. 180 mg/100 ml of blood
d. 400 mg/min

**20. Which is the loop diuretic among the following:**
a. Spironolactone
b. Furosemide
c. Chlorothiazide
d. Ethanol

**21. Renin is released from the juxtaglomerular apparatus when afferent arteriolar:**
a. Hydrostatic pressure increases
b. Hydrostatic pressure decreases
c. Oncotic pressure increases
d. Oncotic pressure decreases

**22. Glucose transport in the PCT of kidney takes place by:**
a. Active transport
b. Passive transport
c. Bulk flow
d. Secondary active transport

**23. Which of the following causes the greatest increase in the amount of $K^+$ excreted in the urine:**
a. Mannitol
b. Calcium chloride
c. Aldactone
d. Furosemide
e. Ethanol

**24. GFR is increased when:**
a. Plasma oncotic pressure is increased
b. Glomerular hydrostatic pressure is increased
c. Tubular hydrostatic pressure is increased
d. Renal blood flow is increassed

**25. Where is active $Na^+$-$K^+$-$2Cl^-$ pump located:**
a. Proximal tubule
b. Thick ascending limb of loop of Henle
c. Distal convoluted tubule

**26. In renal glycosuria, the renal thresold for glucose is:**
a. Low
b. High
c. Same
d. Greatly increased

**27. Major portion of glomerular filtrate is reabsorbed in:**
a. Loop of Henle
b. Distal convoluted tubule
c. Collecting duct
d. Proximal segment

**28. Regarding potassium reabsorption in kidneys all are true except:**
a. Partly in PCT and loop of Henle
b. Under the influence of ADH
c. Coupled with sodium loss
d. Only in PCT.

**29. Ammonia in the kidney tubules is excreted in exchange for**
a. $HCO_3^-$
b. $Na^+$
c. $Cl^-$
d. $PO_4^{3-}$

**30. Two substances that can be used to determine filtration fraction are:**
a. Insulin and mannitol
b. Urea and diodrast
c. PAH and phenol red
d. Diodrast and PAH

**31. Diuresis is caused by:**
a. Mannitol
b. Glycerol
c. Urea
d. All of the above

**32. Where in the kidney does active reabsorption of sodium ions occur:**
a. Collecting duct
b. Distal tubule
c. Ascending limb of loop of Henle
d. All of the above
e. b and c

**33. One of the following does not form filtration barrier in nephrons:**
a. Mesangium
b. Podocytes
c. Endothelial cells
d. Parietal layer of Bowman's capsule

**34. Blood flows in glomerular capillaries with a pressure of about:**
a. 30 mm Hg
b. 60 mm Hg
c. 15 mm Hg
d. 18 mm Hg

**35. What is the normal urea clearance (nearest correct value):**
a. 4.4 ml/min
b. 88 ml/min
c. 440 ml/min
d. 44 ml/min
e. 22 ml/min

**36. Automatic bladder is seen in:**
a. Spinal shock
b. Cauda equina lesion
c. Filum terminale lesion
d. Superior sagittal sinus thrombosis

**37. The major source of $NH_3$ produced by the kidney is:**
a. Glycine
b. Alanine
c. Glutamine
d. Uric acid

**38. If the renal plasma flow is 600 ml /min and the hematocrit is 40%, what is the renal blood flow in ml/min (nearest value):**
a. 1,500
b. 1,000
c. 960
d. 1,800

**39. The glomerular filtration rate is regulated primarily by:**
a. Glomerular capillary pressure
b. Glomerular capillary blood flow
c. Plasma-colloid osmotic pressure
d. All

**40. Hydrostatic pressure in glomerular capillary (mm Hg) is**
a. About 45
b. About 10
c. About 5
d. 60

**41. Which of the following changes would tend to decrease glomerular filtration rate:**
a. Increased afferent arteriolar resistance
b. Increased glomerular capillary filtration coefficient
c. Decreased hydrostatic pressure in Bowman's capsule
d. Decreased plasma colloid osmotic pressure.

**42. The maximum amount of each substance that can be transported in one minute by the kidney tubules is called:**
a. Transport maximum
b. Tubular maximum
c. Secretion maximum
d. Diodrast clearance

**43. Action of renal nerves on urine formation is limited to their effect on:**
a. Release of angiotensin
b. Pressure and flow of renal blood
c. Reabsorption of glucose
d. Reabsorption of sodium by the tubules

**44. The glomerular:**
a. Efferent arteriole is smaller in diameter
b. Capillaries are more permeable than are most other capillaries in the body
c. Capillary blood is separated from glomerular filtrate by the capillary membrane only
d. Capillary ressure is normally 15–35 mm Hg.

**45. Normal filtration fraction is:**
a. 0.12–0.16
b. 0.16–0.20
c. 0.20–0.25
d. 0.25–0.30

**46. Hyperosmolar coma is seen in all except:**
a. Hyperglycemia
b. Uremia
c. Increased concentration of plasma proteins
d. Increase in plasma $Na^+$ concentration

**47. Glucose reabsorption occurs in:**
a. PCT
b. LH
c. Distal tubule
d. Cortical collecting tubule
e. Medullary collecting tubule

**48. $H^+$ secretion in renal tubule is affected by**
a. Increase in $pCO_2$
b. Minerelocorticoids
c. Decreased $K^+$ level
d. Carbonic anhydrase inhibitor

## REPRODUCTIVE SYSTEM

**1. Normal average sperm count in semen is:**
a. 5 million/cumm
b. 50 million/ml
c. 100 million/cumm
d. 100 million/ml

**2. Mechanism of action of IUCD is by:**
a. Preventing LH surge
b. Making the vaginal mucosa hostile for sperms
c. Preventing the implantation of fertilized ovum
d. Preventing fertilization

**3. Testosterone is secreted by:**
a. Sertoli cells
b. Leydig cell
c. Epididymis
d. Seminiferous tubules

**4. The precursor of testosterone is:**
a. Aldosterone
b. Estradiol
c. Androsterone
d. Pregnenolone

**5. The number of chromosomes in human sperm is:**
a. 42
b. 23
c. 21
d. 46

**6. Ovarian follicle growth is influenced by:**
a. FSH
b. ACTH
c. TSH
d. Progesterone

**7. Postmenopausal women:**
a. Have decreased libido
b. Have no circulating estrogen in the blood
c. Sexual activity persists in them due to release of estrogen by adrenals
d. Are less prone for fractures due to decreased estrogen level.

**8. Estrogen:**
a. Is secreted by theca interna cells of grafian follicle
b. Has no effect on epiphyseal closure
c. Has plasma cholesterol lowering activity
d. Both a and c are correct

**9. Capacitation of the sperms:**
a. Occurs mainly in the testis
b. Involves very gross morphological changes of the sperm
c. Is not required for the fertilization function of the sperm
d. Is an important physiological event for fertilization

**10. Uterine endometrium is thinnest:**
a. At the end of bleeding phase
b. On the 14th day of menstrual cycle
c. On the 25th day of menstrual cycle
d. Before the start of menstruation

**11. Oral contraceptive pills contain:**
a. Testosterone
b. Human chorionic gonadotropin
c. Relaxin
d. Estrogen

**12. Cryptorchidism means:**
a. A method of family planning
b. Disturbances in menstrual cycle
c. Delayed puberty
d. Undescended testis

**13. The hormone responsible for conversion of Wolffian: duct into vas deferens in male fetus is:**
a. Estrogen
b. Progesterone
c. Testosterone
d. Cortisone

**14. Thermogenesis shown during ovulation is because of:**
a. Estrogen
b. Progesterone
c. FSH
d. LH

**15. Sertoli cell secrete all the following except:**
a. Inhibin
b. ABP
c. cytokines
d. Testosterone

**16. Menopause means:**
a. Excessive bleeding
b. Intermittent bleeding
c. Absence of menstrual cycle
d. Stoppage of menstrual cycle

**17. Entire period of spermatogenesis:**
a. 8 days
b. 74 days
c. 700 days
d. none of the above

**18. Lactation:**
a. Is inhibited by estrogen and progesterone
b. Is initiated due to lactogenic effect of prolactin within 1 to 7 days after the birth of baby
c. Is controlled by hypothalamus
d. All the above

**19. Fertilization of the ovum normally occurs in:**
a. Uterus
b. Cervix of uterus
c. Fallopian tube
d. None of the above

**20. Basis of pregnancy immunologic test is:**
a. Excretion of hCG in urine
b. Presence of progesterone in urine
c. Excretion of estrogen in urine
d. None of the above

**21. Blood testis barrier is chiefly produced by:**
a. Sertoli cells
b. Leydig cells
c. Both the cells
d. Mesangial cells

**22. Life span of corpus luteum in absence of fertilization:**
a. 7 days
b. 28 days
c. 4 days
d. 14 days

**23. All are true regarding vasectomy, except:**
a. It is easily reversible
b. It is a surgical method
c. It is a permanent method
d. It is done in males

**24. Sperms have:**
a. 22 autosomes + Y chromosome
b. 22 autosomes + X chromosome
c. 23 pairs of chromosomes
d. 22 autosomes + either X or Y chromosome

**25. Which of the following contraceptive method has high failure rate:**
a. IUCD
b. Oral pills
c. Tubectomy
d. Rhythm method

**26. Human chorionic gonadotropin is secreted from:**
a. Ovary
b. Pituitary gland
c. Placenta
d. Corpus luteum

**27. Spermatozoa matures in the following organs:**
a. Prostate gland
b. Epididymis
c. Vas deferens
d. Rete testis

**28. The role of progesterone is:**
a. To thicken myometrium
b. To increase blood supply to uterine wall
c. To build up fat and glycogen in uterine wall
d. All of the above

**29. A decrease in blood levels of estrogen and progesterone causes:**
a. Loss of endometrium
b. Release of ova from ovaries
c. Growth and dilatation of myometrium
d. Constriction of uterine blood vessels leading to sloughing of uterine epithelium

**30. Uterine contractility is increased by the hormone:**
a. Vasopressin
b. LH
c. FSH
d. oxytocin

**31. Which one is not found in semen:**
a. Testosterone
b. Fructose
c. Citric acid
d. Ascorbic acid
e. Acid phosphatase

**32. Ejection of milk from the breast or let down:**
a. Frequently occurs in both breasts even though the baby is nursing at only one breast
b. Can be stimulated by mechanical stimulation of the breast
c. Can be stimulated by the sight or sound of the baby
d. Is caused by oxytocin-induced contraction of the myoepithelial cells

**33. Important effects of testosterone include all of the following except:**
a. Formation of fetal penis
b. Descent of testis into the scortum
c. Increased muscle development
d. Initiation of ejaculation
e. Increased thickness of the skin

**34. Which of the following statements regarding capacitation of spermatozoa is true:**
a. It occurs in epididymis
b. It is stimulated by testosterone
c. It is accompanied by release of acrosomal enzymes

**35. Which of the following hormones is responsible for the development of ovarian follicles prior to ovulation:**
a. Follicle-stimulating hormone (FSH)
b. Human chorionic gonadotropin (hCG)
c. Estradiol
d. Leutenising hormone (LH)

**36. Functions of the Sertoli cells in the seminiferous tubules include:**
a. Synthesis of estrogen after puberty
b. Synthesis of androgen-binding protein
c. Secretion of testosterone into the tubular lumen

**37. Progesterone has the ability to:**
a. Inhibit ferning of cervical mucus
b. Antagonize the effect of aldosterone
c. Give rise to secretory endometrium
d. Prevent ovulation if given in sufficient doses

**38. The site of spermatogenesis is:**
a. Seminiferous tubules
b. Leydig's cells
c. Gram cells

**39. Testis does not produce:**
a. Estradiol
b. Testosterone
c. Fructose
d. Inhibin

**40. Levels of which of the following hormones are increased in postmenopausal women:**
a. Estrogen
b. FSH
c. Progesterone
d. Cortisone

**41. The viability of the spermatozoa within the female genital tract is up to hours:**
a. 6
b. 12
c. 24
d. 48

**42. Function of leutenizing hormone is:**
a. Follicle maturation and ovulation
b. Milk secretion
c. Progesterone secretion during ovulation
d. To maintain placenta

**43. Precursor of testosterone is:**
a. Pregnenolone
b. Methyltestosterone
c. Aldosterone
d. Cortisone

**44. Estrogen receptors are in:**
a. Nucleus
b. Mitochondrion
c. Cell membrane
d. Cytoplasmic receptor

**45. Which is not caused by estrogen:**
a. Decreased folate levels
b. Decreased HDL
c. Increased blood sugar
d. None

**46. Menopausal hot flushes are due to:**
a. Decreased estrogen
b. Decreased progesterone
c. LH surge
d. FSH surge

**47. Spermatozoa mature in which of the following organs:**
a. Epididymis
b. Vas deferens
c. Rete testis
d. Prostate

**48. If a lady presents with a very regular 29 day menstrual cycle, ovulation should occur on day:**
a. 14
b. 15
c. 17
d. 19

**49. Maturation of graffian follicle occurs under the influence:**
a. FSH
b. ACTH
c. LH
d. Cortisol

**50. The nourishment to the development of spermatozoa is provided by:**
a. Seminiferous tubules
b. Leydig's cells
c. Sertoli's cells
d. Any of the above

**51. The seminiferous tubules require the following for full development:**
a. LH
b. Oxytocin
c. FSH
d. Androgen and FSH

**52. Testosterone, the male sex hormone, is synthesized in:**
a. Interstitial cells
b. Seminiferous tubules
c. Prostate gland
d. Vas deferens

**53. Mature sperms are stored in:**
a. Interstitial cells
b. Seminiferous tubules
c. Prostate gland
d. Epididymis

**54. Alkaline component of the semen is secreted by:**
a. Seminal vesicles
b. The prostate gland
c. Bulbourethral glands
d. Testis

**55. Sertoli cell secretes:**
a. Testosterone
b. Progesterone
c. Androstenedione
d. Inhibin

**56. Testosterone:**
a. Causes salt and water retention
b. Has protein catabolic effect
c. Inhibits erythropoiesis
d. None of the above

**57. Genetic make up in Klinefelter's syndrome is:**
a. XO
b. XX
c. XXY
d. XXYY

**58. Corpus luteum is maintained by:**
a. Progesterone
b. Estrogen
c. LH
d. FSH

## ENDOCRINOLOGY

**1. Effect of epinephrine includes:**
a. Hyperglycemia
b. Decrease in metabolic state
c. Lipid synthesis and promotion
d. Inhibition of phosphorylase

**2. Hyperglycemia is induced by all of the following hormones except:**
a. Cortisol
b. Aldosterone
c. Thyroxin
d. Glucagon

**3. The supraoptic nucleus of hypothalamus controls the secretion of:**
a. Prolactin
b. FSH
c. Vasopressin
d. TSH

**4. Thyroid hormones act on the target cells via:**
a. Receptors in cytoplasm
b. Receptors in plasma membrane
c. Cyclic AMP second messenger system
d. Receptors in the nucleus

**5. Myxoedema is due to:**
a. Hypothyroidism
b. Hypopituitarism
c. Hyperthyroidism
d. Hyperpituitarism

**6. The organ not directly involved in the control of $Ca^{2+}$ level in blood is:**
a. Skin
b. Bone
c. Kidney
d. GIT

**7. Insulin is not involved in the glucose transport to the following cell:**
a. Adipose tissue
b. Liver
c. Alveolar epithelial cells
d. Muscle

**8. All are true regarding adrenocorticotropic hormone except:**
a. It causes pigmentation
b. Its concentration increases during Cushing's syndrome
c. Its secretion increases during stress
d. It is a polypeptide

**9. Acromegaly is due to:**
a. Hyposecretion of ACTH
b. Hyposecretion of growth hormone in children
c. Hypersecretion of growth hormone in adults
d. Hypersecretion of thyroxin in adults

**10. Glucagon secretion is decreased by all except:**
a. Hyperglycemia
b. Starvation
c. Somatostatin
d. Insulin

**11. Insulin increases glucose entry into:**
a. Skeletal muscle
b. Intestine
c. Renal tubular cells
d. Cortical neuron

**12. Glucocorticoids can induce:**
a. Neutropenia
b. Eosinopenia
c. Anemia
d. Thrombocytosis

**13. Growth hormone:**
a. Enhances utilization of glucose by cells
b. Favors utilization of amino acids for energy
c. Favors utilization of fatty acids for energy
d. Promotes deposition of fat in adipose tissue
e. All are true

**14. In Addison's disease:**
a. There is decreased volume of ECF
b. Pigmentation of skin
c. Extreme muscle weakness
d. All the above

**15. Cortisol release increases:**
a. In trauma
b. When ACTH level in blood increases
c. In mental stress
d. All the above

**16. Parathyroid hormone:**
a. Is a polypeptide
b. Increases Ca excretion in urine
c. Reduces blood Ca level
d. Causes reduced excretion of phosphate in urine

**17. Milk secretion by mammary gland occurs due to:**
a. Estrogen
b. Prolactin
c. Oxytocin
d. Progesterone

**18. All the statements are true regarding cortisol except:**
a. It increases blood sugar level
b. Hyposecretion of it produces Cushing's syndrome
c. Increases blood volume
d. It shows anti-inflammatory action

**19. All are steroid hormones except:**
a. Relaxin
b. Estrogen
c. Testosterone
d. Progesterone

**20. All are true regarding Diabetes Insipidus, except:**
a. It is caused due to the lesion of hypothalamus
b. Increased water reabsorption at renal tubule
c. Polyuria
d. Polydipsia

**21. The active form of Vitamin D is:**
a. Cholecalciferol
b. Calcitonin
c. 1,25 DHCC
d. Parathyroid hormone

**22. Normal body temperature can be raised by:**
a. Estrogen
b. Progesterone
c. Gonadotropins
d. Androgens

**23. Beta cells of pancreas secrete:**
a. Glucagon
b. Insulin
c. Gastrin
d. Somatostatin

**24. Oxytocin causes all except:**
a. Milk ejection
b. Contraction of uterine muscle
c. Lactogenesis
d. Myoepithelial cell contraction

**25. Hyperglycemia is induced by all of the following hormones except:**
a. ACTH
b. Aldosterone
c. Thyroxine
d. Epinephrine
e. Glucagon

**26. Thyroid gland function is best monitored by which of the following:**
a. BMR
b. Total thyroxine and tri-iodothyronine uptake
c. Level of protein bound iodine
d. Level of thyroid stimulating hormone

**27. Which of the following statements about the action of the somatomedins is not true:**
a. Inhibit protein synthesis
b. Promote growth of the bone and cartilage
c. Stimulate the secretion of hormones by pancreatic islet cells

**28. A true statement about calmodulin is that it is:**
a. A plasma binding protein for calcium
b. An intracellular calcium binding protein
c. Involved in intestinal absorption of calcium

**29. Thyroxine and tri-iodothyronine are transported in plasma bound to several different proteins which do not include:**
a. Thyroglobulin
b. Thyroxine binding globulin (TBG)
c. Albumin
d. Thyroxine binding prealbumin

**30. Glucocorticoids decrease the number of circulating:**
a. Eosinophils
b. Platelets
c. Leukocytes

**31. Somatostatin is produced in the:**
a. Hypothalamus
b. Anterior pituitary
c. Delta cells of pancreas
d. Both a and c

**32. Panhypopituitarism causes all except:**
a. Pigmentation
b. Infertility
c. Loss of secondary sexual character
d. Cold tolerance
e. a and d

**33. In Addison's disease, the following is seen:**
a. Hyperkalemia
b. Hypernatremia
c. Hyperglycemia
d. High blood pressure

**34. Calcium necessary for blood coagulation and muscle contraction is:**
a. Bound, nonionized calcium
b. Free, ionized calcium
c. Both

**35. Increased fetal cortisol just before birth results in:**
a. Uterine contraction
b. Release of oxytocin
c. Placental steroid biogenesis
d. Fetal lung maturation

**36. The "diuretic" activity of the anterior pituitary can be explained in terms of the actions of:**
a. ACTH
b. TSH
c. Growth hormone
d. All of the above

**37. Which is false regarding insulin:**
a. Secreted by beta cells
b. Glycopeptide in nature
c. Causes lipogenesis
d. Promotes glycogenesis

**38. A patient with hypothyroidism is likely to have all except:**
a. Subnormal mouth temperature
b. Tendency to fall asleep frequently
c. Decreased body hair
d. Moist hands and feet

**39. Cortisol:**
a. Secretion increases following gross injury
b. Favors protein synthesis
c. Enhance effects of antigen-antibody reactions
d. Tends to lower blood pressure

**40. Adrenal insufficiency causes:**
a. A rise in plasma sodium/potassium ratio
b. Low blood pressure
c. A fall in extracellular fluid volume
d. Both b and c

**41. In Cushing's syndrome the following features are found except:**
a. Rapidly increasing adiposity
b. Polycythemia
c. Hypotension
d. Impotence with atrophy of testes

**42. Regarding myxoedema the following are true except:**
a. Swollen, Edematous look of the face
b. Amenorrhea
c. BMR increased by 30-45%
d. Dullness, loss of memory

**43. Polypeptide hormone includes all except:**
a. Insulin
b. Angiotensin
c. Growth hormone
d. Progesterone

**44. If piluitary is surgically removed, blood level of sodium falls and that of potassium rises because of:**
a. Atrophy of adrenal cortex
b. Atrophy of adrenal medulla
c. The fact that LTH from pituitary is no longer available
d. The fact that oxytocin from pituitary is no longer available

**45. The hormone secretin is produced in:**
a. Pancreas and influences conversion of glycogen into glucose
b. Adrenal glands and accelerates heart beat
c. Testis and produces male secondary sexual charecteristics
d. Small intestine and stimulate pancreas

**46. Renal calculi is seen in:**
a. Hyperthyroidism
b. Hyperparathyroidism
c. Cushing's disease
d. Addison's disease

**47. The excretion of estrogen and progesterone are through:**
a. Bile
b. Sweat
c. Urine
d. Feces

**48. Cortisol increases the blood glucose concentration either directly or indirectly by:**
a. Decreasing glucose uptake by the cells
b. Decreasing the rate of gluconeogenesis
c. Increasing the rate of glucose utilization by the cells
d. Inhibiting hormone sensitive lipase

**49. All of the following hormones mediate their major effects without actually entering the target cell except:**
a. Cortisol
b. Insulin
c. Growth hormone
d. Glucagon
e. Parathyroid hormone

**50. Growth hormone increases all of the following except:**
a. Blood glucose concentration
b. Blood free fatty acid concentration
c. Protein synthesis
d. Storage of proteins in cells
e. Metabolism of carbohydrates
f. All

**51. Thyroid stimulating hormone stimulates thyroid function in many ways but it does not increase:**
a. Synthesis of thyroxine-binding globulin
b. Rate of synthesis of thyroglobulin
c. Iodine uptake from the blood
d. Iodination of tyrosine
e. Size of the thyroid gland

**52. Which of the following is true about adrenalin:**
a. Converted to norepinephrine by methylation
b. Increases glygogen breakdown in liver and muscle
c. Is a polypeptide
d. Increases triglyceride deposition in adipose tissue

**53. The coupling of MIT and DIT and iodination of thyroglobulin is blocked by:**
a. TSH
b. TRH
c. Propylthiouracil
d. Monovalent anions

**54. Steroid hormone has:**
a. Receptors in cytoplasm or nucleus of the target cell
b. Receptor in the plasma membrane of the target cell
c. Both

**55. Anti-inflammatory action of glucocorticoid is due to:**
a. Stabilization of lysosomal membrane
b. Decreased capillary permeability
c. Inhibition of WBC migration
d. All of the above

**56. Cyclic AMP mediate the action of all except:**
a. Glucagon
b. FSH
c. LH
d. Estrogen

**57. Hormone that is a derivative of a single amino acid is:**
a. Estrogen
b. Epinephrine
c. Thyroxine
d. Progesterone

**58. True about insulin action is:**
a. Causes gluconeogenesis
b. Not useful for growth and development
c. Required for transport of glucose, amino acid, $K^+$
d. Catabolic hormone

**59. Cushing's syndrome is characterized by:**
a. Eosinophilia
b. Hypericalemia
c. Nitrogen retention
d. Poor wound healing

**60. Action of epinephrine in liver is:**
a. Glycogenolysis
b. Gluconeogenesis
c. Glycolysis
d. Lipolysis

**61. Acidophil cells of pituitary secrete:**
a. ACTH
b. Prolactin
c. Growth hormone
d. TSH
e. Both b and c

**62. Neurotransmitter which controls secretion of prolactin is:**
a. Serotonin
b. GABA
c. Somatostatin
d. Dopamine

**63. Parathyroid hormones are responsible for all EXCEPT:**
a. Increases the absorption of phosphorus from the renal tubule
b. Increases the formation of 1, 25 dihydroxy cholecalciferol
c. Mobilizes calcium from bone
d. Increases intestinal absorption of calcium

**64. The testes does not produce:**
a. Estradiol
b. Testosterone
c. Fructose
d. Inhibin

**65. The chemical nature of hormones of adrenal cortex is:**
a. Amino acids
b. Steroids
c. Eicosanoids
d. Glycoproteins

## NERVE MUSCLE PHYSIOLOGY

**1. During isotonic contraction:**
a. I band remains constant
b. A band changes in length
c. Z line approach each other
d. H zone remains constant

**2. Troponin C binds with:**
a. Actin
b. ATP
c. Tropomyosin
d. Calcium

**3. At neuromuscular junction, the receptor present are:**
a. Adrenergic
b. Nicotinic
c. Muscarinic
d. Dopaminergic

**4. Which of the ion is responsible for release of transmitters by exocytosis at nerve endings:**
a. $Mg^{2+}$
b. $Ca^{2+}$
c. $Na^+$
d. $K^+$

**5. The nerve fiber easily blocked by local anesthetics is:**
a. C type
b. A beta
c. A alpha
d. A gamma

**6. Depolarizing type of neuromuscular blocking agent is:**
a. Neostigmine
b. Physostigmine
c. Succinyl choline
d. Tubocurarine

**7. The fastest conducting nerve fiber is:**
a. B fiber
b. C fiber
c. δ fiber
d. Aα fiber

**8. Glial cell responsible for the formation of BBB is:**
a. Microglia
b. Astrocyte
c. Ependymal cells
d. Oligodendrocytes

**9. The part of sarcomere that disappears on muscle contraction:**
a. M line
b. H zone
c. I band
d. A band

**10. Phagocytosis in CNS is done by:**
a. Astrocytes
b. Schwann cells
c. Microglia
d. Oligocytes

**11. Chronaxie is minimum in:**
a. Large myelinated nerve fiber
b. Skeletal muscle fiber
c. Unmyelinated nerve fiber
d. Cardiac muscle

**12. Glycogen content is lowest in:**
a. Slow oxidative fibers
b. Fast glycolytic fibers
c. Fast oxidative fibers
d. All the above

**13. Ryanodine receptor control:**
a. $K^+$ efflux from the sarcoplasmic reticulum
b. $Na^+$ influx from the sarcoplasmic reticulum
c. $Ca^{2+}$ efflux from the sarcoplasmic reticulum
d. $Cl^-$ influx from the sarcoplasmic reticulum

**14. Myasthenia gravis is due to:**
a. Old age
b. Non-production of ACh
c. Excess destruction of ACh
d. Destruction of ACh receptors

**15. Force of contraction of following muscle does not depend on the extracellular calcium ion concentration:**
a. Skeletal muscle
b. Sphincter muscle
c. Smooth muscle
d. Cardiac muscle

**16. Energy for muscle contraction is:**
a. Actin-tropomyosin
b. ATP
c. Lactic acid
d. Nicotinamide

**17. The nuclear bag portion of the muscle spindle is innervated by:**
a. Type I fiber
b. Type II fiber
c. Both
d. None

**18. The band which disappears on muscular contraction is:**
a. H
b. I
c. A
d. Z

**19. A decrease in extracellular calcium causes:**
a. Decreased membrane permeability
b. Hyperpolarization
c. Increased excitability
d. All of the above

**20. Myosin found in muscle cell is:**
a. Myosin I
b. Myosin II
c. Both
d. None

**21. The value of resting membrane potential in a nerve fiber is:**
a. –50 mV
b. –70 mV
c. –110 mV
d. –130 mV

**22. All are steps in contraction of skeletal muscle except:**
a. Discharge of motor neuron
b. $Ca^{2+}$ release from sarcoplasmic reticulum
c. Binding of $Ca^{2+}$ to troponin C
d. Release of $Ca^{2+}$ from troponin C

**23. Which of the following is an excitatory neurotransmitter:**
a. GABA
b. Glycine
c. Melatonin
d. Glutamate

**24. The strength of contraction of an entire skeletal muscle is dependent on the:**
a. Number of muscle fibers that contract simultaneously
b. Frequency of contraction of each muscle fiber
c. Number of active cross-bridges in each muscle fiber
d. Degree of plasticity of the muscle

**25. Which of the following statements about release of acetyl choline at the neuromuscular junction is not correct?**
a. Produces an endplate potential
b. Increases sodium movement into the muscle cell
c. Always causes the muscle fiber to contract
d. Is followed by rapid destruction of acetylcholine
e. Both c and d

**26. The repolarization of an action potential is associated with all of the following except:**
a. Loss of-positive charges from inside the cell
b. Outward diffusion of $K^+$
c. Return of the membrane potential toward its resting value
d. Closure of sodium channels in the cell membrane
e. Decreased potassium permeability of cell membrane

**27. Resting membrane potential of a cell is established by or maintained by all of the following except:**
a. Sodium and potassium pump
b. Outward Movement of sodium ions
c. Inward movement of potassium ions
d. A net inward movement of positive ions
e. Adenosine triphosphate

**28. Enzyme involved in acetylcholine synthesis is:**
a. Choline acetyl transferase
b. Choline esterase
c. Pseudocholinesterase
d. Glycine

**29. Which of the following statements is true:**
a. The transmitter secreted at the endings of sympathetic preganglionic neurons is norepinephrine
b. The transmitter secreted at the endings of the preganglionic neurons of the parasympathetic neuron is epinephrine
c. The transmitter secreted at the postganglionic neuron ending of the parasympathetic neurons is atropine
d. The transmitter secreted at most postganglionic neuron endings of sympathetic nervous system is norepineiphrine

**30. When energy is derived from creatine phosphate to cause muscle contraction, what is the first step in the transfer of energy:**
a. Creatine phosphate transfers the energy to the cross-bridges to cause them to become locked
b. Creatine phosphate causes the power stroke of the cross-bridges
c. Creatine phosphate transfers its energy to the myosin filament
d. The energy of creatine phosphate is used to convert ADP into ATP

**31. End plate potential is characterized by:**
a. Hyperpolarization
b. Normal polarity
c. Depolarization
d. None

**32. The type of nerve fiber that has a conduction velocity of approximately 1 meter per second:**
a. Type A alpha
b. Type A beta
c. Type A delta
d. Type A gamma
e. Type C

**33. Which of the following transmitter substances always or almost always tend to inhibit the postsynaptic neuron?**
a. GABA
b. Dopamine
c. Norepinephrine

**34. The motor unit is:**
a. Muscle fiber and neuron supplying it
b. Afferent fiber-center-efferent fiber
c. Motor neuron and muscle fibers supplied by it
d. Single muscle fiber with its nerve

**35. At a given load, the velocity of muscle contraction is maximal at:**
a. The resting length
b. Twice the resting length
c. Half the resting length
d. The equilibrium length

**36. Neurotransmitter in nigrostrial pathway is:**
a. Dopamine
b. Epinephrine
c. Norepinephrine
d. Acetylcholine

**37. Myosin light chain kinase plays an important role in the contraction of:**
a. Skeletal muscle
b. Smooth muscle
c. Cardiac muscle

**38. Smooth muscle has the following characteristic:**
a. Threshold is higher
b. RMP is greater
c. Action potential is greater
d. Chronaxie is longer

**39. Which of the following is caused by acetylcholine through nicotinic receptors?**
a. Contraction of skeletal muscle
b. Decrease of heart rate
c. Secretion of saliva
d. Contraction of pupils

**40. A patient complains of muscle weakness; on administration of neostigmine it disappears. Its mechanism of action is:**
a. It blocks action of acetylcholine
b. It interferes with the action of amino-oxidase
c. It interferes with the action of carbonic anhydrase
d. It interferes with the action of acetylchlorine esterase

**41. Actin combines with myosin to form actomyosin in the presence of:**
a. $Ca^{2+}$ and $Mg^{2+}$
b. $Mg^{2+}$ and ATP
c. $Ca^{2+}$ and ATP
d. $Ca^{2+}$ and $K^{+}$

**42. Repetitive stimulation of the muscle results in:**
a. Tetany
b. Tetanus
c. Summation
d. None of the above

**43. The action potential of skeletal muscle:**
a. Has a prolonged plateau phase
b. Spreads inward to all parts of the muscle via T tubules
c. Causes immediate uptake of $Ca^{2+}$ into the lateral sacs of the sarcoplasmic reticulum
d. Is longer than the action potential of cardiac muscle
e. Is not essential for contraction

**44. The function of tropomyosin in skeletal muscle is:**
a. Sliding on actin to produce shortening
b. Releasing $Ca^{2+}$ after initiation of contraction
c. Binding to myosin during contraction
d. To act as a relaxing protein at rest by covering up the sites where myosin binds to actin

**45. The cross-bridges in skeletal muscle are made up of:**
a. Actin
b. Myosin
c. Troponin
d. Tropomyosin
e. Myelin

**46. Denervation of skeletal muscle leads to all except:**
a. Atrophy
b. Flaccid paralysis
c. Spastic paralysis
d. Fibrillations

**47. Gap junctions:**
a. Not present in cardiac muscle
b. Are present, but of little functional importance in case of cardiac muscle
c. Are present and are important in initiation of pathway for rapid spread of excitation from one cardiac muscle fiber to another
d. Are not present in smooth muscle

**48. The I-bands of a sarcomere contains molecules of:**
a. Mainly actin
b. Mainly myosin
c. Mainly troponin
d. Mainly tropomyosin

**49. When the muscle is at rest, the myosin-binding sites on the actin molecule are blocked by:**
a. Troponin
b. Tropomyosin
c. Collagen

**50. Group A fibers are most susceptible to:**
a. Pressure
b. Hypoxia
c. Local anesthetics
d. Temperature

**51. All or none response in a nerve is applicable to:**
a. A mixed nerve
b. A sensory nerve
c. A motor nerve
d. A single nerve fiber

**52. Tropomyosin:**
a. Helps in the fusion of action and myosin
b. Slides over myosin
c. Covers myosin and prevent attachment of actin and myosin
d. Causes calcium release

**53. d-tubocurarine in therapeutic doses:**
a. Competes with Acetyl choline for same nicotinic receptors on motor end plate
b. Prevents propagation of action potential in skeletal muscle
c. Enhances the action of catecholamines
d. Enhances the action of choline esterase

## CENTRAL NERVOUS SYSTEM

**1. Normal blood flow to the brain in ml/min:**
a. 150
b. 500
c. 750
d. 1000

**2. The following is not related to stretch reflex:**
a. Response is shortening of the same muscle
b. It is a monosynaptic reflex
c. It is a polysynaptic reflex
d. Voluntary movement
e. Involuntary movement

**3. Pain is carried by:**
a. A delta fibers
b. A beta fibers
c. C fibers
d. Both a and c

**4. Nucleus Gracilis and Nucleus Cuneatus are the first synapse for:**
a. Dorsal column tract
b. Dorsolateral tract
c. Lateral spinothalamic tract
d. Ventral spinothalamic tract

**5. In the spinal cord:**
a. Dorsal roots are motor and ventral roots are sensory
b. Dorsal roots are sensory and ventral roots are motor
c. There is no relay of sensory nerves
d. There is no crossing of nerve fibers

**6. Primary visual area is located in the:**
a. Limbic system
b. Parietal lobe
c. Occipital lobe
d. Frontal lobe

**7. The area responsible for short term memory is located in:**
a. Cerebellum
b. Hypothalamus
c. Thalamus
d. Hippocampus

**8. Lateral spinothalamic tract carries the following sensation:**
a. Vibration
b. Proprioception
c. Pain
d. Fine touch

**9. Which of the following is the part of limbic system:**
a. Red nucleus
b. Corpus striatum
c. Prefrontal lobe
d. Cingulate cortex

**10. Nerve supply to the sweat glands is by:**
a. Parasympathetic cholinergic
b. Sympathetic cholinergic
c. Sympathetic adrenergic
d. None of the above

**11. Dominant hemisphere:**
a. Is located on the right side in most of the people
b. Is also known as representational hemisphere
c. Is concerned with language functions
d. Concept does not apply to deaf mute

**12. The motor cortex (area 4):**
a. Is in the precentral gyrus of the parietal lobe
b. Receives inputs from a variety of sources, including cortical association fibers, the cerebellum, and the basal ganglia
c. Has the muscles of the feet and legs represented laterally near the sylvian sissure
d. Is the only area involved in motor function

**13. Stereognosis means:**
a. Detecting pressure
b. Detecting vibration
c. Identifying an object by touch
d. Sense of smell

**14. All are symptoms of Parkinsonism except:**
a. Memory loss
b. Mask like face
c. Resting tremor
d. Hypokinasia

**15. If a patient has involuntary athetoid movement probably he may have lesion in:**
a. Thalamus
b. Basal ganglia
c. Cerebellum
d. Limbic system

**16. Satiety center is located in:**
a. Parietal lobe
b. Thalamus
c. Hypothalamus
d. Medulla

**17. Satiety center is located in the following hypothalamic nucleus:**
a. Supraoptic
b. Ventromedial
c. Lateral
d. Dorsomedial

**18. Which of the following is an inhibitory neurotransmitter:**
a. ACh
b. Glutamate
c. GABA
d. Nor epinephrine

**19. Limbic system is mainly concerned with:**
a. Control of emotion
b. Speech execution
c. Voluntary movement
d. Involuntary movement

**20. All are true regarding receptor potential except:**
a. Is a graded response
b. Generates action potential in the nerve fiber attached to receptor
c. Can be propagated
d. Does not obey all or none law

**21. All the following reflexes are multisynaptic except:**
a. Cord righting reflex
b. Withdrawal reflex
c. Stretch reflex
d. Golgi tendon reflex

**22. Parkinson's disease is due to damage to:**
a. Putamen
b. Globus pallidus
c. Dopaminergic cells of substantia nigra
d. All the above

**23. Wernicke's area:**
a. Is present in parietal cortex
b. Lies near auditory area of temporal lobe
c. Is located in occipital cortex
d. Is a motor area

**24. δ waves in EEG:**
a. Occur in deep sleep
b. Occur at a rate below 3 to 5 cycles /second
c. Strictly occur in the cortex independent of activities of lower regions of brain
d. All the above

**25. Dorsal column-medial lemniscal pathway:**
a. Carries sense of temperature to the cortex
b. Carries sense of crude touch and pain to the cortex
c. Carries sensation of fine touch, vibration and proprioception
d. Does not help in detecting movt of different parts

**26. Muscle spindles:**
a. Are stretch receptors
b. Lie with their long axis parallel to extrafusal fibers
c. Are present in more number in antigravity muscles
d. All the above

**27. Brown-Sequard syndrome results:**
a. On spinal transection
b. On hemisection of spinalcord
c. On sectioning brain stem at midcollicular level
d. None of the above

**28. The primary function of basal ganglia is:**
a. Sensory integration
b. Planning motor movements
c. Short-term memory
d. REM sleep

**29. The following are considered as mechano receptors except:**
a. Pacinian corpuscle
b. Krause's end bulb
c. Ruffini's end organ
d. Bare nerve endings

**30. In Brown Sequard syndrome, all the sensations except one is lost on the same side:**
a. Proprioception
b. Stereognosis
c. Vibration
d. Pain

**31. Spastic gait is seen in:**
a. LMN lesion
b. Thalamic syndrome
c. UMN lesion
d. Cerebellar lesion

**32. Crossed extensor reflex is a:**
a. Monosynaptic reflex
b. Postural reflex
c. Sympathetic reflex
d. Withdrawal reflex

**33. All are ascending tracts except:**
a. Tract of Goll
b. Tract of Burdach
c. Rubrospinal tract
d. Lateral spinothalamic tract

**34. Sensory area for speech is situated at:**
a. Broca's area
b. Temporal lobe
c. Occipital lobe
d. Frontal lobe

**35. The wave in EEG with highest frequency is:**
a. Delta wave
b. Beta wave
c. Theta wave
d. Gamma wave

**36. When environmental temperature is above body temperature, heat is lost from the body by:**
a. Conduction
b. Evaporation
c. Radiation
d. Convection

**37. Sensation of fine touch is carried by:**
a. Pyramidal tract
b. Posterior column tract
c. Lateral spinothalamic tract
d. Ventral spinothalamic tract

**38. Flocculonodular lobe of cerebellum is concerned with:**
a. Co-ordination
b. Chemoreception
c. Equilibrium
d. Taste sensation

**39. Center for body temperature regulation is located in:**
a. Pons
b. Medulla
c. Hypothalamus
d. Thalamus

**40. Neurotransmitter at the postganglionic sympathetic fiber is:**
a. ACh
b. Norepinephrine
c. Epinephrine
d. Dopamine

**41. Parkinsonism is due to the lesion of:**
a. Corticostriate fibers
b. Thalamocortical fibers
c. Nigrostriatal fibers
d. Rubrothalamocortical fibers

**42. Delta waves seen in:**
a. REM sleep
b. Awake with eye closed
c. Deep sleep
d. Awake with eye open

**43. Which one is a superficial reflex?**
a. Knee
b. Plantar
c. Ankle
d. Jaw

**44. The frequency of alpha waves in EEG is:**
a. 8-12 cycles/sec
b. 15-25 cycles/sec
c. 2-5 cycles/sec
d. None of the above

**45. Lesions in—lead to sensory ataxia:**
a. Posterior column of cerebellum
b. Vermis of cerebellum
c. Flocculonodular lobe of cerebellum
d. Vestibular apparatus

**46. Basal ganglia include all except:**
a. Caudate nucleus
b. Putamen
c. Globus pallidus
d. Substantia gelatinosa of Rolando

**47. The end plate potential is characterized by:**
a. Propagation
b. All or none loss
c. Depolarization
d. Hyperpolarization

**48. Vomiting center is situated in the:**
a. Hypothalamus
b. Amygdala
c. Pons
d. Medulla

**49. Swallowing center is situated in:**
a. Midbrain
b. Pons
c. Medulla
d. Cerebellum

**50. The intensity of sensory stimuli is determined by:**
a. Frequency of action potential
b. Duration of latent period
c. Amplitude of action potential
d. Amplitude of generation potential

**51. Which sensation is not lost on the side of lesion in Brown Sequard's syndrome:**
a. Touch
b. Vibration sense
c. Muscle sense
d. Temperature

**52. Conduction in which type of nerve is blocked maximally by pressure:**
a. C-fibers
b. A-alpha fibers
c. A-beta
d. A-gamma

**54. Broca's area is present in:**
a. Superior temporal gyrus
b. Precentral gyrus
c. Postcentral gyrus
d. Inferior frontal gyrus

**55. Following are seen in REM sleep except:**
a. Bruxism
b. Hypotonia
c. Tachycardia
d. Dreams

**56. In cerebellar disease all the statements are correct except:**
a. The Romberg's sign is positive
b. There is adiadokokinesia
c. There is pendular knee jerk
d. There is static tremor

**57. The cerebellum:**
a. Has a totally inhibitory output from its cortex
b. Has only excitatory signal output from its deep nuclear layers
c. Has a conscious interpretation of motor activity
d. Has inhibitory influence on muscle tone in human.

**58. The condition known as REM sleep is:**
a. That point at which the individual becomes aware and alert
b. Referred to as paradoxical sleep
c. Characterized by total lack of all muscular activity
d. Characterized by slow high voltage regular EEG activity

**59. True visceral pain arises in normal persons from:**
a. Distension
b. Mechanical irritation
c. Excessive heat
d. Compression
e. Chemical stimulation

**60. Interneurons are:**
a. Essential part of stretch reflex
b. Essential part of all reflexes
c. Always excitatory
d. Always inhibitory
e. None of the above

**61. What is true regarding the gamma efferent neuron:**
a. An 'A' group motor neuron with a smaller diameter than that of alpha efferent neurons
b. Innervates intrafusal fibers
c. Innervates muscle fibers that stretch annulospiral endings
d. All of the above

**62. A unilateral upper motor neuron lesion in the internal capsule is best characterized by:**
a. Diminished use of contralateral limbs below the lesion
b. Muscle fasciculations
c. Ipsilateral hypotonicity
d. Flexion of the leg

**63. Which of the following reflexes disappear in the absence of functional connections between the spinal cord and the brain:**
a. Swallowing reflex
b. Seating reflex
c. Withdrawal reflex
d. Erection of penis
e. All of the above

**64. Hyperkinetic syndromes such as chorea and athetosis are usually associated with pathological changes in:**
a. Motor areas of cerebral cortex
b. Anterior hypothalamus
c. Pathways for recurrent collateral inhibition in the spinal cord
d. Basal ganglia complex

**65. Muscle spindle is:**
a. Receptor for a variety of multisynaptic reflexes
b. Receptor for myotatic or stretch reflex
c. Occurs only in antigravity extensor muscles
d. Excited by both stretch and contraction of the muscles in which it is located

**66. The reticular formation is a diffuse collection of:**
a. Sensory neurons only
b. Motor neurons only
c. Autonomic centers only
d. All the above

**67. Classical decerebrate animal results from the following experimental procedure:**
a. Removal of the cerebrum
b. Transection at the upper border of midbrain

**68. The nerve fiber carrying which of the following sensations is the thickest in human:**
a. Touch
b. Pain
c. Temperature
d. Proprioception

**69. What percentage of pyramidal fibers are unmyelinated:**
a. 20
b. 35
c. 50
d. 75

**70. Gag reflex is mediated by cranial nerve:**
a. VII
b. IX
c. X
d. XII

**71. Flocculonodular lobe of cerebellum is concerned with:**
a. Equilibrium
b. Co-ordination
c. Baroreception
d. Chemoreception

**72. Vestibular fibers relay in:**
a. Vermis
b. Lateral geniculate body
c. Flocculonodular lobe of cerebellum
d. Auditory cortex

**73. Destruction of lateral nucleus of thalamus lead to:**
a. Aphagia
b. Hyperphagia
c. Satiety
d. Somnolence

**74. Chemical transmission of nerve impulses from one neuron to another or from a neuron to a muscle is by:**
a. Cholesterol
b. Acetyl choline
c. CCK
d. ATP

**75. Which part of the mammalian brain controls the voluntary muscular coordination:**
a. Cerebellum
b. Cerebrum
c. Corpus callosum
d. Medulla

**76. Parasympathetic nervous system increases the activity of:**
a. Gut, iris, urinary bladder
b. Heart, adrenal and sweat glands
c. Heart, lacrimal glands, pancreas
d. Lacrimal glands, sweat glands, arrector pilli

**77. Cerebellum of brain is concerned with all except:**
a. Balance
b. Initiation of muscular contraction
c. Regulation of body posture and equilibrium
d. Coordination of muscular movements

**78. Which of these is an example of conditioned reflex:**
a. Withdrawal of hand on touching a hot plate
b. Watering of mouth at the smell of food
c. Flowing of tears while peeling and cutting onion
d. Cycling
e. b and d

**79. During conduction of an impulse electric potential on inside of axolemma changes from:**
a. Negative to positive and remains positive
b. Positive to negative and again positive
c. Negative to positive and again negative
d. Positive to negative and remains negative

**80. The sensory ganglia concerned with spinal reflexes are located in:**
a. Cutaneous sense organs
b. Gray matter of.spinal cord
c. Dorsal root ganglion of spinal nerves
d. Ventral root of spinal nerves

**81. Commonest neurotransmitter in the synapse outside brain is:**
a. Acetylcholine
b. Secretin
c. CCK
d. Acetylcholinesterase

**82. "All or none law" is applicable in the following events:**
a. IPSP
b. EPSP
c. Nerve action potential

**83. Pacinian corpuscles are:**
a. Temperature receptor
b. A-beta nerve fibers
c. Touch - pressure receptor

**84. Which of the following is a characteristic of chemical synapses:**
a. One - way conduction
b. Synaptic delay
c. Susceptible to drugs
d. All the above

**85. Stimulation of which of the following might be expected to produce itching:**
a. Dorsal root C fibers
b. Touch receptors
c. A-beta fibers in peripheral nerves

**86. Primary auditory cortex is located in the:**
a. Limbic system
b. Occipital lobe
c. Parietal lobe
d. Superior part of temporal lobe

**87. The extrapyramidal system is not directly concerned with:**
a. Stretch reflexes
b. Sensation from viscera
c. Spasticity
d. All

**88. Lesions of which of the following hypothalamic nuclei cause loss of the circadian rhythm in plasma cortisol secretion:**
a. Ventromedial nuclei
b. Dorsomedial nuclei
c. Suprachiasmatic nuclei
d. Supraoptic and paraventricular nuclei

**89. Lesions of which of the hypothalamic nuclei cause diabetes insipidus:**
a. Supraoptic nuclei
b. Ventromedial nuclei
c. Dorsomedial nuclei
d. Medial preoptic nuclei

**90. Which of the following are part of the limbic system:**
a. Red nuclei
b. Amygdaloid nuclei
c. Posterior commissure
d. Cingulate cortex

**91. The functions of the limbic system include all except:**
a. Regulation of sexual behavior
b. Influencing rage and fear
c. Temperature regulation
d. Olfaction

**92. A reflex action:**
a. May be carried out by skeletal, smooth and cardiac muscles as well as by glands
b. Pathway is: efferent → spinal cord → brain → afferent
c. Pathway is: spinal cord → brain → afferent → efferent → target tissue
d. Pathway is: receptor → spinal cord → brain → efferent

**93. The ascending reticular formation:**
a. Is located in cerebral hemisphere
b. Has increased activity during sleep
c. Is located in brain stem
d. All

**94. Increased tendon reflexes are likely to be present a patient suffering from long-standing damage to:**
a. Anterior horn cells (poliomyelitis)
b. Primary sensory neurons (tabes dorsalis)
c. Internal capsule

**95. All are features of cerebellar dysfunction except:**
a. Ataxia
b. Scanning speech
c. Dysmetria
d. Resting tremor

**96. Which neurotransmitter is involved in sleep pattern:**
a. Serotonin
b. Acetylcholine
c. Noradrenalin
d. Dopamine

**97. Diseases of basal ganglia can produce:**
a. Athetosis
b. Paralysis agitans
c. Chorea
d. All

**98. Which of the following is the inhibitory neurotransmitter:**
a. Acetylcholine
b. Serotonin
c. GABA
d. Dopamine

**99. The output of cerebellum is:**
a. Mostly inhibitory
b. Mostly excitatory
c. Sometimes inhibitory and sometimes excitatory

**100. Granular cells of cerebral cortex have:**
a. Nutritive role
b. Motor activity
c. Sensory action
d. All

**101. The neurotransmitter released into synapse between neurons and muscle cells is:**

a. Epinephrine
b. Norepinephrine
c. Acetylcholine
d. Gamma-aminobutyric acid

**102. Broca's area:**

a. Is for planning and making decisions o
b. Contains primary visual cortex
c. Contains somatic sensory area
d. Co-ordinates muscles used in speech production.

**103. Parietal lobe:**

a. Is for planning and making decision
b. Contains primary visual cortex
c. Contains somatic sensory area
d. Co-ordinates muscles used in speech production

**104. Neurotransmitter synthesized from tryptophan and responsible for production and regulation of sleep is:**

a. Acetylcholine
b. Serotonin
c. Dopamine
d. Adrenaline

**105. Occipital lobe:**

a. Is for planning and making decision
b. Contains primary visual cortex
c. Contains somatic sensory area
d. Co-ordinates muscles used in speech production

**106. Frontal lobe:**

a. Is for planning and making decisions
b. Contains primary visual cortex
c. Contains somatic sensory area
d. Co-ordinates muscles used in speech production

**107. The reticular formation is mainly responsible for:**

a. Homeostasis and control of emotional responses
b. Control of rate of breathing
c. Regulating brain alertness
d. Conveying visual information to the cortex

**108. Pacinian corpuscles are:**

a. Rapid touch receptors
b. Slow touch receptors
c. Temperature receptors
d. Innevated by A delta nerve fibers

**109. The primary auditory cortex is located in the:**

a. Limbic system
b. Superior part of temporal lobe
c. Posterior part of parietal lobe
d. Posterior part of occipital lobe

**110. Sleep is produced due to the stimulation of which of the following brain areas:**

a. Occipital cortex
b. Posterior hypothalamus
c. Cuneate nucleus
d. Gracile nucleus

**111. Thirst is produced when:**

a. Plasma osmolality is increased and plasma volume decreased
b. Plasma osmolality and volume are increased
c. Plasma osmolality and volume are decreased
d. Plasma osmolality is decreased and plasma volume is increased

**112. Which of the following is not the result of parasympathetic stimulation:**

a. Increased stomach activity
b. Increased saliva formation
c. Constriction of bronchi
d. Dilatation of the pupil

**113. Stimulation of parasympathetic fibers not contained in cranial nerve can lead to:**

a. Contraction of the bladder
b. Constriction of the pupil
c. Increased salivation
d. Simulation of gallbladder activity

**114. The white matter of spinal cord consists mainly of:**

a. Cell bodies
b. Dendrites
c. Axons
d. Synapses

**115. Diencephalon contains:**

a. Cerebral cortex
b. Hypothalamus
c. Olfactory bulbs
d. Basal ganglia

**116. Crude touch sensations are carried by:**

a. Lateral spinothalamic tract
b. Ventral spinothalamic tract
c. Posterior columntract
d. Spinocerebellar tract

**117. The main excitatory neurotransmitter in the central nervous system is:**

a. Glycine
b. Acetyl choline
c. Aspartate
d. Glutamate

**118. Pain transmission is inhibited by all EXCEPT:**

a. Morphine
b. Encephalin
c. Substance P
d. Beta endorphin

**119. Receptor for vision are:**

a. Telereceptor
b. Exteroceptors
c. Interoceptors
d. Chemoreceptors

**120. Phagocytosis in the CNS is done by:**

a. Astrocytes
b. Schwann cells
c. Microglia
d. Oligodendrogliocytes

**121. Modality that is lost on the ipsilateral side in Brown sequard syndrome is:**

a. Pain
b. Temperature
c. Crude touch
d. Proprioception

**122. REM sleep is:**

a. That point at which the individual become aware and alert
b. Referred to as paradoxical sleep
c. Characterized by loss of alt muscular activity
d. Characterized by slow high voltage regular EEG activity

**123. Flocculonodular lobe has direct connection with:**

a. Red nucleus
b. Inferior olivary nucleus
c. Vestibular nucleus
d. Dentate nucleus

**124. Circadian rhythem is controlled by:**

a. Suprachiasmatic nucleus of hypothalamus
b. Postero ventral nucleus of thalamus
c. Dentate nucleus of cerebellum
d. Pineal gland

**125. Crossed extensor response is a:**

a. Withdrawal reflex
b. Postural reflex
c. Monosynaptic reflex
d. Sympathetic reflex
e. Exaggerated in UMN lesion

## SPECIAL SENSES

**1. On comparing with perilymph, endolymph has:**

a. Higher sodium concentration
b. Higher potassium concentration
c. Same sodium concentration
d. Same potassium concentration

**2. Near response include all the following except:**

a. Increase in anterior curvature of lens
b. Constriction of pupil
c. Dialatation of pupil
d. Convergence of eyeball

**3. Refractive power of the lens is measured in:**

a. Decibels
b. Diopters
c. Centimeters
d. Millimeters

**4. Lateral geniculate body (LGB) is concerned with:**

a. Hearing
b. Smell
c. Taste
d. Vision

**5. Flavor of food is due to:**

a. Taste sensation
b. Olfactory sensation
c. Warmth in the tongue
d. A combination of taste,smell and warmth sensations from the food

**6. When light strikes the outer segment of the photoreceptor, the following reactions occur except:**

a. Formation of hyperpolarizing receptor potential
b. Closure of the $Na^+$ channel
c. Activated phosphodiesterase hydrolyses cGMP
d. Opening of the $Na^+$ channel

**7. Bitter taste is produced by:**

a. Acids
b. Alkaloids
c. Organic salts
d. Alcohols

**8. Protonopia means:**

a. Person cannot see green
b. Cannot see blue
c. Cannot see red
d. No color sense

**9. Myopia can be corrected by using _____ lens.**
a. Biconvex
b. Cylindrical
c. Biconcave
d. Plain

**10. Dioptric power of the human eye in diopter is:**
a. 50
b. 60
c. 70
d. 80

**11. Cavity of middle ear contains:**
a. Perilymph
b. Endolymph
c. Air
d. ECF

**12. Which of the following is test for inner ear deafness:**
a. Finger nose test
b. Weber's test
c. Rinne's test
d. Baranys test

**13. Medial geniculate body receives:**
a. Auditory fibers
b. Visual fibers
c. Proprioceptive fibers
d. None of the above

**14. If light source in front of the eye suddenly becomes bright:**
a. Focus of lens will change
b. Retinal blood supply will be cut off
c. Intraocular pressure will rise
d. Pupils will constrict

**15. Which one of the following procedures is most likely to increase intraocular pressure of glaucoma patient:**
a. Use of atropine
b. Decreased pressure in jugular vein
c. High doses of vitamin C
d. Exposure to brilliant sunlit environment

**16. The Helmholtz theory of color vision states that**
a. There are three kinds of cones in the retina responding to the three primary colors
b. There are two kinds of cones called dominators and modulators
c. There is only one kind of cone and the color is recognized only in area 17
d. There are seven types of cones responding to the seven colors of the spectrum

**17. Which structure in the eye is pain-sensitive?**
a. Iris
b. Choroid
c. All of the above

**18. Red color blindness is called:**
a. Deuteranopia
b. Protanopia
c. Protanomaly
d. Deuteranomaly

**19. Medial geniculate body is concerned with:**
a. Hearing
b. Vision
c. Smell
d. Taste

**20. Smell receptors are seen in:**
a. Lower 1/3 of nasal mucosa
b. Upper 1/3 of nasal mucosa
c. Amygdaloid body
d. Cribriform plate

**21. Intraocular fluid:**
a. Is produced at the canal of Schlemm
b. Is reabsorbed by ciliary process
c. Helps to maintain the curve of cornea
d. None of the above

**22. Most of the refraction in the eye occurs at the:**
a. Anterior surface of cornea
b. Posterior surface of cornea
c. Anterior surface of lens
d. Posterior surface of lens

**23. The medium with highest refractive index in the eye is:**
a. Cornea
b. Nucleus of the lens
c. Cortex of the lens
d. Aqueous humor

**24. The optical power of the eye is:**
a. 25 diopters
b. 50 diopters
c. 59 diopters
d. 75 diopters

**25. The portion of the ear involved in balancing is:**
a. Sacculus
b. Cochlea
c. Three semicircular canals with ampullae
d. Utriculus

**26. Impulses generated by the olfactory receptors in the nasal mucous membrane:**

a. Relay through the thalamus
b. Relay through the internal capsule
c. Relay through the hypothalamus
d. Pass through mitral cells and from there directly to olfactory cortex

**27. Impulses generated in the taste buds of the tongue reach the cerebral cortex via:**

a. Thalamus
b. Internal capsule
c. Trochlear nerve
d. Hypoglossal nerve

**28. Olfactory sensory cells:**

a. Relay in the thalamus
b. Are of little importance in appreciating the flavor of food after it enters the mouth
c. Show adaptation
d. All

**29. The cones in the eye:**

a. Are responsible for dim light vision
b. Are much more sensitive to light than the rods
c. Have higher visual acuity than rods
d. Have impaired function in the absence of vitamin A

**30. The rods in the retina:**

a. Contain visual pigment which is more sensitive to dim light than cone pigments
b. Are relatively more numerous in night shift workers
c. Comprise one-fifth of the receptors cells in the fovea

**31. The stapes rests on:**

a. Round window
b. Oval window
c. Tympanic membrane
d. Semicircular canal

**32. In nerve deafness:**

a. Air conducted sounds are perceived well
b. Bone conducted sounds are perceived well
c. Both air and bone conducted sounds are not perceived well

**33. Argyll Robertson pupil is a condition in which the pupillary constriction in response to light stimulus:**

a. Is absent
b. Is delayed
c. Is not affected
d. Is present only in one eye

**34. Myopia (shortsightedness) is a defect in human eyes where image is formed:**

a. In front of retina and can be corrected by using concave lens
b. In front of retina and can be corrected by using convex lens
c. Behind retina and can be corrected by using concave lens
d. Behind retina and can be corrected by using convex lens

**35. Function of iris is to:**

a. Move the lens forwards and backwards
b. Alter the diameter of pupil
c. Close the eyelids
d. Secrete aqueous humor

**36. Blind spot in an eye is located:**

a. In fovea centralis
b. In the middle of the lens
c. Where optic nerve leaves the retina
d. In the center of the pupil

**37. Area of the most acute vision in eyes which contains only cone and where sharp and bright images are formed is:**

a. Blind spot
b. Yellow spot (macula lutea)
c. Pupil
d. Lens
e. Fovea centralis

**38. The low intensity light during night is detected by:**

a. Cones
b. Rods
c. Both
d. Crystalline lens

**39. Ear ossicles are arranged in the following order from eardrum:**

a. Malleus, stapes, incus
b. Malleus, incus, stapes
c. Incus, malleus, stapes
d. Stapes, malleus, incus

**40. Vitreous humor lies:**

a. Behind the lens
b. In front of the lens
c. Between the choroid and retina
d. Between sclera and choroid

**41. Chief function of semicircular canals of the internal ear is:**
a. To perceive sound of high or low frequencies
b. To transmit sound to the auditory nerves
c. To maintain dynamic equilibrium of moving body
d. To perceive changes in orientation of body in relation to gravity

**42. Internal ear is responsible for:**
a. Fixation of gaze
b. Sensing changes in atmospheric pressure
c. Maintaining rotational balance of body at rest
d. Maintaining gravitational balance of body at rest

**43. Organ of Corti is found in:**
a. Middle ear
b. Utriculus
c. Sacculus
d. Cochlea
e. External ear

**44. Otoconia are suspended in:**
a. Synovial fluid
b. Endolymph
c. Perilymph
d. Hemolymph

**45. Membranous labyrinth is called statoacoustic organ because it is concerned with:**
a. Hearing
b. Balancing
c. Both
d. Sound production

**46. Taste and smell receptors are:**
a. Mechanoreceptors
b. Chemoreceptors
c. Thermoreceptors
d. Electromagnetic receptors

**47. The sensory cell for smell is a:**
a. Receptor cell
b. Sensory neuron
c. Motor neuron
d. Photoreceptor

**48. The part of the eye which transduces blue, green and red light is:**
a. Cornea
b. Fovea
c. Periphery of retina
d. Optic nerve

**49. The part of eye which bends light and protects inner eye is the:**
a. Cornea
b. Fovea
c. Pupil
d. Ciliary muscle

**50. Transduction of light is responsible for functioning of:**
a. Rods and cones in the retina
b. Opsin and retinal rhodopsin
c. Rods and retinal
d. Opsin and cones

**51. The part of the ear where sound is transduced is:**
a. Outer ear
b. Tympanic membrane
c. Semicircular canals
d. Cochlea

**52. Impulses of the taste buds of the tongue come from cerebral cortex through:**
a. Internal capsule
b. Thalamus
c. Trochlear nerve
d. Hypoglossal nerve

**53. Visual accommodation involves:**
a. Contractions of ciliary muscles
b. Increased intraocular pressure
c. Decrease in the curvature of lens
d. Increased tension on the lens ligaments

**54. The fovea centralis of the eye:**
a. Contains only rods
b. Is the region of highest visual acuity
c. Has lowest light threshold

**55. To correct myopic vision one should use:**
a. Concave lens
b. Convex lens
c. Plane glass plates
d. Convex glass plates

**56. Bitter taste is mediated by the action of:**
a. Guanyl cyclase
b. G protein
c. Tyrosine kinase
d. Epithelial Na channels

## ANSWERS

### GENERAL PHYSIOLOGY

| | | | | | |
|---|---|---|---|---|---|
| 1. c | 2. a | 3. c | 4. b | 5. a | 6. a |
| 7. d | 8. c | 9. a | 10. b | 11. d | 12. a |
| 13. b | 14. c | 15. b | 16. d | 17. c | 18. e |
| 19. a | 20. a | 21. c | 22. c | 23. a | |

### CIRCULATING BODY FLUIDS

| | | | | | |
|---|---|---|---|---|---|
| 1. c | 2. c | 3. d | 4. a | 5. c | 6. c |
| 7. c | 8. b | 9. b | 10. c | 11. a | 12. d |
| 13. a | 14. a | 15. c | 16. d | 17. a | 18. d |
| 19. b | 20. b | 21. d | 22. b | 23. a | 24. a |
| 25. d | 26. c | 27. b | 28. a | 29. b | 30. d |
| 31. d | 32. d | 33. c, d | 34. d | 35. a | 36. a |
| 37. b | 38. c | 39. a | 40. c | 41. b | 42. c |
| 43. c | 44. b | 45. b | 46. a | 47. c | 48. c |
| 49. b | 50. b | 51. d | 52. a | 53. c | 54. c |
| 55. c | 56. a | 57. c | 58. c | 59. c | 60. a, c |
| 61. e | 62. c | 63. a | 64. a | 65. b | 66. a |
| 67. a | 68. d | 69. a | 70. a | 71. b | 72. a |
| 73. b | 74. a | | | | |

### RESPIRATORY SYSTEM

| | | | | | |
|---|---|---|---|---|---|
| 1. c | 2. d | 3. b | 4. b | 5. d | 6. d |
| 7. c | 8. b | 9. b | 10. a | 11. c | 12. b |
| 13. c | 14. c | 15. c | 16. d | 17. c | 18. b |
| 19. b | 20. b | 21. b | 22. a | 23. a | 24. c |
| 25. b | 26. c | 27. a | 28. a | 29. d | 30. b |
| 31. a | 32. c | 33. b | 34. b | 35. d | 36. a |
| 37. b | 38. d | 39. b | 40. b | 41. c | 42. b |
| 43. a | 44. b | 45. b | 46. c | 47. d | 48. b |
| 49. a,b,d | 50. a | 51. d | 52. b | 53. a | 54. d |
| 55. d | 56. b | 57. d | 58. c | 59. b | 60. a |
| 61. a | 62. d | 63. e | 64. a | 65. b | 66. e |
| 67. b | 68. c | 69. d | 70. a | 71. d | 72. a |
| 73. d | 74. b | 75. d | 76. d | 77. a | 78. d |
| 79. d | 80. a | 81. b | | | |

### CARDIOVASCULAR SYSTEM

| | | | | | |
|---|---|---|---|---|---|
| 1. d | 2. c | 3. b | 4. b | 5. d | 6. b |
| 7. a | 8. d | 9. c | 10. b | 11. c | 12. a |
| 13. a | 14. c | 15. a | 16. b | 17. c | 18. a |
| 19. d | 20. b | 21. b | 22. b | 23. c | 24. c |
| 25. c | 26. b | 27. d | 28. c | 29. d | 30. d |
| 31. c | 32. a | 33. a | 34. b | 35. c | 36. b |
| 37. a | 38. b | 39. b | 40. c | 41. b | 42. a |
| 43. c | 44. c | 45. c | 46. b | 47. d | 48. c |
| 49. d | 50. a | 51. c | 52. b | 53. c | 54. a |
| 55. b | 56. a | 57. a | 58. a | 59. a | 60. d |
| 61. a | 62. d | 63. d | 64. b | 65. d | 66. b |

### GASTROINTESTINAL SYSTEM

| | | | | | |
|---|---|---|---|---|---|
| 1. d | 2. a | 3. c | 4. d | 5. d | 6. c |
| 7. c | 8. c | 9. d | 10. d | 11. a | 12. d |
| 13. b | 14. a | 15. c | 16. a | 17. c | 18. c |
| 19. d | 20. c | 21. c | 22. a | 23. d | 24. c |
| 25. b | 26. c | 27. c | 28. a | 29. c | 30. d |
| 31. c | 32. a | 33. e | 34. a | 35. b | 36. d |
| 37. c | 38. a | 39. e | 40. d | 41. a | 42. a |
| 43. c | 44. d | 45. d | 46. d | 47. b | 48. b |
| 49. a | 50. b | 51. b | 52. d | 53. d | 54. c |
| 55. b | 56. a | 57. b | 58. b | 59. c | 60. d |
| 61. d | 62. b | 63. b | 64. b | 65. b | 66. a |
| 67. d | 68. b | 69. c | | | |

### RENAL PHYSIOLOGY

| | | | | | |
|---|---|---|---|---|---|
| 1. a | 2. d | 3. b | 4. b | 5. d | 6. a |
| 7. b | 8. c | 9. a | 10. c | 11. c | 12. d |
| 13. a | 14. b | 15. b | 16. a,d | 17. d | 18. a |
| 19. a | 20. b | 21. b | 22. d | 23. d | 24. b,d |
| 25. b | 26. a | 27. d | 28. d | 29. b | 30. d |
| 31. d | 32. e | 33. d | 34. b | 35. b | 36. a |
| 37. c | 38. b | 39. d | 40. d | 41. a | 42. b |
| 43. a,b | 44. a | 45. b | 46. c | 47. a | 48. d |

### REPRODUCTIVE SYSTEM

| | | | | | |
|---|---|---|---|---|---|
| 1. d | 2. c | 3. b | 4. c | 5. b | 6. a |
| 7. c | 8. d | 9. d | 10. a | 11. d | 12. d |
| 13. c | 14. b | 15. c | 16. d | 17. b | 18. d |
| 19. c | 20. a | 21. a | 22. a | 23. a | 24. d |
| 25. d | 26. c | 27. b | 28. d | 29. d | 30. d |
| 31. a | 32. c | 33. d | 34. c | 35. a | 36. b |
| 37. a | 38. a | 39. c | 40. a | 41. c | 42. a |
| 43. a | 44. a | 45. c | 46. a | 47. a | 48. b |
| 49. a | 50. c | 51. d | 52. a | 53. d | 54. b |
| 55. d | 56. a | 57. c | 58. a | | |

### ENDOCRINOLOGY

| | | | | | |
|---|---|---|---|---|---|
| 1. a | 2. b | 3. c | 4. d | 5. a | 6. a |
| 7. c | 8. c | 9. c | 10. b | 11. a | 12. b |
| 13. e | 14. d | 15. d | 16. a | 17. b | 18. b |
| 19. a | 20. b | 21. c | 22. b | 23. b | 24. c |
| 25. b | 26. d | 27. c | 28. b | 29. a | 30. a |
| 31. d | 32. e | 33. a | 34. b | 35. d | 36. d |
| 37. b | 38. d | 39. a | 40. d | 41. c | 42. c |
| 43. d | 44. a | 45. d | 46. b | 47. c | 48. a |

49. a 50. d 51. a 52. b 53. c 54. a
55. d 56. d 57. b 58. c 59. d 60. a
61. e 62. d 63. a 64. c 65. b

## NERVE MUSCLE PHYSIOLOGY

1. c 2. d 3. b 4. b 5. a 6. c
7. d 8. b 9. b 10. c 11. a 12. a
13. c 14. d 15. a 16. b 17. a 18. a
19. c 20. b 21. b 22. d 23. d 24. c
25. e 26. e 27. d 28. a 29. d 30. d
31. c 32. e 33. a 34. c 35. a 36. a
37. b 38. d 39. a 40. d 41. a 42. a
43. c 44. d 45. b 46. c 47. c 48. a
49.b 50. a 51. d 52. c 53. a

## CENTRAL NERVOUS SYSTEM

1. c 2. c 3. d 4. a 5. b 6. c
7. d 8. c 9. d 10. b 11. c 12. a
13. c 14. a 15. b 16. c 17. b 18. c
19. a 20. c 21. c 22. d 23. b 24. a
25. c 26. d 27. b 28. b 29. d 30. d
31. c 32. d 33. c 34. b 35. d 36. b
37. b 38. c 39. c 40. b,c 41. c 42. c
43. b 44. a 45. a 46. d 47. c 48. d
49. c 50. a 51. d 52. c 53. d 54. d
55. a 56. d 57. a 58. b,c 59. a 60. a
61. d 62. a 63. a 64. d 65. b 66. d
67. c 68. d 69. c 70. b 71. a 72. c
73. b 74. b 75. a 76. a 77. b 78. e
79. c 80. c 81. a 82. c 83. c 84. d
85. a 86. d 87. a,b 88. c 89. a 90. b,d
91. c 92. a 93. c 94. c 95. d 96. a,c
97. d 98. c 99. c 100. b 101. c 102. d
103. c 104. b 105. b 106. a 107. c 108. a
109. b 110. b 111. a 112. d 113. a 114. c
115. b,c 116. c 117. b 118. d 119. a 120. c
121. d 122. b 123. c 124. d 125. a

## SPECIAL SENSES

1. b 2. c 3. b 4. d 5. d 6. d
7. b 8. c 9. c 10. b 11. c 12. b,c
13. a 14. d 15. a 16. a 17. c 18. b
19. b 20. b 21. c 22. a 23. b 24. c
25. c 26. d 27. a 28. c 29. b 30. a
31. b 32. c 33. a 34. a 35. b 36. c
37. b 38. b 39. b 40. a 41. c 42. a,d
43. d 44. b 45. c 46. b 47. a 48. b
49. a 50. b 51. d 52. b 53. a 54. b
55. a 56. b

*Chapter*

# 17

# Reasoning Type Questions

## CIRCULATING BODY FLUIDS

1. Blood does not clot *in vivo* (Page no. 23; anticlotting mechanism, velocity of blood flow)
2. Reverse anemia occurs after gastrectomy (Page no. 17)
3. Opsonization aids phagocytosis (Page no. 20)
4. Aspirin is given in MI (Page no. 21)
5. Dicumarol cannot be used as an *in vitro* anticoagulant (Page no. 24; In a collected blood sample, i.e. *in vitro*, the clotting factors are already present, so dicumarol (vitamin K antagonist) has practically no effect.
6. Bleeding disorders in vitamin K deficiency or in liver diseases clotting time is prolonged (Page no. 24)
7. In thrombocytopenic purpuras BT is prolonged but CT remains normal (Page no. 24)
8. Reticulocyte count increases after vitamin $B_{12}$ therapy (Page no. 16; reticulocyte response-due to proliferation of bone marrow and numerous young RBCs pass into circulation)
9. Parentral administration of vitamin $B_{12}$ in pernicious anemia (Page no. 15)
10. Hematocrit value of capillary blood is lower than that of actual blood (Page no. 276)
11. Edema develops in hypoalbunemia (Page no. 30)
12. Bleeding tendency in obstructive jaundice (In obstructive jaundice, there is no release of bile from liver into the intestine, so no absorption of fat soluble vitamin, i.e. Vitamin K, thereby vitamin K deficiency so bleeding tendancy is there)
13. Bleeding occurs in chronic liver diseases (Page no. 24)
14. PCV of venous blood is greater than that of arterial blood (Page no. 43)
15. Calcium deficiency does not lead to bleeding disorders (Page no. 23)
16. Clot does not spread in the injured vessel after blood coagulation (Page no. 23)
17. In a Rh-negative mother carrying an Rh-positive fetus, the first child is usually normal (Page no. 25)
18. Stored blood is not suitable for transfusing WBCs and platelet to a recipient (Blood stored for longer than 24 hours contains virtually no viable WBCs and platelets )
19. In case of extreme emergency, 'O' Rh negative blood should be transfused (As 'O' Rh negative blood contains no antigens and therefore no antigen - antibody reaction)
20. ABO incompatibilities rarely produce hemolytic disease of newborn (Page no. 25)

## RESPIRATORY SYSTEM

1. Intrapleural pressure is always negative/subatmospheric (Page no. 35)
2. Alveoli are always kept dry (Page no. 38)
3. Pulmonary TB affects apex of lung first (Page no. 39)
4. Expiratory phase is longer than inspiratory phase of respiratory cycle (During expiration bronchial constriction occurs thereby resistance to air flow increases, more work has to be done)
5. Bronchial asthma is a disease of expiratory obstruction (During inspiration expansion of bronchioles take place but on expiration there is constriction of already constricted bronchioles)
6. High V/P ratio in the apices of lungs (Page no. 39; At the apex intrapleural pressure more negative, so alveoli expand more $\rightarrow$ greater alveolar ventilation, perfusion also less at apex relative to base)
7. Compliance of lungs alone is greater than the combined compliance (Inside thorax, some energy is required to expand the thorax also)
8. Lung compliance increases in old age (Due to some modification in the knitting arrangement of the elastic tissues)
9. Arterial $pO_2$ is less than alveolar $pO_2$ (Blood leaving the pulmonary capillaries is joined by venous blood from bronchial circulation and from anterior cardiac and the basian veins)
10. Sigmoid shape of oxygen-hemoglobin dissociation curve (Page no. 41)
11. Myoglobin acts as a temporary $O_2$ storehouse (Page no. 42)
12. Blood is an ideal vehicle for $O_2$ transport (It can give off more $O_2$ to tissues at lower $pO_2$)
13. Central chemoreceptors respond only to abrupt changes in $pCO_2$ ($H^+$ penetrates blood brain barrier slowly, $CO_2$ penetrate rapidly thereby leading to increased $H^+$

concentration in brain interstitial fluid stimulating central chemoreceptors)
14. Respiratory chemoreceptors are not stimulated in anemia or CO poisoning (Page no. 45)
15. Mild-to-moderate hypoxia stimulates the respiration but severe hypoxia depresses it (Severe hypoxia causes direct inhibition of respiratory center)
16. Pulmonary ventilation is not much affected until $pO_2$ of inspired air falls below 60 mm Hg (Hypoxia increase the amount of reduced Hb (weaker acid), bind with $H^+$ reducing $H^+$ concentration tending to inhibit respiration)
17. $CO_2$ increases pulmonary ventilation primarily by stimulating central chemoreceptors. ($CO_2$ is a potent stimulant of central chemoreceptors, it crosses the blood-brain barrier and results in increase $H^+$ concentration in brain interstitial fluid and thereby stimulating central chemoreceptors)
18. Apnea occurs after voluntary hyperventilation (Page no. 46, $CO_2$ washout)
19. Cyanosis is not seen in anemic hypoxia (Page no. 48 decrease in Hb concentration in anemia)
20. Cyanosis is a common occurrence in hypoxic hypoxia. (In hypoxic hypoxia there is increase in reduced Hb, so cyanosis results)
21. Histotoxic hypoxia cannot cause cyanosis (Because reduced Hb is either not produced or produced in very small amount)
22. Babies of diabetic mothers are prone to develop IRDS (Page no. 36 and 37)
23. Systemic circulation has a low $pO_2$ than pulmonary circulation (Page no. 38)
24. In venous blood, RBCs have higher hematocrit than in arterial (Page no. 41)
25. Lesions in I neurons does not abolish respiratory activity (Page no. 47; PBZ)
26. Increase in $H^+$ ion concentration in blood cannot activate central chemoreceptors (Page no. 44)
27. $O_2$-He mixture is used in SCUBA (To avoid $N_2$ narcosis, he being low density gas is less soluble in fat than $N_2$)
28. Relief of orthopnea on sitting up (Lying down position increases pulmonary congestion and aggrevates dyspnea)
29. Headache is experienced while staying in an over crowded room for long time (Due to increased level of $CO_2$ accumulation in the room and thereby leading to $O_2$ depletion within the body)
30. Severe joint pain occurs in decompression sickness ($N_2$ bubbles in tissues and blood around the joint causes severe joint pain).

## CARDIOVASCULAR SYSTEM

1. Bradycardia in raised intracranial tension (Page no. 77)
2. Tachycardia in old age (due to fall in vagal tone)
3. Physiological hypertrophy of the left ventricle (LV has to do more work than RV, so LV wall becomes thicker than RV)
4. Heart sounds are not produced during opening of valves (Opening of valves is a slowly developing process and so produce no sound)
5. Myocardium is well perfused during diastole (Page no. 82)
6. Fainting during emotions (Page no. 86)
7. The thin walled and delicate capillaries are less prone to rupture (Page no. 57)
8. Dilated heart has to do more work than a non-dilated heart (Because when the radius of a cardiac chamber is increased, a greater tension must be developed in myocardium to produce any given pressure)
9. Veins are called capacitance vessels (Page no. 56)
10. Variation in arteriolar diameter has marked effect on the systolic blood pressure (Page no. 79; BP = CO × PR. Peripheral resistance inversely proportional to radius raised to the power of 4)
11. Cardiac muscle cannot be tetanized/Cardiac muscle shows no signs of fatigue (Page no. 62)
12. Atrial and ventricular muscles do not show autorythmicity (Potential in them is plateau potential, it is not spontaneous and is produced only by stimulus from pacemaker cells which is spontaneous)
13. During BP measurements, systolic BP should be first measured by palpatory method (Page no. 297; Auscultatory gap)
14. Heart rate increases in inspiration (Page no. 77)
15. Increased stroke volume during exercise (Due to skeletal muscle pump, there is increase in venous return leading to increased in stroke volume)
16. Pressing the carotid sinus increases the heart rate (Baroreceptor reflex)
17. Extracellular concentration of calcium influences the force of conduction in cardiac muscle. (For cardiac muscle AP the source of calcium for muscle contraction is not any stores in sarcoplasmic reticulum, but also extracellular calcium which enters from ECF to ICF)
18. Cold clammy skin and rapid pulse occurs in hypovolemic shock (Due to activation of baroreceptor reflex and continuous vasoconstriction due increased sympathetic activity)
19. Body of a patient in shock should not be covered with blanket (Because if covered with blanket body temperature raises, leading to increased metabolic activity making the condition of shock worser).

## GASTROINTESTINAL SYSTEM

1. Postprandial alkaline tide or alkaline urine after heavy meal (Page no. 95)
2. Bulky, clay colored stools in obstructive jaundice (Page no. 93; Stercobilinogen gives normal color to stool)
3. A patient suffering from aptyalism has high risk of dental caries (Page no. 93)
4. Steatorrhea occurs in pancreatic insufficiency (Page no. 100)

5. Gastrin release though vagally mediated is not blocked by atropine (Because the transmitter secreted by the postganglionic vagal fibers that innervate the gastrin cells is 'GRP' and not ACh)
6. Gastric mucosa is resistant to autodigestion (Page no. 98; Mucosal barrier)
7. Alcohol intoxication can be avoided if it is consumed after ingestion of a drink rich in fat (Gastric emptying time is the slowest for a fat rich food)
8. Duodenal ulcer can be treated by vagotomy (Vagotomy results in decreased gastric juice secretion during all its phases)
9. Resection of large segment of ileum can result in steatorrhea (Page no. 100)
10. Achlorhydria is associated with iron deficiency anemia (Iron is readily absorbed in ferrous state, but most of the dietary iron is in ferric form and HCl is needed for its reduction)
11. Ranitidine or Omeprazole is given in peptic ulcer (Page no. 98)
12. Dizziness after a heavy meal in gastrectomized patient (Page no. 113, dumping syndrome)
13. Rapidly changing movement causes vomiting (Stimulation of vomiting center)
14. Loss of fluid from the colon in chronic diarrhea results in severe hypokalemia (Because net movement of $K^+$ is directly proportional to the potential difference between blood and intestinal lumen)
15. Appreciable amounts of faces continue to be passed during prolonged starvation (Large fraction of facal mass is of non-dietary origin)
16. Majority of bile reaches circulation (Page no. 102)
17. Misoprostol given to patients on treatment of arthritis with NSAIDs (Page no. 98)
18. Glucose is not formed by the action of salivary amylase on starch (Salivary amylase acts on alpha 1, 4 linkage, but spares alpha 1, 6 linkage, terminal alpha 1, 4 linkage and alpha 1, 4 linkage next to branching points. Hence, the end products of alpha amylase digestion are oligosaccharides, disaccharides and trisaccharides).

## RENAL PHYSIOLOGY

1. PCT has a high rate of $O_2$ consumption. (PCT cells are rich in mitochondria)
2. High resistance is offered to blood flow in efferent arteriole (efferent arteriole diameter is smaller compared to afferent arteriole)
3. Medullary blood flow does not show autoregulation (As medullary blood flow is only 8% of total RBF, the effect of BP on the RBF due to changes of medullary flow are marked)
4. Renal failure develops in persons with poor renal perfusion (At low perfusion pressure, angiotensin II helps in maintaining GFR by constricting afferent arteriole)
5. Chronic renal disease produces anemia (Erythropoietin production decreases)
6. Predicted renal threshold for glucose is more than the actual value (Page no. 125)
7. Hyperventilation is associated with alkaline urine (Hyperventilation causes decreased $CO_2$ in cells $\rightarrow$ decreased $H^+$ formation within tubular cells leading to decreased $HCO_3^-$ reabsorption)
8. Angiotensin II plays an important role in the body response to hypovolemia. (Angiotensin II has generalized vasoconstrictor effect, stimulate aldosterone, and ADH secretion)
9. Increase in ANP secretion leads to natriuresis. (Increase in ANP leads to efferent arteriolar constriction resulting in increased glomerular capillary resistance and thereby increases GFR, resulting in natriuresis)
10. Hemoglobin is the main buffer system in the body (Hb is present in large amounts and it contains 38 histidine molecules)
11. There is increased frequency of micturition during nervousness (During emotional stress, the power of urinary bladder to elongate its fibers as its contents increase is in suspension).
12. High protein diet increases the ability of kidney to concentrate the urine (Page no. 128)
13. Albuminuria in nephrotic syndrome (Page no. 136)
14. Splay in glucose titration curve (Page no. 125)
15. Hyperosmolarity in medullary interstitium (Page no. 128)
16. Plateau phase in cystometrogram (Page no. 133)
17. Renal medulla is exposed to hypoxic damage than cortex (Cortex has more blood supply than the medulla. $O_2$ extraction of the cortex is also less compared to the medulla)
18. PAH is used to determine the renal blood flow (Page no. 131).

## ENDOCRINOLOGY

1. Iodine preparation is given before thyroidectomy (Iodides in high concentration decrease all phases of thyroid activity, they slightly decrease the size of the thyroid gland and decrease its blood supply. This decrease the necessary amount of surgery, the amount of bleeding).
2. Hypothyroid patients prefer hot environment. (Because of decreased heat production, hypothyroid are hypersensitive to cold and prefer hot environment)
3. Even though prolactin increases during pregnancy, there is no milk secretion (Prolactin plays an important role in development of lobuloalveolar system, its role in milk production is minimal).

4. Epinephrine does not produce reflex bradycardia (Page no. 165)
5. High levels of aldosterone cause diuresis and natriuresis (Page no. 161)
6. Perimetry is indicated in acromegaly (Due to pituitary tumor the optic chiasma is getting compressed)
7. Purple striae, truncal obesity, red cheeks and moon like face are seen in cushings syndrome (Page no. 162)
8. Centripetal distribution of fat in Cushings syndrome. (Page no. 163)
9. Polyuria, polydypsia and polyphagia in DM (Page no. 159)
10. Amenorrhea during postpartum lactation (Page no. 146)
11. Exophthalmos in hyperthyroidism (Page no. 152)
12. Myxodema and carotinemia in hypothyroidism (Page no. 152)
13. Hypothyroidism retards growth (Page no. 143)
14. Muscle weakness in both hypothyroidism and hyperthyroidism (Page no 152; hyperthyroidism cause weakness of muscle due to catabolism of proteins in physilogical amounts thyroid hormone is essential for skeletal maturation)
15. Use of T4 metabolites as cholesterol lowering agents (T4 metabolites increase breakdown of cholesterol in liver and increases excretion of cholesterol in bile)
16. Alteration of thyroid activity impairs fertility in women (Page no. 150; because of disordered cyclic ovarian activity)
17. Diabetes mellitus is usually seen in hyperthyroid patients (Thyroid hormones cause hyperglycemia)
18. A person suffering from hypothyroidism is advised to avoid cabbage in his diet (Cabbage is a goitrogen, which forms goitrin, an active anti-thyroid agent and it prevents incorporation of iodine with tyrosine)
19. Children with cretinism have short stature and mental defect (Page no. 152)
20. Milk ejection in a lactating mother in response to cry of the baby (Oxytocin secretion can be conditioned, the physical stimulation of nipples is no longer required)
21. Sexual precocity individuals are dwarf (Although androgen initially stimulate growth, yet ultimately terminates growth by causing epiphyseal closure, thereby decreasing linear growth)
22. Diabetic children fail to grow (Due to impaired glucose utilization)
23. Diabetic patient fails to gain weight inspite of polyphagia. (Due to impaired glucose utilization)
24. Bile increases calcium absorption from the GIT (Bile and bile salts increase the solubility of Ca salts).
25. Higher incidence of fractures after 40 years of age (After 40 years of age, there is normally a progressive loss of skeletal mass, leading to 'senile' osteoporosis)
26. Neuromuscular hyperexcitability is seen in tetany (Page no. 155)
27. Glucocorticoids are used in prevention of rejection of a tissue transplant. (Glucocorticoids in the late stages, decreases antibody formation by its destructive effect on fixed lymphoid tissues)
28. Osteoporosis is associated with glucocorticoid excess (Page no. 157)
29. Anemia in persons suffering from chronic adrenal insufficiency (Page no. 161)
30. Glucocorticoids have hyperglycemic effect (Page no. 161)
31. Hyperpigmentation in aldosteronism (High aldosterone levels leads to indirect stimulation of melanocyte stimulating hormone)
32. Dopamine is used in management of shock (Page no. 166)
33. Carpopedal spasm is seen in tetany (Decrease in $Ca^{2+}$)
34. Injection of epinephrine produces a biphasic effect on BP (Page no. 165, Dales vasomotor reversal)
35. Non-pitting edema in hypothyroidism (Increased quantities of hyaluronic acid and chondritin sulphate bound with protein form excessive tissue gel in the interstitial spaces. Because of gel nature of excess fluid, the edema is non-pitting type)
36. Alloxan administration leads to DM and not DI (Pancreatic cell destruction)
37. In Conn's syndrome there is no peripheral edema (Due to aldosterone escape and here there is increased of ANP leading to increased $Na^+$ excretion, so no accumulation thereby no edema)
38. $V_2$ receptor mutation results in diabetes insipidus. (Vasopressin causes rapid insertion of aquaporin-2 on collecting duct through $V_2$ receptor).

## REPRODUCTIVE SYSTEM

1. Oral contraceptives prevent pregnancy (Page no. 183)
2. Sterility in a man working in hot surroundings (Spermatogenesis requires a temperature considerably lower than that of the interior of the body, high temperature impairs spermatogenesis)
3. Androgen when given orally is ineffective. (It is inactivated in the liver by converting it into less potent androsterone and dehydroepiandrosterone)
4. Menstrual blood does not normally contain clots (Page no. 174; it is liquefied by fibrinolysin in the vagina)
5. There is usually swelling and tenderness of breasts prior to menstruation (These are cyclic changes occurring in the breasts under the influence of estrogen and progesterone)
6. LH surge is necessary for ovulation (Page no. 175)
7. Ovulation occurs around the 14th day of normal menstrual cycle (Occurs due to a sudden rise in LH secretion secondary to rise in estrogen concentration)

8. Higher incidences of patent ductus arteriosus in children with history of fetal distress (Decreased $PO_2$ of ductus blood in cases of fetal distress)
9. Removal of ovaries in the 6th week of pregnancy results in termination of pregnancy (Because during the first 3 months corpus luteum in the ovaries secrete estrogen and progesterone, the hormone maintaining pregnancy and later only the placenta takes over).

## CENTRAL NERVOUS SYSTEM

1. Acupuncture lessens pain (Page no. 216)
2. Gentle rubbing over the area reduces pain sensation (Page no. 216)
3. Discharge of postsynaptic neuron even after cessation of pre-synaptic impulse (Page no. 206; after discharge)
4. Prefrontal lobotomy is done in untreatable cases of pain.
5. Over reaction to pain occurs in thalamic lesions (Thalamic syndrome)
6. Wounded soldiers in battlefield are unaware of pain (Page no. 216; stress analgesia)
7. Discrimination of power is greater on the thumbs than on the back. (In the thumb, the receptors are closely placed compared to back of the body)
8. Phantom limb (Page no. 204)
9. Clasp knife effect and clonus-physiological basis (Page no. 208)
10. Spinal man cannot stand unsupported (Page no. 232)
11. Rigidity occurs in lesion of basal ganglia (Page no. 245)
12. Pendular knee jerk in cerebellar lesion (Page no. 238)
13. Finger nose test is positive in cerebellar lesion (Page no. 238; damping function)
14. L-dopa in parkinsonism (Page no. 245)
15. Resting tremors in basal ganglia dysfunctions (Page no. 245)
16. Cerebellar lesions affect the same side of the body (Double crossing; each cerebellar hemisphere influences the opposite cortex; which in turn the motor cortex via the corticospinal tracts controls the movement of the opposite side of the body. Because of the double decussation, each cerebellar hemisphere controls the voluntary movements on its own side of the body)
17. Babinski's sign positive in UMN lesion (Page no. 221)
18. Stimulation of gamma efferent system causes reflex contraction of all muscles (Stimulation of gamma efferents shortens the contractile ends of intrafusal fibers which stretches nuclear bag portion of spindles, deforming the annulospiral endings and initiate impulses in the Ia fiber leading to reflex contraction of muscle)
19. Jendrassik's maneuver facilitates deep tendon reflex (Reinforcement acts by increasing the excitability of alpha motor neurons and by increasing the sensitivity of the muscle spindle primary sensory endings to stretch)
20. Ankle clonus in UMN lesion (In UMN lesion there is increased activity of facilitatory area leading to increased tone and also there is increased gamma efferent discharge leading to clonus)
21. Deep tendon reflex is exaggerated in spastic paralysis (decrease in supraspinal inhibition on gamma efferents)
22. REM sleep is called paradoxical sleep (Page no. 242).

## SPECIAL SENSES

1. Vision is not possible over the optic disk (Optic disk contains no light sensitive receptors)
2. Visual acuity is maximum over fovea (Fovea is a rod free portion where the cones are densely packed and there are few cells and no blood vessels overlying the receptors)
3. High incidence of cataract in diabetes mellitus patients (Due to the action of glucose on lens protein which makes them easily coagulable by light)
4. Retinal detachment damages photoreceptors. (Photoreceptors are mainly nourished by the capillary plexus in the choroid)
5. Blurring of vision when a person is inside water (When a person is inside water, no refraction occurs at the cornea as refractive index of water and cornea becomes the same)
6. Blurred vision following instillation of homatropine in to the eye (local administration of homatropine causes mydriasis (dilatation of pupil) and cyclopegia (loss of accommodation)
7. Reading or close work becomes progressively difficult with advancing age (Near point becomes progressively distant with advancing age)
8. Ultraviolet and infrared are not perceived by the human eye (Eye responds to light of wavelength between 400 nm and 750 nm called visibility or sensitivity range of vision)
9. Cones are responsible for color vision (Different color sensations are produced by stimulation of various combination of 3 types of receptors–cyanolabe, chlorolabe and erythrolabe)
10. Radiologists and aircraft pilots wear red goggles when in bright light. (They need maximum visual sensitivity in dim light. They can avoid having to wait 20 minutes in the dark to become dark adapted if they wear red goggles, light wavelength in the red end of the spectrum stimulate the rods to only a slight degree while permitting the cones to function reasonably well. Therefore, a person wearing red goggles can see in bright light, during the time it takes for the rods to become dark adapted )
11. Transient blue green color blindness occurs in patients taking sildenafil (viagra). (Drug inhibit retinal as well as penile form of phosphodiesterases) (Page no. 265)

*Chapter*

# 18

# Question Bank

## GENERAL PHYSIOLOGY

1. Transport across cell membrane (3)
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*Chapter*

# 19

# Normal Values

## CIRCULATING BODY FLUIDS

1. RBC count:
   Males: $5.4 \times 10^6$ /µL
   Females: $4.8 \times 10^6$ /µL
2. WBC count
   Total: 9,000 cells/µL (average)
   Range: 4000 – 11000 cells/µL

| 3. Granulocyte | Average | Range |
|---|---|---|
| • Neutrophils | 5400 cells/µL | 3000–6000 cells/µL |
| • Eosinophils | 275 cells/µL | 150–300 cells/µL |
| • Basophils | 35 cells/µL | 0–100 cells/µL |
| 4. Lymphocytes | 2750 cells/µL | 1500–4000 cells/µL |
| 5. Monocytes | 540 cells/µL | 300–600 cells/µL |
| 6. Platelets | 3,00,000 cells/µL | 2,00,000–5,00,000 cells/µL |

7. Hematocrit (Hct)
   Males : 47%
   Females : 42%
8. Hemoglobin (Hb)
   Males : 16 g/dL
   Females : 14 g/dL
9. Mean corpuscular volume (MCV)
   Males : 87 fL or $\mu m^3$
   Females : 87 fL or $\mu m^3$
10. Mean corpuscular hemoglobin (MCH)
    Males : 29 pg
    Females : 29 pg
11. Mean corpuscular hemoglobin concentration (MCHC)
    Males : 34 g/dL
    Females : 34 g/dL
12. Mean cell diameter (MCD)
    Males : 7.5 µm
    Females : 7.5 µm
13. Protein (Serum concentration)
    - Total : 6.0–8.0 g/dL
    - Albumin : 3.1–4.3 g/dL
    - Globulin : 2.6–4.1 g/dL
    - Fibrinogen : 1.5–4 g/dL
14. Bilirubin(Serum)
    Conjugated (direct) : up to 0.4 mg/dL
    Unconjugated (indirect) : 0.6 mg/dL
    Total (conjugated plus free) : up to 1.0 mg/dL
15. Normal bleeding time : 1–5 min
16. Normal clotting time : 3–6 min

***Note:***

a. Mean cell diameter is the mean diameter of 500 cells in smear.
b. Cells with MCVs >95 fL are called macrocytes; cells with MCVs <80 fL are called microcytes; cells with MCHs <25 g/dL are called hypochromic.

17. Glucose, fasting (plasma): 70–110 mg/dL
18. Normal serum concentrations
    - Sodium : 135–145 meq/L
    - Potassium : 3.5–5.0 meq/L
    - Phosphorous (inorganic): 2.6–4.5 mg/dL
19. Normal blood uric acid: 4 mg/dL(0.24 mmol//L)
20. Total blood cholesterol:150–200 mg/dL
21. HDL fraction
    Males: 30–60 mg/dL
    Females: 35–75 mg/dL
22. LDL fraction (30–39 years): 80–175 mg/dL
23. Normal prothrombin time: 11–16 sec

## RESPIRATORY SYSTEM

1. Arterial blood
   - $pO_2$: 95 mm Hg
   - $pCO_2$: 40 mm Hg
   - Hb saturation: 97 %
   - $O_2$ content: 19.8 ml $O_2$/dL
2. Venous blood
   - $pO_2$: 40 mm Hg
   - $pCO_2$: 46 mm Hg
   - Hb saturation: 75%
   - $O_2$ content: 15.2 ml $O_2$/dL

| | *Males* | *Females* |
|---|---|---|
| 3. Tidal volume (TV) | 0.5 L | 0.5 L |
| 4. Inspiratory reserve volume (IRV) | 3.3 L | 1.9 L |
| 5. Expiratory reserve volume (ERV) | 1.0 L | 0.7 L |
| 6. Residual volume (RV) | 1.2 L | 1.1 L |

| | | |
|---|---|---|
| 7. Vital capacity (VC) | 4.8 L | 3.1 L |
| 8. Inspiratory capacity(IC) | 3.8 L | 2.4 L |
| 9. Expiratory capacity(EC) | 1.5 L | 1.2 L |
| 10. Functional residual capacity(FRC) | 2.2 L | 1.8L |
| 11. Total lung capacity(TLC) | 6.0 L | 4.2 L |

12. Respiratory minute volume (rest): 6 L/min
13. Alveolar ventilation (rest): 4.2 L/min
14. Maximal voluntary ventilation: 125-170 L/min
15. Timed vital capacity: 83% of total in 1sec, 97 % in 3 sec
16. Work of quiet breathing: 0.5 kg-m/min
17. Maximal work of breathing: 10 kg-m/breath
18. Compliance of lungs alone: 0.22 L/cm $H_2O$
19. Compliance of lungs and thoracic wall: 0.11 L/cm $H_2O$
20. Normal respiratory rate: 14–16/min
21. Normal intrapleural pressure: 754–757 mm Hg
22. Normal intra-alveolar pressure: 759–761 mm Hg

## CARDIOVASCULAR SYSTEM

1. Normal cardiac output: 5 L/min (4.5–6 L/min)
2. Cardiac index: 2.5–3.6 L/min/$m^2$ BSA
3. Stroke volume: 70–90 ml
4. Normal heart rate: 60–100/min
5. End diastolic ventricular volume: 130 ml
6. ECG waves duration

| | Average | Range |
|---|---|---|
| • PR interval | 0.18 s | 0.12–0.20 s |
| • QRS duration | 0.08 s | 0.08–0.10 s |
| • QT interval | 0.40 s | 0.40–0.43 s |
| • ST interval | 0.32 s | - |

7. Conduction speeds in cardiac tissue
   - SA node : 0.05 m/s
   - Atrial pathways : 1 m/s
   - AV node : 0.05 m/s
   - Bundle of His : 1 m/s
   - Purkinje system : 4 m/s
   - Ventricular muscle : 1 m/s
8. Average rate of impulse production
   - SA node : 72/min
   - AV node : 50/min
   - Ventricle : 30/min
9. Cardiac cycle
   - Atrial systole (0.1 sec)
   - Ventricular systole (0.3 sec)
   - Ventricular diastole (0.5 sec)
   - Atrial diastole (0.7 sec)
10. Ventricular systole (0.3 sec)-3 phases:
    - Isovolumetric (Isometric) ventricular contraction (0.05 sec)
    - Maximum (rapid) ejection phase (0.1 sec)
    - Reduced ejection phase (0.15 sec)
11. Ventricular diastole (0.5 sec)-4 phases
    - Protodiastole (0.04 sec)
    - Isovolumetric relaxation phase (0.06 sec)
    - Ventricular diastole proper (0.3 sec)
    - Last rapid filling phase (0.10 sec).
12. Resting blood flow and % of CO flow through various organs

| *Organ* | *Blood flow (ml/min)* | *% of CO* |
|---|---|---|
| • Liver | 1500 | 27.8 |
| • Kidneys | 1260 | 23.3 |
| • Brain | 750 | 13.9 |
| • Skin | 462 | 8.6 |
| • Skeletal muscle | 840 | 15.6 |
| • Heart muscle | 250 | 4.7 |
| • Rest of body | 336 | 6.2 |
| • Whole of body | 5400 | 100 |

13. Normal blood pressure
    - Systolic pressure: 100–140 mm Hg (average-120 mm Hg)
    - Diastolic pressure: 60–90 mm Hg (average-70 mm Hg)
    - Pulse pressure: 50 mm Hg
    - Mean arterial blood pressure: 90 mm Hg

## GASTROINTESTINAL SYSTEM

1. Gastric emptying time: 3–4 hours
2. Normal pH of saliva: 7–8
3. Normal pH of gastric juice: 1–2
4. Normal pH of pancreatic juice: 6–7
5. Normal pH of hepatic duct bile: 7.8–8.6
6. Normal pH of gallbladder bile: 7.0–7.4

## RENAL PHYSIOLOGY

1. Glomerular filtration rate (GFR): 125 ml/min or 180 L/day.
2. Filtration fraction: 0.16–0.2
3. Transport maximum ($T_M G$ ) for glucose
   Male: 375 mg/min Female: 300 mg/min
4. Renal threshold value for glucose: 300 mg/dL
   Actual renal threshold of:
   - Arterial blood: 200 mg/dL
   - Venous blood: 180 mg/dL
5. Renal blood flow:1273 mL/min
6. Actual renal plasma flow: 700 mL/min
7. Effective renal plasma flow: 625 mL/min(average)
8. Inulin clearance value: 125 mL
9. Normal plasma creatinine: 0.6–1.5 mg/dL

## ENDOCRINOLOGY

1. Growth hormone (GH): 3 ng/mL (plasma)
2. Thyroid binding globulin (TBG): 7–17 mg/l (plasma)
3. Thyroxine (T4): 70–140 nmol/l (plasma)
4. Thyroxine (free) plasma: 9–22 pmol/l
5. Triiodothyronine (T3): 1.2–3.0 nmol/l (plasma)
6. Parathyroid hormone (PTH): 10–55 pg/mL
7. Plasma testosterone (free and bound)
   Adult male: 300–1000 ng/dL (10.4–34.7 nmol/L)
   Adult female: 30–70 ng/dL (1.04–2.43 nmol/L
8. Plasma progesterone
   Male: 0.3 ng/mL (1 nmol/L)
   Female: 0.9 ng/mL (3 nmol/L)—During the follicular phase of menstrual cycle
9. Plasma prolactin concentration
   Male: 5 ng/mL
   Female: 8 ng/mL
11. Insulin (plasma): 0.3–2 ng/mL
12. Hormonal levels in human maternal blood during normal pregnancy

| *Hormone* | *Approx peak value* |
|---|---|
| • HCG | 5 mg/mL |
| • Relaxin | 1 ng/mL |
| • HCS | 15 mg/mL |
| • Estradiol | 16 ng/mL |
| • Estriol | 14 ng/mL |
| • Progesterone | 190 ng/mL |
| • Prolactin | 200 ng/mL |

## REPRODUCTIVE SYSTEM

1. Normal sperm count: 80–120 million/ml (average-100 million/ml)
2. Average volume of semen per ejaculate: 2.5–3.5 mL
3. Testosterone secretion rate: 4–9 mg/day (normal adult males)
4. Normal duration of menstrual flow: 3–5 days
5. Normal blood loss during menstruation: 30–80 mL

## NERVE AND MUSCLE PHYSIOLOGY

1. RMP of neurons: –70 mV
2. RMP of skeletal muscle: –80 mV to –90 mV
3. RMP of cardiac muscle: –90 mV
4. RMP of smooth muscle: –55 mV
5. Normal synaptic delay: 0.5 ms

### CENTRAL NERVOUS SYSTEM

1. EPSP: 60 mV to –6 mV
2. IPSP: –80 mV to –90 mV
3. Reaction time to monosynaptic system: 19–24 msec
4. Central delay: 0.6–0.9 msec
5. Important cortical areas
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   - Primary sensory area: 3, 1, 2
   - Primary auditory area: 41, 42
   - Primary visual area: 17
   - Visual association area: 18, 19
   - Wernicke's area: 22

## SPECIAL SENSES

1. Aqueous humor
   - Refractive index: 1.336
   - pH: 7.1–7.3
2. Intraocular pressure: 10–20 mm Hg
3. Venous plexus pressure: 10–15 mm Hg
4. Number of rod cells: 120 million
5. Number of cone cells: 6 million
6. Dark adaptation
   - Fast response: 4–5 min
   - Slow response: 20–25 min
7. Normal frequency of human hearing: 20–20000 Hz

## GENERAL

1. Normal body temperature: 37°C (98.6°F)
   - Hypothermia: < 35°C
   - Hyperthermia: >38°C
2. Normal temperature of the scrotum: 32°
3. Respiratory quotient

| | |
|---|---|
| • Carbohydrate | 1.00 |
| • Fats | 0.70 |
| • Protein | 0.82 |

4. CSF

| | |
|---|---|
| • Glucose | 70% of serum mg/dL |
| • Immunoglobulin G | < 40 mg/L |
| • Lactate | 1.1–2.8 mmol/L |
| • Protein | <400 mg/L (< 40 mg/dL) |

5. Normal lumbar CSF pressure: 70–180 mm CSF

## BIBLIOGRAPHY

### Theory

1. Review of Medical Physiology: *William F Ganong*
2. Textbook of Medical Physiology: *Guyton and Hall*
3. Concise Medical Physiology: *Chaudhuri*
4. Textbook of Physiology: *AK Jain*

5. Textbook of Physiology: *Berne and Levy*
6. Essentials of Medical Physiology: *Indu Khurana*
7. Essentials of Medical Physiology:*Sembulingam*
8. Textbook of Physiology: *L Prakasham Reddy*
9. Textbook of Physiology: *Mahapatra*
10. Understanding Medical Physiology: *RL Bijlani*

## Practical

1. Practical Record: Kannur Medical College
2. Practical Record: Calicut Medical College
3. Practical Record: Pariyaram Medical College
4. A textbook of Practical Physiology: *CL Ghai*

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